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Research paper

Synthesis of novel monostyryl and distyryl boron dipyrromethenes bearing 4-((2-hydroxyethyl)(methyl)amino group as cholinesterase and tyrosinase inhibitors

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ABSTRACT

In this study, the synthesis of novel Monostyryl and Distyryl boron dipyrromethene dyes containing 4-((2-hydroxyethyl)(methyl)amino) group to determine neuroprotective potential has been reported for the first time. They were synthesized starting from BODIPY dye 1. Their inhibitory properties against Acetylcholinesterase/Butyrylcholinesterase (AChE/BuChE) and tyrosinase (Tyr) were evaluated according to Ingkaninan's and Masuda's methods and kinetic analysis of compounds was done using Lineweaver-Burk and Dixon plots.

1. Introduction

BODIPY (4,4-difluoro-4-bora-3a,4a-diaza-s-indacene) and its analogs have gained significance for varied applications such as chemosensors [1], laser dyes [2,3], drug delivery [4], electroluminescent films [5], photodynamic therpy [6,7], solar cells [8,9], fluorescent labels [10], optoelectronic devices [11]. These photosensitizers are strongly UV–visible absorbing small molecules that demonstrate relatively intense and tunable fluorescence with excellent quantum yields [12,13], so that they have been widely used for medicinal studies [6,14–18]. Especially, the distyryl BODIPY's absorb in the red visible to near infrared region, making them particularly useful for biomedical applications as this allows a deeper light penetration into tissues [19,20]. Moreover, BODIPY containing by *N*-methyl-4- pyridyl group was exhibited to be efficient against planktonic and biofilms of Pseudomonas aeruginosa [21,22]. They also demonsrated antiviral, antibacterial and antifungal photoinactivation [23].

Neurodegenerative diseases which are defined by the progressive degeneration of the function and structure of the central or peripheral nervous system, include Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease etc. [24]. AD, is one of the forms of dementia affecting elderly people via oxidative damage, cholinergic neuronal loss and formation and deposition of β-amyloid peptides in the brain, is characterized by decline in cognitive skills and function of memory [25]. According to The World Alzheimer Report 2015, there were 36 million people in worldwide with AD in 2010, this population is expected to increase to 66 million by 2030 and to 115 million by 2050 [26]. This disease has become a major health issue in the developing countries thereby prevention of this disease is very important in terms of decreasing medical expenditure and mortality. Although the pathogenesis of AD still remains unknown, the cholinergic hypothesis is the most accepted theory [27]. Therefore acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) inhibitors are currently used for AD due to increasing the neurotransmitters such as acetylcholine and butyrylcholine levels in the brain [28,29]. Although, there are several cholinesterase inhibitors approved by Food and Drug Administration (FDA) in the United States such as ensaculin, donepezil, rivastigmine and galantamine, they have several side effects containing hepatotoxicity, gastrointestinal problems, liver disorders, aggression and depression [30–32].

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PD is the second most common neurodegenerative disease after AD. It results from a pathophysiologic loss or degeneration of dopaminergic neurons in the substantia nigra [33,34]. It is known that tyrosinase oxidizes dopamine to produce melanin in the brain but excessive production of dopaquinones causes neuronal damage [35,36]. Hence, tyrosinase inhibition is a pivotal target for treatment of this disease.

We report herein, the synthesis and characterization of novel Monostyryl (**2**) and Distyryl (**3**) BODIPY Dyes and their AChE/BuChE, Tyr inhibitory properties were investigated for the first time to determine neuroprotective potential.

2. Experimental

2.1. Materials and methods

The IR spectra were recorded on a Perkin Elmer 1600 FT-IR spectrophotometer, using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 (100) MHz spectrometers and chemical shifts were reported (δ) relative to Me_4Si as internal standard. MALDI-MS of complexes were obtained in dihydroxybenzoic acid as the MALDI matrix, using a nitrogen laser accumulating 50 laser shots, with a Bruker Microflex LT MALDI-TOF mass spectrometer. Optical spectra in the UV–vis region were recorded with a Perkin Elmer Lambda 25 spectrophotometer. Acetylcholinesterase enzyme (AChE) from electric eel, acetylthiocholine iodide (AChI), butyrylcholinesterase enzyme (BuChE), butyrylthiocholine iodide (BTCI) dimethyl sulfoxide (DMSO), 5,5-dithio-bis(2-nitrobenzoic)acid (DTNB), L-DOPA tyrosinase from mushroom (Tyr), trisma-base and sodium phosphate buffer were purchased from Sigma-Aldrich (St. Louis, MO). Enzyme inhibition studies were performed by Multikan^{Tm} Go Microplate Spectrophotometer using a 96-well microplate reader. The InChI codes were supplied as Supplementary information.

