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Research Article

DESIGN AND SYNTHESIS OF SMALL MOLECULES CAPABLE OF BINDING TO β-AMYLOID PROTIEN FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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ABSTRACT

In the present study a hybrid molecule was designed and synthesised which contains a Benzothiazole moiety and cinnomoyl moiety. The first part was specifically chosen for the amyloid protein binding and the remaining part is for its anti-oxidant properties. The molecule was synthesised using a straight forward synthesis as shown in the scheme. In this study two such derivatives were synthesised and fully characterised spectroscopically.

KEYWORDS: *Alzheimer's disease, β-Amyloid protien, Benzothiazole, Cinnomoyl.*

INTRODUCTION

Alzheimer's disease:

Alzheimer's disease has been hypothesized to be a protein misfolding disease (proteopathy), caused by accumulation of abnormally folded beta amyloid and tau proteins in the brain. Plaques are made up of small peptides, 39–43 amino acids in length, called beta-amyloid (also written as A-beta or Aβ). Beta-amyloid is a fragment from a larger protein called amyloid precursor protein (APP), a transmembrane protein that penetrates through the neuron's membrane. APP is critical to neuron growth, survival and post-injury repair. In Alzheimer's disease, an unknown process causes APP to be divided into smaller fragments by enzymes through proteolysis. One of these fragments gives rise to fibrils of beta-amyloid, which form clumps that deposit outside neurons in dense formations known as senile plaques. One of the pathological landmarks found in post-mortem brains of patients is the abundance of senile plaques containing β-amyloid (Aβ) peptides. While the exact mechanisms underlying the pathology of AD are not fully understood, reducing deposition of amyloid plaques is believed to be potentially useful to benefit patients[3]. Currently, inhibitions of β-secretases responsible for Aβ formation as well as Aβ immunization to reduce Aβ plaques are proposed as potential treatments for AD. The pivotal role of Ah aggregates in AD provides a strong impetus to search for specific Aβ-aggregate-binding agents to target this devastating disease [1-13].

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One of the pathological hallmarks of Alzheimer's disease is the presence of amyloid-β plaques in the brain and the major constituent of these plaques is aggregated amyloid-β peptide. Amyloid deposition in the brain is an early, causative event in the pathogenesis of Alzheimer's disease (AD), the principal component of the amyloid core is a protein called amyloid-beta (Aβ). Since the initial deposition of amyloid may occur long before clinical symptoms of AD are noticeable, the detection and quantification of amyloid deposits could facilitate the diagnosis of AD in its early, pre-symptomatic stages. Small molecules having capability of binding to the β-Amyloid protein can be used as diagnostic marker for the AD. In the present study two molecules consisting of benzothiazole moiety and anti-oxidant moiety were synthesized [14-32].

