Berberine target key enzymes and amino acid inibitiors in AD treatment-----creation from berberine-based structure screening

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Abstract

The main components of berberine from coptis have a variety of pharmacological activity include the treatment of neurodegenerative diseases, Alzheimer's disease (AD). The principle of berberine is inhibiting the lower activity of enzyme and amino acid to prevent (AD). Enzyme like acetylcholinesterase enzyme (AchE), butyrylcholinesterase enzyme (BchE) and monoamine oxidase (MAO); Amino acid like beta-amyloid (Aβ). Unfortunately, the single chemical structures of berberine is no significance to regulation effect. As a part of our consideration, the review paper studies on chemically modified and synthesis from berberine-derivatives. Results show that the structures of (23), (10), (86), (52), and (61) have a potential effect for AchE, BuChE and Aβ-amyloid inhibitors for the first time. Especially in (23) and (52) also has better than two western medicine were compared.

Introduction

Alzheimer's disease (AD) is one of the most common neurodegenerative disorders, which causes cognitive dysfunction and memory loss related to hippocampal damage. It has affected approximately 36 million people, with an estimated prevalence of 30 million people worldwide in 2010 year. The treatment approaches and major therapeutic strategies for this disease are focused on the cholinergic hypothesis, the AD treatment of a natural product (namely berberine) have be explain it in recently[1-3].

Coptidis rhizoma is belongs to the Berberidaceae family, are wide distributed in Europe, Africa and Asia. The main bioactive compounds from an isoquinoline alkaloid, namely Berberine (Ber). It has multiple neuropharmacological properties including neuroprotective and neurotrophic effects, through the blood-brain barrier and reach the brain into central nervous system. It has been widely used as an effective alternative in the treatment of neuropsychiatric diseases, including neurodegenerative diseases and neuronal injure, might be of considerable benefit in a number of psychiatric disorders especially in Alzheimer's disease (AD)[4]. Numerous experimental studies reported to exhibits inhibitory effects of ber against several key enzymes and an amino acid implicated in the pathogenesis of AD by oxidative processesed, including acetylcholinesterase enzyme (AChE), butyrylcholinesterase enzyme (BChE), monoamine oxidase (MAO)(which the isoforms are MAO-A and MAO-B), and also in the beta-amyloid (Aβ) aggregation[5-7]. In the paper, the inhibition of berberine on key enzymes and amino acid in AD treatment were reviewed, but the major focues on synthesis and modification of berberine screening target AchE, BchE and Aβ regulation for the first time.

The concept description of berberine on key enzymes and amino acid

Monoamine oxidase (MAO)

In pharmacological studies on Monoamine oxidase (MAO) are an enzymes that catalyze the oxidation of monoamines. It was find two relevant isoforms of MAO-A and MAO-B in humans. Which increases in MAO-A and MAO-B expression level are thought to contribute to the progression of AD diseases[8]. Known that the Ber as MAO-A and MAO-B inhibitors. It could be an increase the concentrations of noradrenaline (NA), 5-HT and dopamine (DA) by inhibiting MAO activity in neuronal injure and memory functions. Dolores Vina et al, reported that the Ber on aluminum-indued changes of monoamine oxidase-B (MAO-B) mRMA and the protein expression at 100mg/kg in rats test. Data showed to inhibit the MAO-B mRMA and protein expression of Bar with 0.669±0.032 and 3.24±0.28, respectively[9]. In addition, the Bar to inhibit MAO-A with an IC50 values of 126um and 98.2um or 98.4um from in MAO-B were observed[10].

Acetylcholinesterase enzyme (AChE) and butyrylcholinesterase enzyme (BChE)

The two types of cholinesterase: AChE and BuChE, with plays an important role in the pathogenesis of AD. The berberine as AchE and BuChE inhibitors. Especially in inhibition of AChE was observed by interaction and minor conformation changed.

Beta-amyloid (Aβ)

The amine acid: beta-amyloid (Aβ) from the location of the gene for the amyloid precursor protein (APP). The accumulation of APP, as amyloid plaques were found in the brains of Alzheimer's disease patients. Thus, the aggregation of Aβ in the pathogenesis of AD is a general recognition. The berberine (Ber) can descrease Aβ levels by inhibiting C-terminal fragments of APP processed, to reversing learning defects in several animal and human cells tests [11]. It goes further decreases the production of Aβ was identified, through Ber reduce the expression of beta secretase when activation of ERK1/2 pathway[12].

The addition to findings of above results, there are interesting to find, that the target AchE, BchE and Aβ inhibitied by the synthetic or modification of berberine-based structure were reviewed in up-data infromation. The general procedures for the preparation using various structure activity relationship analysis[13]. Which the design and screening of berberine-derivatives for preparation are shown in belows:

Chemically modified of the berberine-derivatives for preparation

Chemical modification of the relevant 9-Substituted berberine-derivatives , namely (1-13) and 9-N-substituted berberine-derivatives, namely (9-32) were evaluated toward AchE, BuChE and a part of the Aβ regulation.

*A comprehensive database of berberine-derivatives for AchE inhibited to strong to weak activity as: (23)> (24)> (3)> (27)> (26)> (15)> (21)> (8)> (10)> (1)> (28)> (4)> (25)> (7)> (2)> (6)> (32)> (10)> (18)> (5)> (16)> (9)> (22)> (14)> (20)> (12)> (31)> (19)> (29)> (17)> (13)> (30). Above results clearly showed that the based structures activity were also found to be effective in AchE inhibition. Maximum inhibition is (30), and the highly inhibition is (23), were also observed, are shown in Figure 1 and Table 1.