2.2. Synthesis of BODIPY dye (1)

A 500 ml round bottomed flask was charged with dichloromethane (150 ml) and purge with N_2 for 20 min. (0.25 g, 1.39 mmol) 4-((2-hydroxyethyl)(methyl)amino)benzaldehyde were added to reaction flask and 2,4-dimethyl-1H-pyrrole (0.3 ml, 2.8 mmol) were dissolved in 30 ml of dichloromethane and poured to that. One drop of trifluoroacetic acid was added to mixture and stirred for one day. Then, 2,3-dichloro-5,6-dicyano-p-benzoquinon (DDQ) (0.32 g, 1.4 mmol) was dissolved in dichloromethane and slowly poured to reaction flask with separating funnel after this reaction mixture was stirred for 30 min at room temperature. Subsequently, 1.3 ml of triethyl amine (NEt_3) (9 mmol) was added to reaction mixture drop by drop after 2 ml of BF_3 .OEt_2 (15.4 mmol) was slowly added to reaction mixture and stirred for one day. This reaction mixture was filtered from G4 sintered fitler. Then, solid matter was purified with aluminum oxide column chromatography, using diethyl eter as eluent. Yield: (195 mg, 35%), melting point: 122–124 °C

IR (ATR) ν (cm^{-1}): 3222 (O—H), 3079 (Ar-H), 2919–2866 (Aliph. C—H), 1690, 1598, 1569, 1516, 1436, 1369, 1281, 1186, 1118, 968, 807, 697. ^{1}H NMR (400 MHz, $CDCl_3$), (δ:ppm): 7.65 (d, 2H, J = 8, Ar-H), 7.15 (d, 2H, J = 8, Ar-H), 6.43 (s, 1H, -CH), 5.95 (s, 1H, -CH), 3.85 (m, 2H, CH_2-O), 3.54 (m, 2H, CH_2-N), 3.05 (s, 3H, CH_3-N), 2.38 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.08 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$), (δ:ppm): 172.18, 149.57, 145.07, 133.86, 131.89, 131.46, 127.95, 125.55, 121.75, 119.13, 116.05, 111.55, 110.93, 60.02, 55.40, 38.93, 29.68, 25.21, 24.98, 14.11. UV–Vis ($CHCl_3$) λ_{max} nm (log ε): 474 (5.03). MALDI-TOF-MS *m*/*z* calc. 397.26; found: 348.71 $[M\text{-}BF_2]^+$.

2.3. Synthesis of monostyryl BODIPY dye (2)

BODIPY dye (**1**) (150 mg, 0.38 mmol), 4-((2-hydroxyethyl)(methyl)amino)benzaldehyde (85 mg, 0.38 mmol) were dissolved with 60 ml toluene in a 100 ml round bottomed reaction flask. Then, 0.4 ml (6.65 mmol) acetic acid, 0.4 ml (3.8 mmol) piperidine and small amount of $Mg(ClO_4)_2$ were added to reaction flask. The reaction was refluxed via Dean-Stark trap apparatus for one day. This reaction mixture was cooled to room temperature and solvent was removed by rotary evaporator. Resudie was purified with aluminum oxide column chromatography, using diethyl eter as eluent. Yield: (150 mg, 71%)