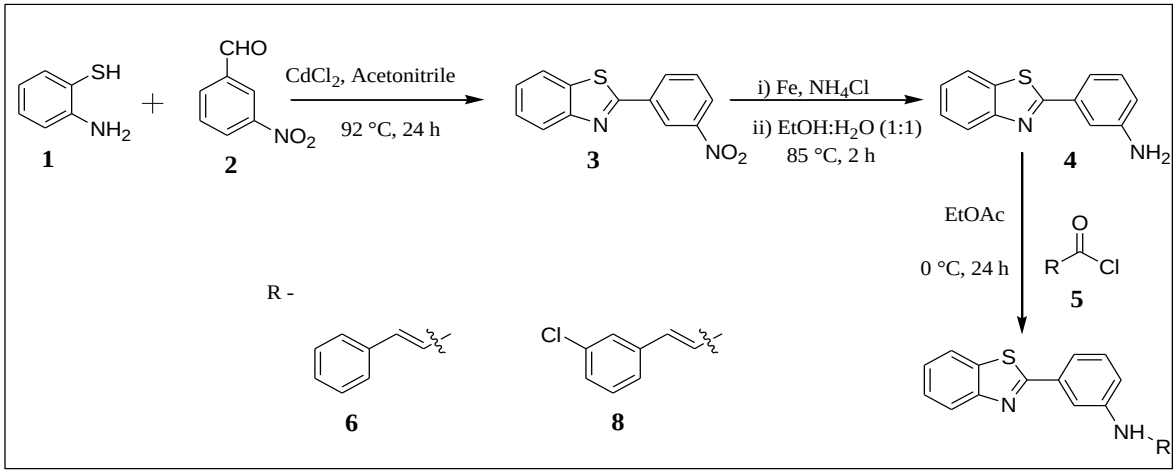
METHODS AND MATERIALS

The aim of the work is the design and synthesis of small and novel amyloid imaging agents. This work describes the design and synthesis of compounds which may contribute to the development of novel amyloid imaging agents. In the present study we tried to develop a small and novel amyloid imaging agent. For this purpose we designed a molecule having 3-Benzothiazol-2-yl-phenylamine (which is previously reported as amyloid binding scaffold) as main scaffold, along with this we introduced different anti-oxidant molecules In view of the fact that in AD oxidative stress is the main cause. Small molecule-based benzothiazole derivatives were designed and synthesized.

The purpose of this study is to develop potential diagnostic imaging agents targeting amyloid plaques in Alzheimer's disease (AD). Formation and accumulation of aggregates of beta amyloid (Aβ) peptides in the brain are critical factors in the development and progression of AD. Developing Aβ-aggregate-specific imaging agents is now an emerging field of research. Oxidative stress (OS) plays a major role in the

pathogenesis of Alzheimer's disease (AD). Antioxidants might theoretically act to prevent propagation of tissue damage and improve both survival and neurological outcome. Here we tried to synthesise a small library of molecules containing Aβ-aggregate-specific imaging moiety along with different anti-oxidant moieties.

General reaction scheme for synthesis of compounds:



Scheme1: General reaction scheme for synthesis of compounds

RESULTS AND DISCUSSION

In the present study 2-Aminobenzenethiol and 3-nitro benzaldehyde were used as starting materials and subjected to various reactions as shown in general reaction scheme to get our target molecule in moderate to good yield.

Synthesis of 2-(3-nitrophenyl) benzo[d]thiazole:

2-(3-Nitrophenyl)benzo[d]thiazole compound (**3**) was synthesized by adding 2-Amino thiophenol compound **(1)** to 3-Nitro Benzaldehyde **(2)** in the presence of Cadmium chloride by using acetonitrile as a solvent , reaction carried out at 92 °C temperature for 24h (Scheme. 2).

Synthesis of 3-(benzo[d]thiazol-2-yl) aniline:

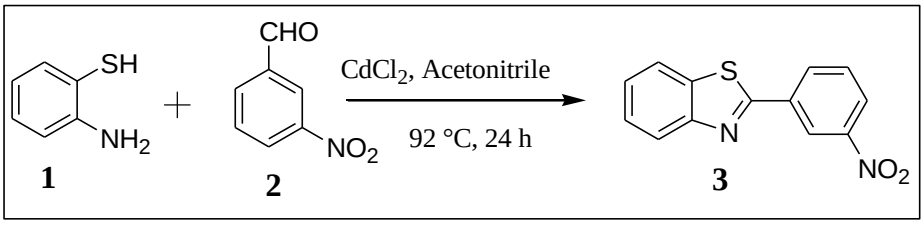
3-(benzo[d]thiazol-2-yl) aniline compound **(4)** has been synthesized by adding 2-(3-Nitrophenyl) benzo[d]thiazole compound **(3)** to iron and ammonium chloride by using ethanol: water (1:1) as a solvent system, reaction carried out at 80 °C temperature for 2h (Scheme. 3).

Synthesis of N-(3-(benzo[d]thiazol-2-yl) phenyl) cinnamamide:

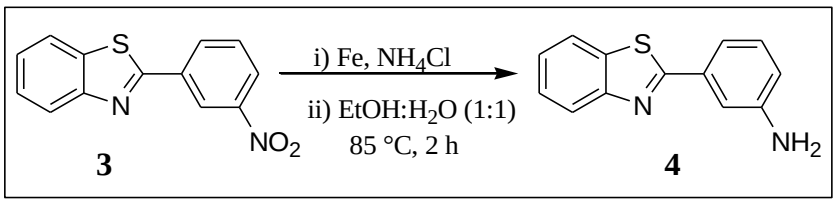
N-(3-2,3-dihydro-1H-inden-2-yl)phenyl)cinnamide compound **(6)** which has been synthesized by adding 3-(benzo[d]thiazol-2-yl) aniline compound **(4)** to cinnomoyl chloride , acetonitrile used as a solvent, reaction carried out at 0 °C temperature to room temperature for 24 h (Scheme. 4).