*The screening of berberine derivatives on BuChE inhibitied were compared, showing strong to weak activity were listed as: (10)> (15)> (27)> (21)> (28)> (18)> (24)> (23)> (9)> (16)> (25)> (22)> (8)> (5)> (10)> (13)> (17)> (12)> (2)> (31)> (7)> (3)> (14)> (6)> (19)> (4)> (20)> (29)> (30)> (26)> (32)> (1). Above results clearly

showed that the regulation of (10) on BuChE is better than other berberine-structure, are shown in Fig. 1 and Table 1.

*The Aβ-amyloid inhibitied by a past of berberine derivatives were compared from strong to weak activity as: (23)> (25)> (24)= (27)> (7)> (20)> (21)> (8)> (5)> (3)> (2)> (22)> (6)> (26)> (4)> (1). Above results clearly showed that the inhibition(%) of (23) on Aβ-amyloid is better than other berberine-structure, are shown in Figure 1 and Table 1.

Data showed that the AchE and Aβ-amyloid also inhibition of berberine-derivatives, showing the chemically modified of (23) sturcture was better than other compounds. The 8d sturcture for preparation by berberine was treated with 2-(o-tolyl)ethanamine and using NMR and HRMS analysis method, showing the molecular formula is: C28H26N2O3. In addition, that the BuChE inhibition of berberine-derivatives, showing the chemically modified of (10) sturcture is better than other compounds. The sturcture for preparation by berberine was treated with 3-phenoxypropylamine and using NMR analysis method.

Synthesis of the berberine-derivatives for preparation

In biosynthetic studies were reviewed by the design, synthesis, and the biologically evaluated, for part A and part B. Part A: Synthesis of the 17, 18 and 19 based structures by berberine-melatonin hybrids process was obtained. And the 21 based structures (9-O-[3-(Ferulic acid)propyl] berberine bromide) by berberine-ferulic acid hybrid process was obtained [14]. The synthetic pathway of 9-substituted berberine-derivatives (1-8,17-18 and 21-25) based structures were obtained, namely 31-38, 39-40, 41-45 [15]. As well as, the preparation of hybrids 34-35 by indole-2-carboxylic acid (30) and benzofuran-2-carboxylic acid (31) production. In addition, 26-29 were obtained via the synthetic pathway of 7, 12, 15, 18 were observed [16]. Part B: The 3 synthetic pathway of berberine-derivatives, including 47a, 47b, 48a; 49a, 49b, 49c and 11c, 18d. The results clearly shows in belows, Fig. 2 (part A and part B) and Table 2.

*A comprehensive database of berberine-derivatives for AchE inhibited to strong to weak activity are shown belows: (86)> (70)> (85)> (79)> (47)> (83)> (71)> (48)> (89)> (74)> (72)> (90)> (73)> (81)> (42)> (84)> (80)> (87)> (72)> (46)> (69)= (49)> (44)> (82)> (45)> (51)> (53)> (77)> (78)> (40)> (43)> (39)> (83)> (75)> (37)> (76)> (58)> (38)> (62)> (33)> (88)> (52)> (34)> (35)> (54)> (65)> (55)> (56)> (57)> (41)> (64)> (50)> (61)> (59)> (67)> (36)> (66)> (60).

*A comprehensive database of berberine-derivatives for BuChE inhibitied from strong to weak activity are shown belows: (52)> (74)> (66)> (62)> (72)> (51)> (65)> (67)> (66)> (83)> (61)> (55)> (50)> (72)> (64)> (54)> (88)> (59)> (83)> (33)> (56)> (47)> (40)> (37)> (34)> (90)> (45)> (81)> (48)> (53)> (58)> (41)= (49)> (87)> (39)> (78)> (77)= (36)> (70)> (35)> (68)> (44)> (38)= (85)> (89)> (46)> (79)= (42)> (84)> (76)> (75)> (43)> (57)> (82)> (80)> (86)> (69)> (71).

*The Aβ-amyloid inhibitied by a past of berberine derivatives at 20um concentration were compared from strong to weak activity are shown belows: (61)> (33)> (35)> (65)> (90)> (78)> (34)> (58)> (6)> (82)> (59)> (80)> (76)> (4)> (88)> (86).

Data showed that the AchE inhibition of berberine-derivatives, showing the synthesis of (86) based sturcture is better than other derivatives. The (86) was find as yellow solid for preparation by CuSO, sodium ascorbate, and using NMR and HRMS analysis methods, showing the molecular formula is: C32H39N5O4. As well as, that the BuChE inhibition of berberine-derivatives, showing the synthesis of (52) sturcture is better than other compounds. The structure was synthesized by berberrubine, and using NMR and LC/MS analysis methods, showing the molecular formula is: C33H30BrNO4S. In addition, that the Aβ-amyloid inhibition (%) of berberine-derivatives, showing the synthesis of (61) sturcture is better than other compounds. The structure was

synthesized by berberrubine, and using NMR and HRMS analysis methods, showing the molecular formula is: C36H29NO6.

COMPARISON oOF CHINESE AND WESTERN DRUG ACTIVITY

According to the western medicine research, the following two of the cholinesterase inhibitors have been approved by the US Food and Drug Administration, namely tacrine and Galantamine. They have beneficial effects on cognitive, functional and behavioural symptoms of AD treatment, which was mostly based on the 'cholinergic hypothesis'. Comprehensive study of tacrine, galantamine, berberine, and it based-derivatives towards AchE and BuChE effect in AD treatment. Reported to have shows the AchE and BuChE regulation of berberine with an IC50 of 0.44±0.04 and 3.44+0.26um, respectively. By synthesizing and modification of berberine-derivatives, that the based structures of (86) and (23) are strongly in AchE regulation. Another, that the (52) and (10) are better than other drugs were observed, all details for more information in belows: [17]

Comprehensive study of Tacrine, Galantamine, (86) (Synthesis of berberine derivatives) and (23) (Chemical derivatives of berberine) in regulation of AchE effect. Results clearly showed that the (23) is better than other compounds.

