European Journal of Medicinal Chemistry 78 (2014) 43–53

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis, cytotoxicity and molecular modelling studies of new phenylcinnamide derivatives as potent inhibitors of cholinesterases

Aamer Saeed [a], Parvez Ali Mahesar [a], Sumera Zaib [b], Muhammad Siraj Khan [b], Abdul Matin [c], Mohammad Shahid [d], Jamshed Iqbal [b,e,*]

[a] Department of Chemistry, Quaid-I-Azam University, Islamabad 45320, Pakistan
[b] Centre for Advanced Drug Research, COMSATS Institute of Information Technology, Abbottabad 22060, Pakistan
[c] Institute of Biomedical and Genetic Engineering, PO Box 2891, Sector G-9/1, Islamabad, Pakistan
[d] Department of Bioinformatics, Fraunhofer Institute SCAI, Sankt Augustin, Germany
[e] Department of Pharmaceutical Sciences, COMSATS Institute of Information Technology, Abbottabad 22060, Pakistan

ARTICLE INFO

Article history:
Received 12 October 2013
Received in revised form
15 February 2014
Accepted 6 March 2014
Available online 7 March 2014

Keywords:
Phenylcinnamide derivatives
Alzheimer's disease
Cholinesterases inhibitors
Cytotoxicity
Molecular docking

ABSTRACT

The present study reports the synthesis of cinnamide derivatives and their biological activity as inhibitors of both cholinesterases and anticancer agents. Controlled inhibition of brain acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) may slow neurodegeneration in Alzheimer's diseases (AD). The anticholinesterase activity of phenylcinnamide derivatives was determined against *Electric Eel* acetylcholinesterase (EeAChE) and horse serum butyrylcholinesterase (hBChE) and some of the compounds appeared as moderately potent inhibitors of EeAChE and hBChE. The compound 3-(2-(Benzyloxy) phenyl)-N-(3,4,5-trimethoxyphenyl)acrylamide (**3i**) showed maximum activity against EeAChE with an IC_{50} 0.29 ± 0.21 μM whereas 3-(2-chloro-6-nitrophenyl)-N-(3,4,5-trimethoxyphenyl)acrylamide (**3k**) was proved to be the most potent inhibitor of hBChE having IC_{50} 1.18 ± 1.31 μM. To better understand the enzyme–inhibitor interaction of the most active compounds toward cholinesterases, molecular modelling studies were carried out on high-resolution crystallographic structures. The anticancer effects of synthesized compounds were also evaluated against cancer cell line (lung carcinoma). The compounds may be useful leads for the design of a new class of anticancer drugs for the treatment of cancer and cholinesterase inhibitors for Alzheimer's disease (AD).

© 2014 Elsevier Masson SAS. All rights reserved.

1. Introduction

Acetylcholine (ACh) is a cholinergic neurotransmitter, released presynaptically by cholinergic terminals, and it interacts with either nicotinic or muscarinic receptors thereby affecting function of postsynaptic cells. Signalling action of ACh is terminated by the action of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) [1,2]. Both enzymes are widely distributed throughout the body; however, AChE remains the major cholinesterase within the human brain. All the brain parts that are innervated by cholinergic transmission in a normal brain hold AChE and BChE activity [3].

Alzheimer's disease is a long lasting neurodegenerative disorder that brings about irreversible memory loss in elderly individuals. Furthermore, this disease has not only been reported of having defined accumulation of amyloid-β peptide plaques at extracellular level but also characterized with the intracellular neurofibrillary tangles (NFTs) in the brains of suffering patients. With the progression of disease, the prominent indications are the continuous memory loss, confusion, petulance, anger and the lack of vigour in body to function evenly which eventually become the ultimate cause of death [4–6]. It is estimated that 24.3 million people were suspected to have Alzheimer's disease (AD) in 2005; also the projected number of individuals with AD at world level in 2020 and in 2040 would be 42.3 and 81.1 million, respectively [7]. In this situation, global escalating occurrence of AD has compelled researchers to undertake studies on neurodegenerative disorders (NDDS) [8].

Cholinesterases belong to a family of serine hydrolases that split acetylcholine into choline and acetic acid, an unavoidable step in retaining the function of cholinergic neuron [9]. AChE has five important regions within active site and these are important to understand substrate and inhibitor binding pattern. These regions are, 1) catalytic triad residues, 2) acyl pocket, 3) oxyanion hole, 4) anionic site (AS), 5) and a peripheral anionic site (PAS) [10–15]. The

* Corresponding author. Centre for Advanced Drug Research, COMSATS Institute of Information Technology, Abbottabad 22060, Pakistan.
E-mail addresses: drjamshed@ciit.net.pk, jamshediqb@gmail.com (J. Iqbal).

http://dx.doi.org/10.1016/j.ejmech.2014.03.015
0223-5234/© 2014 Elsevier Masson SAS. All rights reserved.

AChE binds to PAS resulting in the formation of amyloid-β peptide plaques and acetylcholinesterase inhibitors (AChEIs) bind to the PAS to prevent amyloid-β peptide plaques formation [16,17]. However, such treatment (using AChEIs) only relieves the symptoms for short term and do not eradicate the disease eternally [18]. The major role of acetylcholinesterase (AChE) is to catalyze the hydrolysis of acetylcholine (ACh) in cholinergic synapses and replacement of AChE function in Alzheimer's brains [19]. Some of the important cholinesterase inhibitors which are employed in the treatment of AD are rivastigmine, galantamine, tacrine, ensaculin and donepezil. Among these remedies the rivastigmine is broader in its action as it non-specifically inhibits AChE as well as BChE, whereas galantamine and donepezil specifically inhibit AChE thus increasing ACh level at neuronal level and relieving AD symptoms but they all cannot stop progress of dementia [20]. Various compounds like carbamates (e.g., neostigmine and physostigmine etc), organophosphates, coumarine and cinnamide derivatives are reported in literature as inhibitors of cholinesterases [18,21,22]. Apart from anticholinesterase and cytotoxic activity cinnamide derivatives (N-(carboxyaryl)-phenylcinnamide) have shown their activity against leukotriene B_4 (LTB_4), which is a metabolic product of arachidonic acid and a potent inflammatory mediator [23,24]. LTB_4 has important role in a range of diseases, like psoriasis, adult respiratory distress syndrome, inflammatory bowel disease and rheumatoid arthritis, it makes cinnamide derivatives as potent therapeutic agents against inflammatory disorders [25–29].