Synthesis of (E)-N-(3-(benzo[d]thiazol-2-yl) phenyl)-3-(3-chlorophenyl) acryl amide:

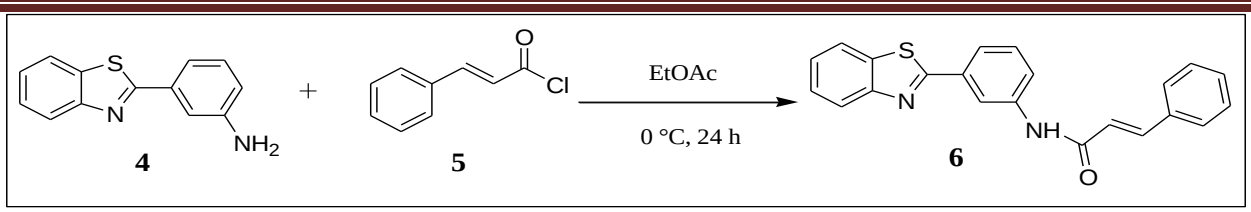
(E)-N-3-(Benzo[d]thiazol-2-yl)phenyl)-3-(3-chloro phenyl)acrylamide compound**(8)** which has been synthesized by adding 3-(benzo[d]thiazol-2-yl) aniline compound **(4)** to chloro cinnomoyl chloride, acetonitrile used as a solvent, reaction carried out at 0 °C temperature to room temperature for 24 h (Scheme. 5).



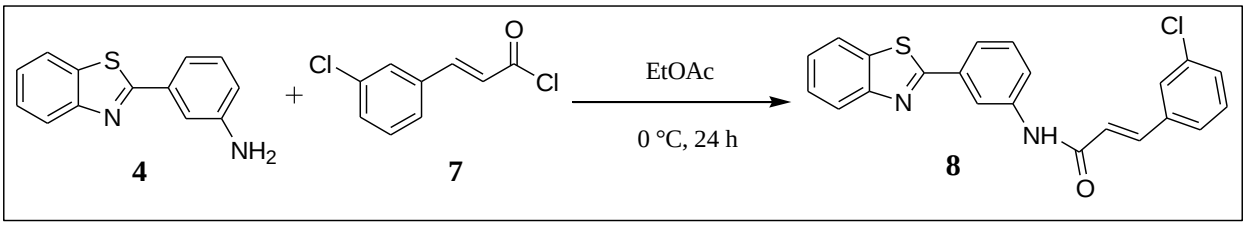
Scheme 2: Synthesis of 2-(3-nitrophenyl) benzo[d]thiazole



Scheme 3: Synthesis of 3-(benzo[d]thiazol-2-yl) aniline



Scheme 4: Synthesis of N-(3-(benzo[d]thiazol-2-yl) phenyl) cinnamamide.



Scheme 5: Synthesis of (E)-N-(3-(benzo[d]thiazol-2-yl) phenyl)-3-(3-chlorophenyl) acryl amide.

Experimental section:

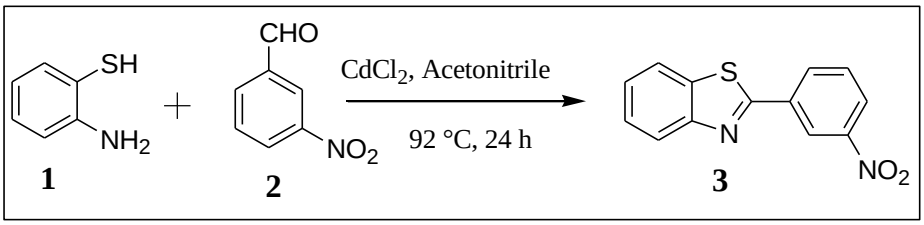
Procedure for thesynthesis of 2-(3-nitrophenyl)benzo[d] thiazole:

To a solution of 2-Amino thiophenol (1 gm, 1eq) in acetonitrile (15 ml) were added 3-Nitro Benzaldehyde (1.2 gm, 1.5 eq) followed by $CdCl_2$ (602 mg, 0.5eq) at 92 °C. The reaction mixture was stirred for 24 h,and it was monitored through TLC and after the total consumption of starting material, the solvent was evaporated. The residue was dissolved in EtOAc, washed with water and brine (10ml × 3).The organic layer was separated, dried over Na_2SO_4, filtered and the filtrate was evaporated under reduced pressure to get a crude brown solid, which was further purified by column chromatography [silica gel (60-120 mesh), EtOAc: Pet ether] to yield the desire product **(3)** in 80% as a white powder.

Characterization of compound (3):

^{1}H NMR, (300 MHz, $CDCl_3$) δ (ppm): 7.45 (t, *J* = 7.2, 1 H), 7.53 (t, *J* = 7.5, 1 H), 7.69 (t, *J* = 7.8, 1 H), 7.95 (d, *J* = 9 Hz, 1 H), 8.11(d, *J* = 9Hz, 1 H), 8.32-8.35 (m, 1 H), 8.42(d, *J* = 6Hz, 1 H), 8.93 (s, 1 H).

Mass: [EI$^+$ H]: Calculated for $C_{13}H_8N_2O_2S$: 256.09, Found: 257.10 $[M+H]^+$.



Scheme 1: Scheme for synthesis of compound (3)

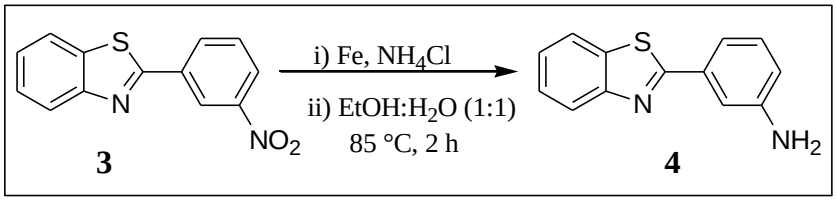
Procedure for the Synthesis of 3-(benzo[d]thiazol-2-yl) aniline:

To a solution of 2-(3-nitrophenyl)benzo[d]thiazole (500 mg, 1 eq) in ethanol (8 ml) were added Iron powder (438 mg, 4 eq) followed by NH_4Cl (1 gm, 10 eq) at 80 °C. The reaction mixture was stirred for 2 h. And it was monitored through TLC, after the total consumption of starting material, the solvent was evaporated. The residue was dissolved in EtOAc, washed with water and brine (10ml × 3). The organic layer was separated, dried over Na_2SO_4, filtered and the filtrate was evaporated under reduced pressure to get a crude brown solid, which was further purified by column chromatography [silica gel (60-120 mesh), EtOAc : Pet ether] to yield the desire product (4) in 85 % as a white powder.

Characterization of compound (4):

^{1}H NMR, (300 MHz, $CDCl_3$) δ (ppm): 3.85 (s, 2 H), 6.79-6.82 (m, 1H), 7.27 (dd, *J* = 6, 12 Hz, 1 H), 7.35-7. 51 (m, 4 H), 7.89 (d, *J* = 9 Hz, 1 H), 8.05 (d, *J* = 9 Hz, 1 H).

Mass: [EI$^+$ H]: Calculated for $C_{13}H_{10}N_2S$: 226.11, Found: 227.11 $[M+H]^+$.



Scheme 2: Scheme for synthesis of compound (4)

Procedure for the Synthesis of N-(3-(benzo[d] thiazol-2-yl) phenyl) cinnamamide:

To a solution of 3-(benzo[d]thiazol-2-yl) aniline (500 mg, 1eq) in ethyl acetate (8 ml) were added Cinnomoyl chloride (438 mg, 4 eq) followed by TEA (1 gm, 10 eq) at 0 °C. The reaction mixture was stirred for 24 h. And it was monitored through TLC and after the total consumption of starting material, the solvent was evaporated. The residue was dissolved in EtOAc, washed with water and brine (10ml × 3). The organic layer was separated, dried over Na_2SO_4, filtered and the filtrate was evaporated under reduced pressure to get a crude brown solid, which was further purified by column chromatography [silica gel (60-120 mesh), EtOAc: Pet ether] to yield the desire product (**6**) in 79% as a white powder.