Comprehensive study of Tacrine, Galantamine, (52) (Synthesis of berberine derivatives) and (10) (Chemical derivatives of berberine) in regulation of BuChE effect. Results chearly showed that the (52) is better than other compounds [17-19].

Conclusion

In the review paper, screening of the based structures from berberine-derivatives in AchE, BuChE and Aβ-amyloid regulation, namely (23), (10), (86), (52), and (61) for the first time. Research showed that the chemically modified of (23) sturcture for preparation by berberine was treated with 2-(o-tolyl)ethanamine and using NMR and HRMS analysis method. It is showed better than other compounds in AchE and Aβ effect, especially in AchE strongly inhibitied was observed by two western drugs (tacrine, and galantamine) were compared. In addition, the synthesis of (52) for preparation by berberrubine, and using NMR and LC/MS analysis methods. There is a potent BuChE inhibitor, both in all based sturctures and two western drugs (tacrine, and galantamine) has also been identified. Especially in the potential effect of (23) and (52) as key enzymes and amino acid inibitiors in AD treatment were identified ans comfirmed. The 2-(o-tolyl) ethanamine structured from berberine derivatives for preparation by 239c and IR, NMR and HRMS analysis methods. As (23) is red solid, yield 65%, and the molecular formula is C28H26N2O3. The berberrubine structrured from berberine derivatives were determined by NMR,LC/MS analysis methods. As (52) is yellow solid, yield 32%, and the molecular formula is C33H30 BrNO4S. Results exhibited that the potential effect of (23) and (52) in AD treatment processed, they goes further provide information in anit-oxident medenims of (23) and (52) for furture.

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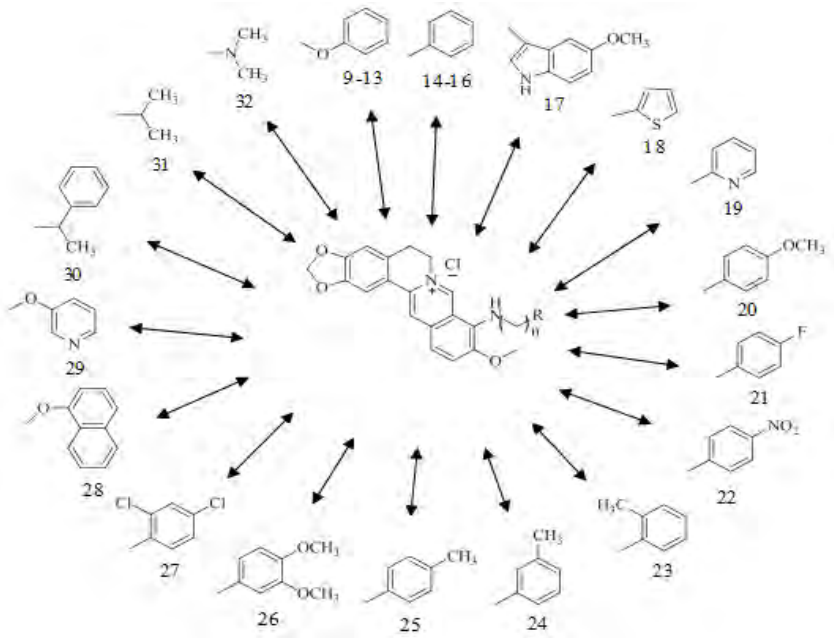
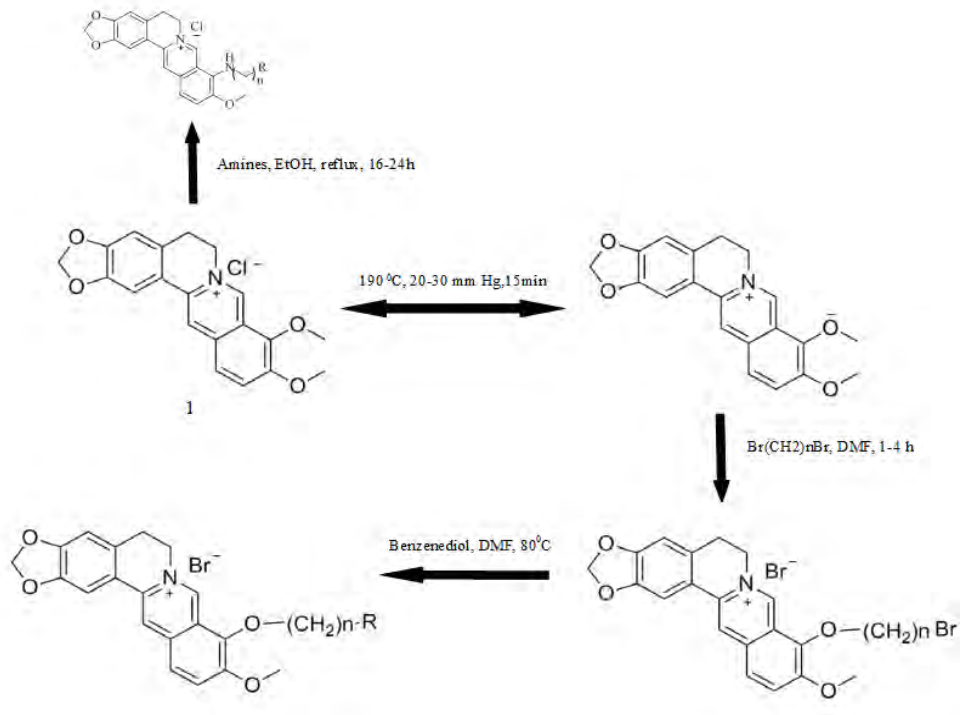