IR (ATR) ν (cm^{-1}): 3264 (O—H), 3032 (Ar-H), 2917–2849 (Aliph. C—H), 1672, 1591, 1519, 1435, 1374, 1351, 1260, 1180, 1116, 1044, 959, 803. ^{1}H NMR (400 MHz, $CDCl_3$), (δ:ppm): 8.32 (d, 1H, J = 16, CH═CH), 7.77 (d, 2H, J = 8, Ar-H), 7.68 (d, 2H, J = 8, Ar-H), 7.02 (d, 2H, J = 8, Ar-H), 7.05 (s, 1H, -CH), 6.59 (d, 1H, J = 16, CH═CH), 6.81 (d, 2H, J = 8, Ar-H), 5.88 (s, 1H, -CH), 3.82 (m, 4H, CH_2-O), 3.46 (m, 4H, CH_2-N), 2.95 (s, 6H, CH_3-N), 2.31 (s, 3H, CH_3), 2.11 (s, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$), (δ:ppm): 170.59, 149.47, 148.48, 144.88, 138.52, 136.65, 131.13, 131.80, 129.55, 125.49, 127.62, 122.44, 120.30, 119.26, 117.17, 116.79, 115.27, 113.47, 111.23, 60.23, 55.66, 37.93, 37.10, 19.73, 18.95, 14.11. UV–Vis ($CHCl_3$) λ_{max} nm (log ε): 630 (4.97). MALDI-TOF-MS *m*/*z* calc. 558.46; found: 558.13 $[M]^+$.

2.4. Synthesis of distyryl BODIPY dye (3)

BODIPY dye (**1**) (150 mg, 0.38 mmol), 4-((2-hydroxyethyl)(methyl)amino)benzaldehyde (170 mg, 0.95 mmol) were dissolved with 30 ml toluene in reaction flask. Respectively, 0.4 ml (6.65 mmol) acetic acid, 0.4 ml (3.8 mmol) piperidine and small amount of $Mg(ClO_4)_2$ were added and reaction mixtture was refluxed via Dean-Stark trap apparatus until was residuum. Then, reaction mixture was cooled to room temperature and solvent was completely removed by rotary evaporator and resudie was purified with aluminum oxide column chromatography, using diethyl eter as eluent. Yield: (69 mg, 25%).

IR (ATR) ν (cm^{-1}): 3297 (O—H), 3016 (Ar-H), 2923–2866 (Aliph. C—H), 1591, 1519, 1374, 1259, 1177, 1042, 799. ^{1}H NMR (400 MHz, $CDCl_3$), (δ:ppm): 8.38 (d, 2H, J = 16, CH═CH), 7.97 (d, 2H, J = 8, Ar-H), 7.50 (m, 4H, Ar-H), 7.05 (d, 2H, J = 8, Ar-H), 7.01 (s, 1H, -CH), 6.90 (m, 4H, Ar-H), 6.50 (d, 2H, J = 16, CH═CH), 6.31 (s, 1H, -CH), 3.78 (m, 6H, CH_2-O), 3.32 (m, 6H, CH_2-N), 2.88 (s, 9H, CH_3-N), 2.12 (s, 6H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$), (δ:ppm): 173.27, 157.10, 151.08, 149.45, 147.07, 146.72, 142.88, 135.65, 135.01, 133.90, 131.12, 130.28, 129.11, 127.89, 127.37, 123.51, 122.13, 119.63, 117.85, 117.11, 116.05, 113.27, 112.98, 110.08, 107.47, 59.02, 58.38, 56.65, 56. 39.87, 18.93, 14.11. UV–Vis ($CHCl_3$) λ_{max} nm (log ε): 709 (4.96). MALDI-TOF-MS *m*/*z* calc. 719.67; found: 719.60 $[M]^+$.

2.5. AChE/BuChE inhibition assays

AChE/BuChE inhibition was examined using the method described by Ingkaninan [42]. All of the compounds were prepared as stock solutions in 20% DMSO. Then different concentrations were prepared in the buffer from the stock solution for experiment. 50 mM Tris-HCl buffer (pH 8.00), 3 mM DTNB (in buffer), 0.2 U/mL AChE/BuChE and compounds at various concentrations (12.5–100 mM) were added in a 96-well microplate. The mixtures were incubated for 15 min at 25 °C. After incubation, 15 mM AChI/BTCI was added in a microplate and incubated for 5 min at room temperature. The absorbance was measured at 412 nm using a 96-well microplate reader. Galantamine was used as the positive control. AChE inhibition percentage was calculated using the Formula 1.