The aim of the present study was to synthesize and investigate phenylcinnamide derivatives as anticholinesterase as well as anticancer agents.

2. Results and discussion

2.1. Chemistry

We envisioned that Doebner–Knoevenagel condensation was the best available route to synthesize cinnamic acids derivatives **(1) (a–y)** [30,31]. It was subsequent one pot activation and coupling which led to formation of corresponding amides with 2,4,6-trichloro-1,3,5-triazine [32] that ultimately afforded the desired products phenylcinnamide **(3a–y)** in a good to excellent yield. Gratifyingly, we came to know that cyanuric chloride (TCT) was cost-effective and stable reagent for amide formation, more importantly it was easily handled and transformation took place at ambient temperature. All of the synthesized compounds were characterized with ^1H and ^{13}C NMR along with IR (Scheme 1).

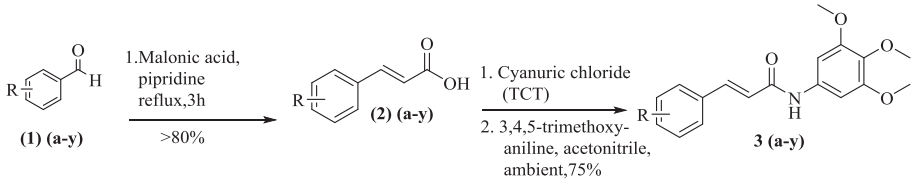
Table 1
Inhibitory potential of phenylcinnamide derivatives against EeAChE and hBChE.

Compounds	EeAChE	hBChE
	IC_{50} ± [a]SEM (μM)/(%Inhibition)	
3a	6.52 ± 0.39	3.93 ± 1.44
3b	4.98 ± 0.27	(31.1)
3c	12.54 ± 0.65	3.85 ± 0.91
3d	12.61 ± 1.48	(32.8)
3e	6.02 ± 2.95	(31.1)
3f	(33.6)	(32.6)
3g	(29.2)	1.25 ± 0.08
3h	1.59 ± 1.45	(27.2)
3i	0.29 ± 0.21	(32.1)
3j	(36.5)	(37.4)
3k	(34.2)	1.18 ± 1.31
3l	12.77 ± 1.06	(35.4)
3m	1.41 ± 0.77	(24.8)
3n	(36.4)	(34.6)
3o	3.24 ± 2.16	(26.2)
3p	(31.2)	(25.7)
3q	12.91 ± 0.98	(41.8)
3r	6.22 ± 0.33	5.19 ± 0.78
3s	4.22 ± 0.03	7.65 ± 0.51
3t	(30.3)	(36.2)
3u	(31.2)	(41.2)
3v	(36.6)	(18.21)
3w	(34.1)	1.32 ± 0.15
3x	3.72 ± 0.13	(33.5)
3y	6.69 ± 4.0	(28.1)
Neostigmine	22.0 ± 3.01	49.1 ± 6.0
Donepezil	0.03 ± 0.003	6.37 ± 0.32

[a] SEM shows standard error of mean of three experiments.

2.2. In vitro inhibition studies of EeAChE and huBChE

In vitro inhibitory studies of synthesized phenylcinnamide derivatives were carried out on EeAChE and hBChE. Inhibition potency of compounds expressed as IC_{50} values is shown in Table 1. Among the phenylcinnamide derivatives, **3i** showed maximum inhibitory activity against EeAChE because of its electron donating benzyloxy ($-OCH_2Ph$) group at *ortho* position, although the same group attached to *meta* and *para* position showed little activity. However, when $-OCH_2CHCH_2$ group was attached to the same *ortho* position then a decrease in the activity of the compound (**3m**) was observed,



3a : R = 3-OCH_2Ph
3b : R = 3-OCH_3, 4-$OOCCH_3$
3c : R = 4-$NHOOCCH_3$
3d : R = 3-OCH_3, 4-OCH_2Ph
3e : R = 3-OCH_2Ph, 4-OCH_3
3f : R = 4-OCH_2CHCH_2
3g : R = 3-$OOCCH_3$
3h : R = 2-OH, 4-OCH_2Ph
3i : R = 2-OCH_2Ph
3j : R = 4-$OOCCH_3$
3k : R = 2-Cl, 6-NO_2
3l : R = 2-OH, 6-NO_2
3m : R = 2-OCH_2CHCH_2
3n : R = 3,4-dihydroxy
3o : R = 3-NO_2
3p : R = 4-Cl
3q : R = 3-OCH_3
3r : R = 2-OH, 3-OCH_3
3s : R = 3-OH, 4-OCH_3
3t : R = 2,5-dihydroxy
3u : R = 2,3-dihydroxy
3v : R = 2,4-dihydroxy
3w : R = 2-F,6-Cl
3x : R =4-OCH_2Ph
3y : R = 3-NO_2,4-OCH_3

Scheme 1. Synthesis of substituted phenylcinnamide derivatives.

Download English Version:

https://daneshyari.com/en/article/1394161

Download Persian Version:

https://daneshyari.com/article/1394161

Daneshyari.com