Fig .1 The chemically modified of berberine-derivatives



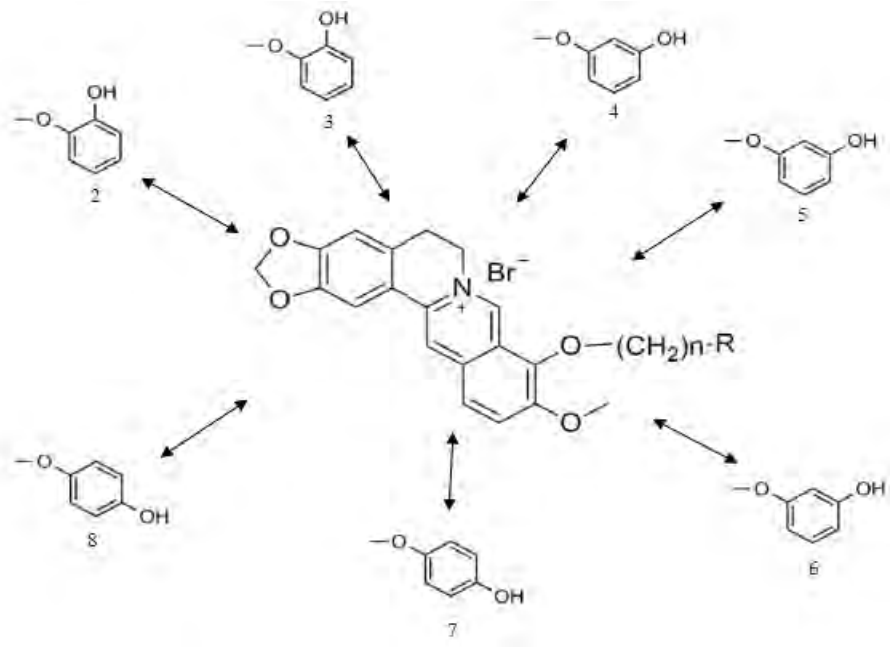
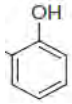
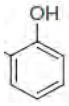
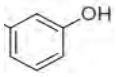
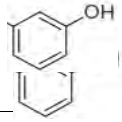
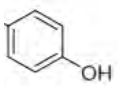
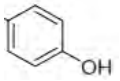
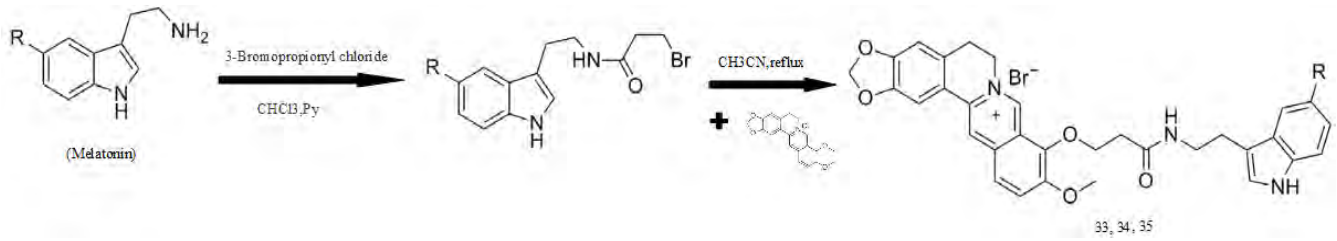


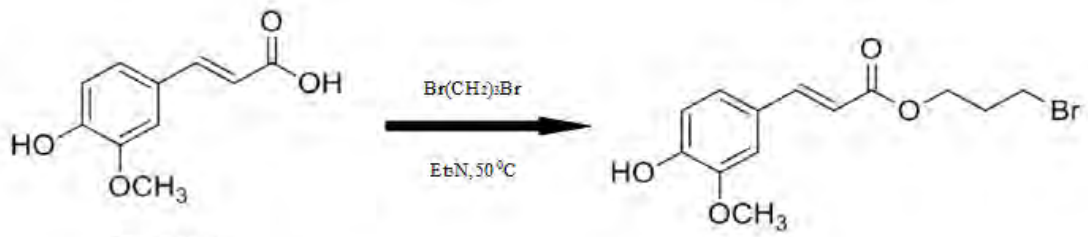
Table 1. The chemically modified of berberine-derivatives, which are based structures 1-32

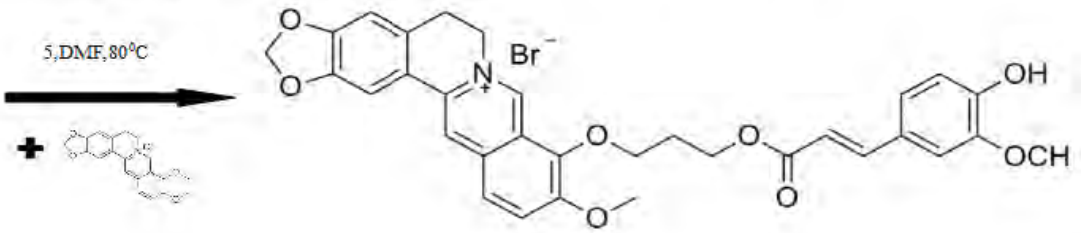
N	Chemical structures		n	Inhibiton activity			Determination
				AchE (IC50μm)	BuChE (IC50μm)	Aβ (%)	
1	berberine	-	-	0.374±0.024	18.2±0.683	36.3	-
2	9-O-[3-(Phenylol-2-yloxy) propyl] berberine bromide		3	0.490±0.032	1.74±0.028	83.5	NMR, HRMS
3	9-O-[4-(Phenylol-2-yloxy)butyl] berberine bromide		4	0.123±0.003	2.09±0.14	84.5	NMR, HRMS
4	9-O-[2-(Phenylol-3-yloxy)ethyl] berberine bromide		2	0.422±0.034	2.64±0.063	62.5	NMR, HRMS
5	9-O-[3-(Phenylol-3-yloxy) prop yl] berberine bromide		3	0.628±0.008	1.13±0.014	85.9	NMR, HRMS
6	9-O-[4-(Phenylol-3-yloxy)butyl] berberine bromide		4	0.547±0.002	2.40±0.021	72.8	NMR, HRMS
7	9-O-[3-(Phenylol-4-yloxy) prop yl] berberine bromide		3	0.460±0.013	2.06±0.035	92	NMR, HRMS