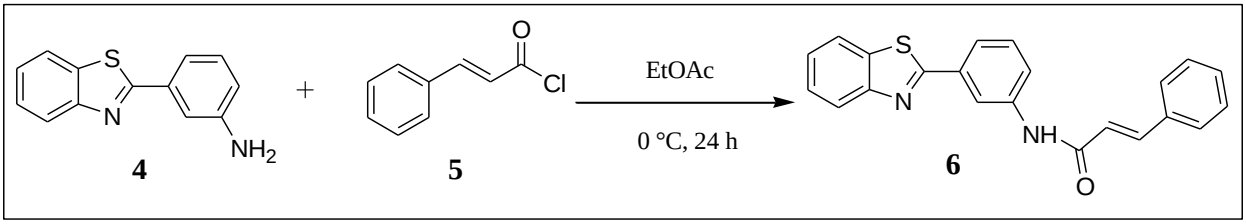
Characterization of compound (6):

^{1}H NMR, (600 MHz, DMSO d_6) δ (ppm): 10.53 (s, 1 H), 8.59 (s, 1 H), 8.16 (d, J = 6 Hz, 1 H), 8.08 (d, *J* = 6 Hz, 1 H), 7.89 (d, *J* = 12 Hz, 1 H), 7.79 (d, *J* = 6 Hz, 1 H), 7.65 (t, *J* = 6 Hz, 3 H), 7.56 (m, 2 H), 7.46 (m, 4 H), 6.86 (d, *J* = 18 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO d_6) δ (ppm): 167.19, 163.90, 153.54, 140.71, 140.19, 134.61(2C), 134.45, 133.37, 130.03, 129.96, 129.09, 128.88(2C), 127.84, 126.74, 125.65, 122.94, 122.44, 122.15, 121.97, 121.84, 117.45.

Mass: [EI-HRMS]: Calculated for $C_{22}H_{16}N_2OS$: 356.09821, Found: 356.0982.

FTIR (KBr) ν (cm^{-1}): 3290.3, 3055.0, 1660.6, 1627.81, 1541.0, 1488.9, 1340.4, 1313.4, 1240.1, 1211.2, 968.2, 757.9 and 680.8.



Scheme 3: Scheme for synthesis of compound (6)

Procedure for the Synthesis of (E)-N-(3-(benzo[d]thiazol-2-yl) phenyl)-3-(3-chlorophenyl) acryl amide:

To a solution of 3-(benzo[d]thiazol-2-yl) aniline (500 mg, 1 eq) in ethyl acetate (8 ml) were added Chloro-cinnomoyl chloride (438 mg, 4 eq) followed by TEA (1 ml, 10 eq) at 0 °C. The reaction mixture was stirred for 24 h, and it was monitored through TLC and after the total consumption of starting material, the solvent was evaporated. The residue was dissolved in EtOAc, washed with water and brine (10ml × 3).The organic layer was separated, dried over Na_2SO_4, filtered and the filtrate was evaporated under reduced pressure to get a crude brown solid, which was further purified by column chromatography [silica gel (60-120 mesh), EtOAc : Pet ether] to yield the desire product (**8**) in 83 % as a white powder.

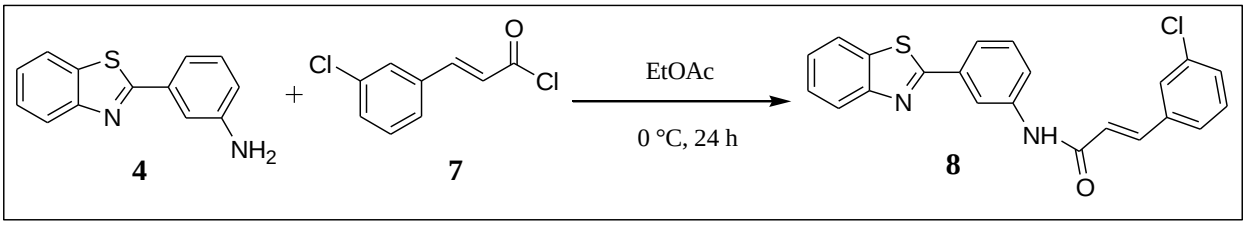
Characterization of compound (8):