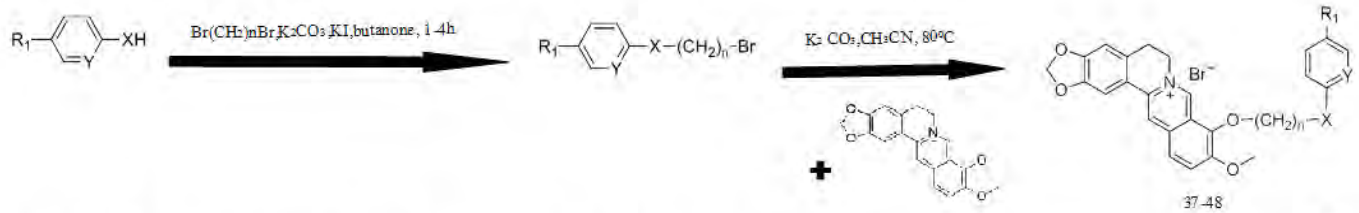
8	9-O-[4-(Phenylol-4-yloxy)butyl] berberine bromide		4	0.304±0.005	1.04±0.077	86.6	NMR, HRMS
9	9-N-2-Phenoxyethyl berberine	-	2	0.688±0.016	0.727±0.038	-	IR, NMR, ESI-MS
10	9-N-3-Phenoxypropyl berberine	-	3	0.588±0.012	0.216±0.007	-	IR, NMR, ESI-MS
11	9-N-4-Phenoxybutyl berberine	-	4	0.349±0.020	1.201±0.028	-	IR, NMR, ESI-MS
12	9-N-5-Phenoxypentyl berberine	-	5	1.094±0.091	1.556±0.126	-	IR, NMR, ESI-MS
13	9-N-6-Phenoxyhexyl berberine	-	6	1.419±0.037	1.300±0.044	-	IR, NMR, ESI-MS
14	9-N-Benzylberberine	-	1	0.936±0.036	2.282±0.061	-	IR, NMR, HRMS
15	9-N-(2-Phenylethyl)berberine	-	2	0.209±0.011	0.406±0.039	-	IR, NMR, HRMS
16	9-N-(3-Phenylpropyl)berberine	-	3	0.680±0.017	0.785±0.013	-	IR, NMR, HRMS
17	9-N-[2-(5-Methoxy-1H-indol-3-yl)]ethylberberine	-	2	1.261±0.106	1.391±0.109	-	IR, NMR, ESI-MS
18	9-N-[2-(Thiophen-2-yl)]ethylberberine	-	2	0.608±0.029	0.555±0.032	-	NMR, ESI-MS
19	9-N-[2-(Pyridin-2-yl)]ethyl berberine	-	2	1.160±0.098	2.495±0.063	-	IR, NMR, ESI-MS
20	9-N-[2-(4-Methoxyphenyl)]ethylberberine	-	2	0.990±0.030	2.885±0.089	91.1	IR, NMR, HRMS
21	9-N-[2-(4-Fluorophenyl)]ethylberberine	-	2	0.238±0.021	0.445±0.017	90.4	IR, NMR, HRMS
22	9-N-[2-(4-Nitrophenyl)]ethylberberine	-	2	0.693±0.021	0.841±0.052	82.6	IR, NMR, HRMS
23	9-N-[2-(o-Tolyl)]ethylberberine	-	2	0.027±0.002	0.713±0.016	95	IR, NMR, HRMS
24	9-N-[2-(m-Tolyl)]ethylberberine	-	2	0.091+0.005	0.674+0.011	93.6	IR, NMR, HRMS
25	9-N-[2-(p-Tolyl)]ethylberberine	-	2	0.449+0.027	0.821+0.011	94	IR, NMR, HRMS
26	9-N-[2-(3,4-Dimethoxyphenyl)] ethylberberine	-	2	0.160±0.010	5.818±5.052	70.1	IR, NMR, HRMS
27	9-N-[2-(2,4-Dichlorophenyl)]ethylberberine	-	2	0.130±0.014	0.424±0.015	93.6	IR, NMR, HRMS
28	9-N-[4-(Naphthalen-1-yloxy) butyl] berberine	-	4	0.400±0.030	0.511±0.032	-	IR, NMR, ESI-MS
29	9-N-[4-(Pyridin-3-yloxy) butyl] berberine	-	4	1.167±0.032	2.936±0.089	-	IR, NMR, ESI-MS
30	9-N-(1-Phenylethyl)berberine	-	0	1.914±0.037	3.280±0.357	-	IR, NMR, ESI-MS
31	9-N-(2-Methylpropyl)berberine	-	1	1.143±0.094	2.016±0.099	-	IR, NMR, ESI-MS
32	9-N-[3-(N,N-Dimethylamino) propyl] berberine	-	3	0.576±0.036	6.323±0.046	-	IR, NMR, ESI-MS

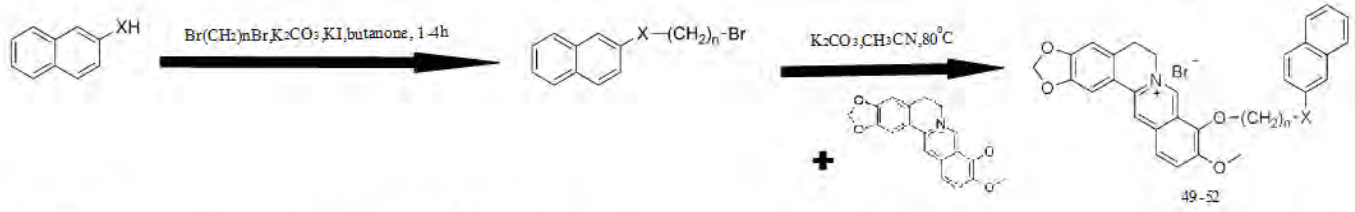
(Figure 2 part: A) Synthesis of the berberine-derivatives hybrid

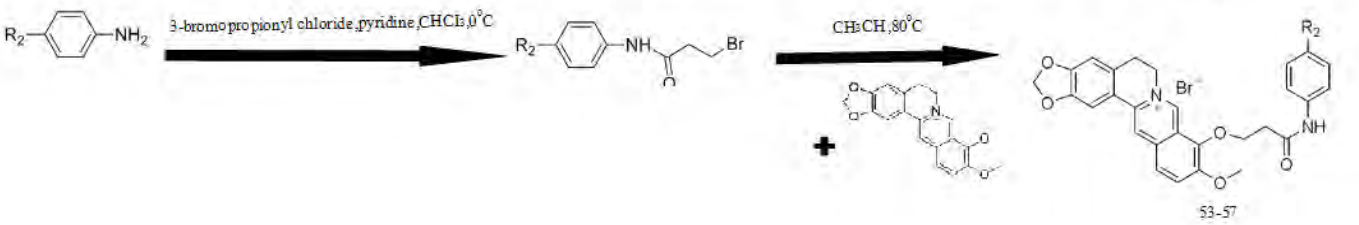


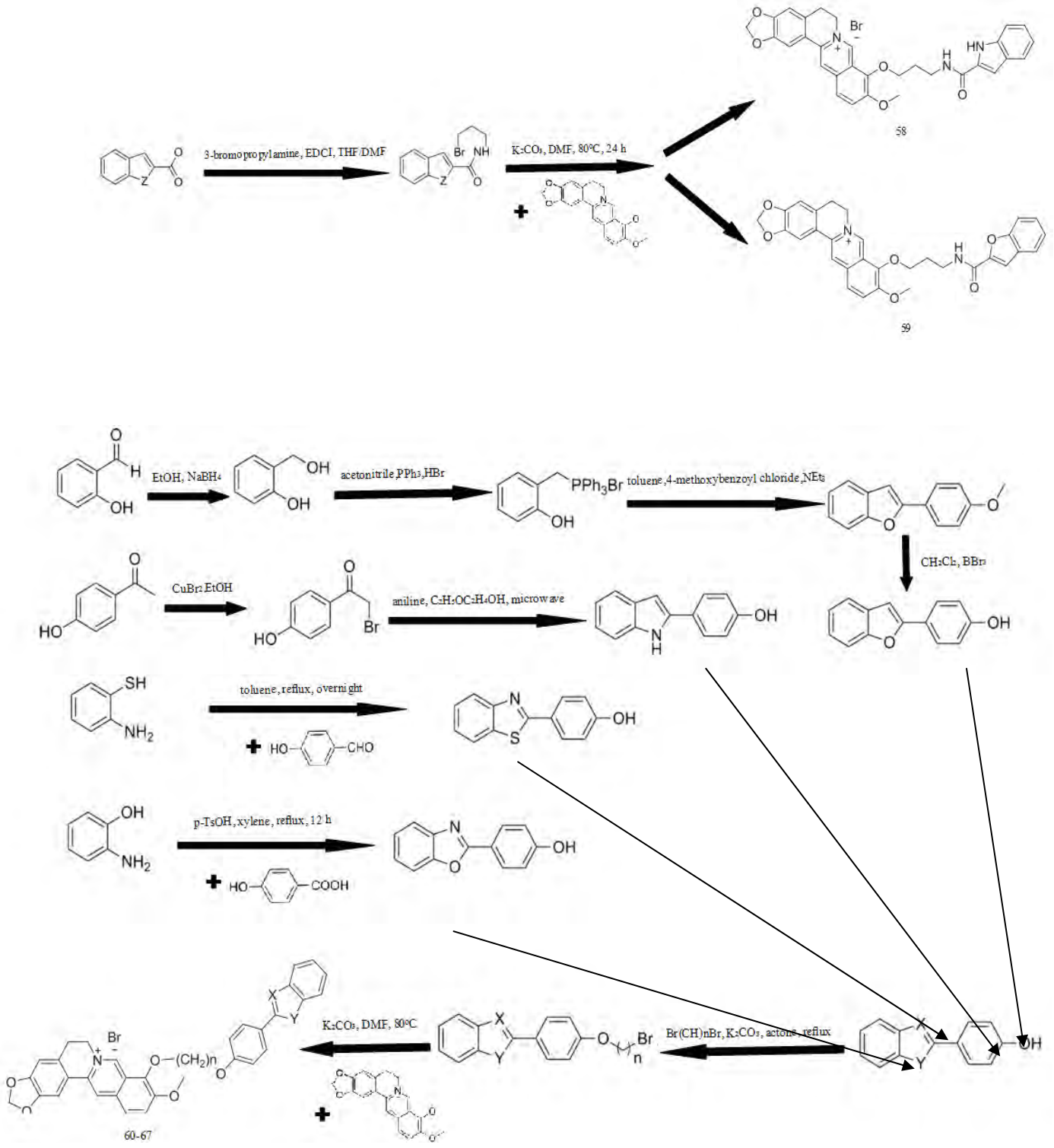











3-bromopropylamine, EDCI, THF/DMF
K2CO3, DMF, 80°C, 24 h
58
59
EtOH, NaBH4
acetonitrile,PPh3,HBr
toluene,4-methoxybenzoyl chloride,NEt3
CH2Cl2, BBr3
CuBr2,EtOH
aniline, C2H5OC2H4OH, microwave
toluene, reflux, overnight
p-TsOH, xylene, reflux, 12 h
K2CO3, DMF, 80°C
Br(CH)nBr, K2CO3, actone, reflux
60-67