^{1}H NMR, (600 MHz, DMSO d_6) δ (ppm): 10.63 (s, 1 H), 8.61 (s, 1 H), 8.16 (d, J = 7.8, 1 H), 8.08 (d , J = 8.4, 1 H), 7.94 (d, *J* = 18 Hz, 1 H), 7.87 (d, *J* = 6 Hz, 1 H), 7.80 (d, *J* = 6 Hz, 2 H), 7.56 (m, 3 H), 7.47 (m, 3 H), 6.92 (d, *J* = 18 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO d_6) δ (ppm): 167.13, 163.38, 153.53, 140.00, 135.84, 134.46, 133.55, 133.41, 132.40, 131.38, 130.14, 130.08, 127.94, 127.79, 126.76, 125.67, 125.04, 122.94, 122.45, 122.36, 121.90, and 117.53.

Mass: [EI-HRMS]: Calculated for $C_{22}H_{15}N_2OSCl$: 390.0591, Found: 390.0591.

FTIR (KBr) ν (cm^{-1}): 3269.1, 3053.1, 2921.9, 1656.7, 1623.9, 1550.6, 1508.2, 1469.6, 1434.9, 1342.3, 1313.4, 1267.1, 1215.0, 1161.0, 968.20, 881.41, 721.3, 696.2, 682.7.



Scheme: 4. Scheme for synthesis of compound (8)

CONCLUSION

In the present study a hybrid molecule was designed and synthesised which contains a Benzothiazole moiety and cinnomoyl moiety. The first part was specifically chosen for the amyloid protein binding and the remaining part is for its anti-oxidant properties. The molecule was synthesised using a straight forward synthesis as shown in the scheme. In this study two such derivatives were synthesised and fully characterised spectroscopically.

Future Scope:

In future the synthetic study can be taken forward and a small library of such designed molecules having different substitutions and different anti-oxidant moieties like Curcumin derivatives, capable targeting β - Amyloid protein to treat Alzheimer's disease may be synthesised. The benzothiazole containing hybrid heterocycles seem to be good candidate to treat Alzheimer's disease.

REFERENCES:

1. Thompson LM. *Neurodegeneration: a question of balance.* Nature **2008**;452(7188):707-708.
2. Rubinsztein DC. *The roles of intracellular protein-degradation pathways in neurodegeneration.* Nature **2006**;443(7113):780-786.
3. Bredesen DE, RV. Rao, and P. Mehlen. *Cell death in the nervous system.* Nature **2006**;443(7113):796-802.
4. Munoz-Ruiz P, et al. *Design, synthesis, and biological evaluation of dual binding site acetylcholinesterase inhibitors: new disease-modifying agents for Alzheimer's disease.* J Med Chem **2005**;48(23):7223-7233.
5. Braak H. and E. Braak. *Neuropathological stageing of Alzheimer related changes.* Acta Neuropathol **1991**; 82(4):239-259.
6. Mirra S, et al. *participating CERAD neuropathologists: The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease.* Neurol **1991**;41(4):479-486.
7. Mirra SS, et al. *The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Part II. Standardization of the neuropathologic assessment of Alzheimer's disease.* Neurol **1991**;41(4):479-479.
8. Klunk W. and D. Abraham. *Filamentous proteins in Alzheimer's disease: new insights through molecular biology.* Psychiatric develop **1987**;6(2):121-152.
9. Tanzi RE. and L. Bertram. *Twenty years of the Alzheimer's disease amyloid hypothesis: a genetic perspective.* Cell **2005**;120(4):545-555.
10. Gilgun-Sherki Y, E. Melamed and D. Offen. *Oxidative stress induced-neurodegenerative diseases: the need for antioxidants that penetrate the blood brain barrier.* Neuropharmacol **2001**;40(8):959-975.
11. Pithadia AS. and MH. Lim. *Metal-associated amyloid-β species in Alzheimer's disease.* Curr Opin in Chem Biol **2012**;16(1):67-73.
12. Ono M, et al. *Benzofuran derivatives as Aβ-aggregate-specific imaging agents for Alzheimer's disease.* Nuclear Med & Biol **2002**;29(6):633-642.
13. Levine H. *Thioflavine T interaction with synthetic Alzheimer's disease β-amyloid peptides: Detection of amyloid aggregation in solution.* Protein Sci **1993**;2(3): 404-410.
14. Mathis CA, et al. *Synthesis and evaluation of 11C-labeled 6-substituted 2-arylbenzothiazoles as amyloid imaging agents.* J Med Chem **2003**;46(13):2740-2754.
15. McKeith IG, et al. *Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB) Report of the consortium on DLB international workshop.* Neurol **1996**;47(5):1113-1124.
16. Henriksen G, et al. *Metabolically stabilized benzothiazoles for imaging of amyloid plaques.* J Med Chem **2007**;50(6):1087-1089.
17. Khokra SL, et al. *Common methods to synthesize benzothiazole derivatives and their medicinal significance.* Int J Pharm Sci Res **2011**;2(6):1356-1378.
18. Esteves AR, et al. *Oxidative stress involvement in α-synuclein oligomerization in Parkinson's disease cybrids.* Antioxidants & Redox Signaling **2009**;11(3):439-448.
19. Sas K, et al. *Mitochondria, metabolic disturbances, oxidative stress and the kynurenine system, with focus on neurodegenerative disorders.* J the Neurol Sci **2007**; 257(1):221-239.
20. Kamat PK, et al. *Autophagy of mitochondria: a promising therapeutic target for neurodegenerative disease.* Cell Biochem & Biophy **2014**;70(2):707-719.
21. Schenk DB, et al. *Therapeutic Approaches Related to Amyloid-. beta. Peptide and Alzheimer's Disease.* J Med Chem **1995**;38(21):4141-4154.
22. Schenk DB, et al. *β-Peptide immunization: A possible new treatment for Alzheimer disease.* Archiv Neurol **2000**;57(7):934-936.
23. Wang X, et al. *Effects of curcuminoids identified in rhizomes of Curcuma longa on BACE-1 inhibitory and behavioral activity and lifespan of Alzheimer's disease Drosophila models.* BMC Complement & Alternat Med **2014**;14(1):88.
24. Attaguile G, et al. *Antioxidant activity and protective effect on DNA cleavage of extracts from Cistus incanus L. and Cistus monspeliensis L.* Cell Biol & Toxicol **2000**; 16(2):83-90.
25. Beal MF. *Aging, energy, and oxidative stress in neurodegenerative diseases.* Annal Neurol **1995**;38(3): 357-366.
26. Ahmed T, S. Enam and A. Gilani. *Curcuminoids enhance memory in an amyloid-infused rat model of Alzheimer's disease.* Neurosci **2010**;169(3):1296-1306.
27. Ali SS, et al. *Indian medicinal herbs as sources of antioxidants.* Food Res Int **2008**;41(1):1-15.
28. Brion JP, et al. *Neurofibrillary tangles of Alzheimer's disease: an immunohistochemical study.* J Submicro scopic Cytol **1985**;17(1):89-96.
29. Terwel D, et al. *Amyloid activates GSK-3β to aggravate neuronal tauopathy in bigenic mice.* The American J Pathol **2008**;172(3):786-798.
30. Martin D, MA. Thompson and JV. Nadler. *The neuroprotective agent riluzole inhibits release of glutamate and aspartate from slices of hippocampal area CA1.* Eur J Pharmacol **1993**;250(3):473-476.
31. Okamura N, et al. *Quinoline and benzimidazole derivatives: candidate probes for in vivo imaging of tau pathology in Alzheimer's disease.* The J Neurosci **2005**; 25(47):10857-10862.
32. Mohamed HM. *A Convenient Synthesis of Ethyl 1-Amino-3-(Substituted Phenyl)-2-Cyano-3H-Benzo[4, 5] Thiazolo -[3, 2-a] Pyridine-4-Carboxylate Derivatives and Some of their Reactions.* World **2014**;2(1):1-8.

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