(Fig. 2 part: B) Synthesis of the berberine-derivatives hybrid

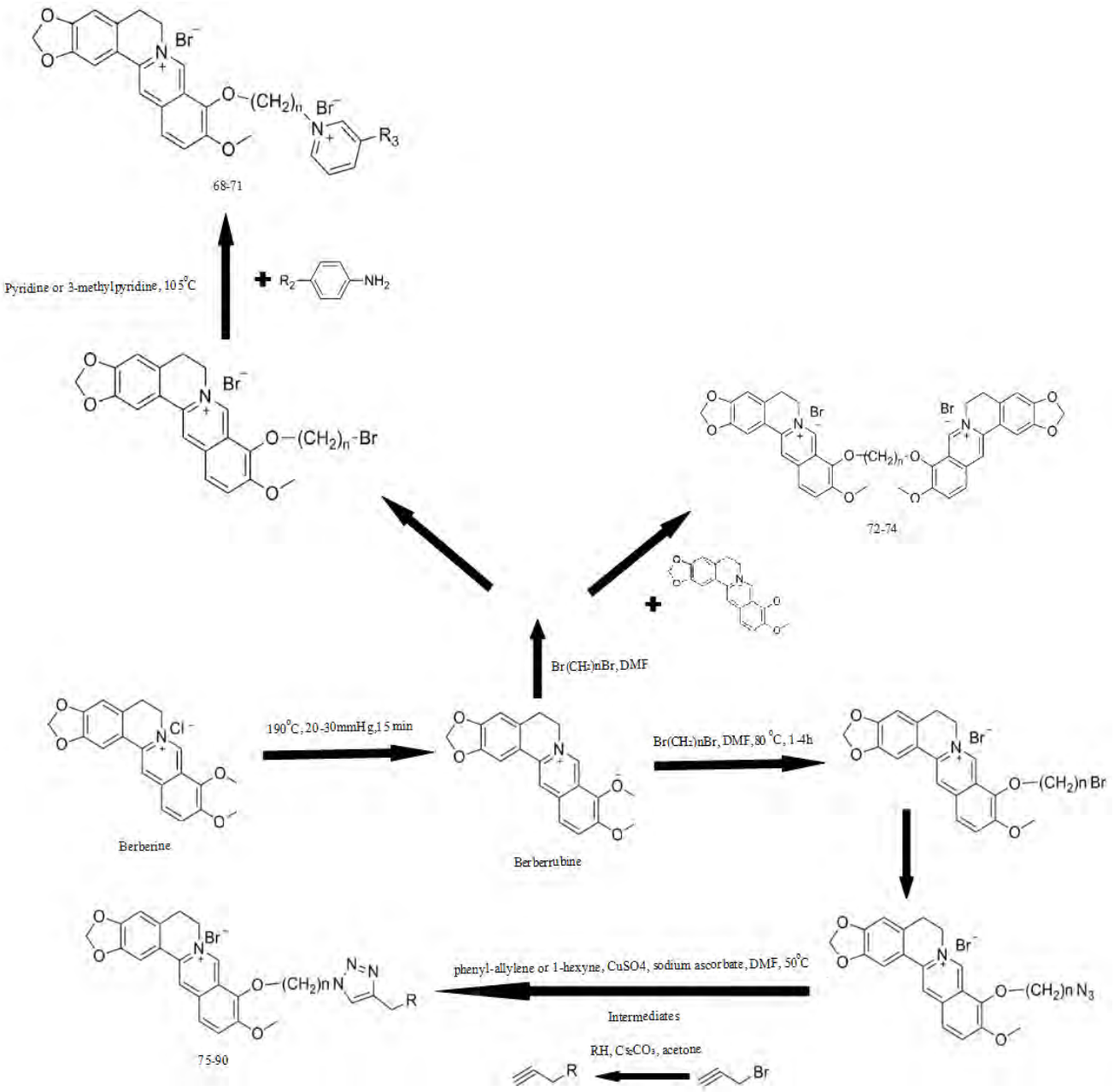


Table 2. Synthesis of the berberine-derivatives hybrid, which are based structures 33-90

N	Chemical structures		n	Inhibiton activity			Determination
				AchE (IC50μm)	BuChE (IC50μm)	Aβ (%)	
33	9-O-[(3-Oxo-tryptamino)propyl]-berberine bromide	H	-	1.11±0.021	1.64±0.206	82.8	NMR, HRMS
34	9-O-[(3-Oxo-5-methyltryptamino)propyl] -berberine bromide	CH3	-	1.42±0.042	1.96±0.014	72.8	NMR, HRMS
35	9-O-[(3-Oxo-5-methoxytryptamino) propyl]-berberine bromide	OCH3	-	1.44±0.054	2.72±0.035	79.5	NMR, HRMS
36	9-O-[3-(Ferulic acid)propyl] berberine bromide	-	-	3.21+0.155	2.40±0.042	75.8	NMR, HRMS
37	9-O-[3-(4-Methyl-phenoxyl) propyl]-berberine bromide	R1=CH3, X=O, Y=C	3	0.878±0.061	1.81±0.134	-	NMR, LC/MS
38	9-O-[3-(4-Methoxy-phenoxyl)-propyl]-berberine bromide	R1=OCH3, X=O, Y=C	3	1.00±0.075	2.86±0.127	-	NMR, LC/MS
39	9-O-[3-(4-Methoxy-phenoxyl)butyl]-berberine bromide	R1=OCH3, X=O, Y=C	4	0.748±0.084	2.29±0.076	-	NMR, LC/MS
40	9-O-[3-(4-Chloro-phenoxyl)propyl]-berberine bromide	R1=Cl, X=O, Y=C	3	0.715±0.109	1.80±0.141	-	NMR, LC/MS
41	9-O-[3-(4-Chloro-phenoxyl) butyl]-berberine bromide	R1=Cl, X=O, Y=C	4	1.50±0.020	2.20±0.170	-	NMR, LC/MS
42	9-O-[3-(4-Bromo-phenoxyl)propyl]-berberine bromide	R1=Br, X=O, Y=C	3	0.265±0.024	4.24±0.148	-	NMR, LC/MS
43	9-O-[3-(4-Bromo-phenoxyl)butyl]-berberine bromide	R1=Br, X=O, Y=C	4	0.743+0.069	5.44+0.050	-	NMR, LC/MS
44	9-O-[3-(4-Nitro-phenoxyl)propyl]-berberine bromide	R1=NO2, X=O, Y=C	3	0.400±0.050	2.83±0.136	-	NMR, LC/MS
45	9-O-[3-(4-Nitro-phenoxyl)butyl]-berberine bromide	R1=NO2, X=O, Y=C	4	0.490±0.087	2.05±0.121	-	NMR, LC/MS
46	9-O-[3-(2-Pyridinoxyl)butyl]-berberine bromide	R1=H, X=O, Y=N	4	0.340±0.013	4.16±0.05	-	NMR, LC/MS
47	9-O-[3-(Phenylamino)propyl]-berberine bromide	R1=H, X=NH, Y=N	3	0.138±0.009	1.76±0.114	-	NMR, LC/MS
48	9-O-[3-(N-Methyl-phenylamino)propyl]-berberine bromide	R1=H, X=NCH3, Y=N	3	0.156±0.013	2.17±0.040	-	NMR, LC/MS
49	9-O-[3-(Naphthalen-2-yloxy)propyl]-berberine bromide	X=O	3	0.359±0.044	2.20±0.127	-	NMR, LC/MS
50	9-O-[3-(Naphthalen-2-yloxy)butyl]-berberine bromide	X=O	4	1.899±0.894	1.10±0.899	-	NMR, LC/MS
51	9-O-[3-(Naphthalene-2-ylthio)propyl]-berberine bromide	X=S	3	0.500±0.015	0.548±0.014	-	NMR, LC/MS
52	9-O-[3-(Naphthalene-2-ylthio)butyl]-berberine bromide	X=S	4	1.35±0.092	0.078±0.011	-	NMR, LC/MS
53	9-O-[(3-Oxo-3-phenylamino)propyl]-berberine bromide	R2=H	-	0.535±0.008	2.18±0.085	-	NMR, LC/MS
54	9-O-[(3-Oxo-3-p-tolylamino)propyl]-berberine bromide	R2=CH3	-	1.46±0.036	1.31±0.148	-	NMR, LC/MS
55	9-O-[(3-Oxo-3-p-methoxyamino)propyl]-berberine bromide	R2=OCH3	-	2.80±0.027	1.01±0.061	-	NMR, LC/MS
56	9-O-[(3-Oxo-3-p-chlorophenylamino) propyl]-berberine bromide	R2=Cl	-	3.86±0.014	1.68±0.190	-	NMR, LC/MS
57	9-O-[(3-Oxo-3-p-nitrophenylamino) propyl]-berberine bromide	R2=NO2	-	6.50±0.056	5.53±0.090	-	NMR, LC/MS

58	9-O-N-(3-Bromopropyl)-1H-indole-2-carboxamideberberine bromide	Z=NH	-	0.976±0.06	2.19±0.127	73.5	NMR, HRMS
59	9-O-N-(3-Propyl)benzofuran-2-carboxamide-berberine bromide	Z=O	-	1.94±0.094	1.54±0.137	69.1	NMR, HRMS
60	9-O-2-(4-(2-Ethoxy)phenyl)benzofuran-berberine bromide	X=C, Y=O	2	3.59±0.270	0.688±0.062	-	NMR, HRMS
61	9-O-2-(4-(3-Propoxy)phenyl)benzofuran-berberine bromide	X=C, Y=NH	3	1.92±0.058	0.990±0.028	84.6	NMR, HRMS
62	9-O-2-(4-(3-Ethoxy)phenyl)-1H-indole-berberine bromide	X=C, Y=S	2	1.07±0.005	0.421±0.001	-	NMR, HRMS
63	9-O-2-(4-(3-Propoxy)phenyl)-1H-indole-berberine bromide	X=C, Y=NH	3	0.774±0.013	0.711±0.048	-	NMR, HRMS
64	9-O-2-(4-(3-Ethoxy) phenyl)benzo [d]thiazole-berberine bromide	X=N, Y=S	2	1.64±0.015	0.175±0.013	-	NMR, HRMS
65	9-O-2-(4-(3-Opropoxy)phenyl) benzo [d]thiazole-berberine bromide	X=N, Y=S	3	1.48±0.091	0.587±0.031	79.2	NMR, HRMS
66	9-O-2-(4-(3-Ethoxy)phenyl)benzo [d]oxazole-berberine bromide	X=N, Y=O	2	3.30±0.018	0.346±0.007	-	NMR, HRMS
67	9-O-2-(4-(3-Propoxy)phenyl)benzo [d]oxazole-berberine bromide	X=N, Y=O	3	2.12±0.021	0.639±0.011	-	NMR, HRMS
68	9-O-[(2-Pyridinium)bromide ethyl]-berberine bromide	R3=H	2	0.196±0.013	2.82±0.183	-	NMR, LC/MS
69	9-O-[(3-Pyridinium bromide)propyl]-berberine dibromide	R3=H	3	0.359±0.044	13.3±0.749	-	NMR, LC/MS
70	9-O-[(2-(3-Methyl)pyridinium bromide)ethyl]-berberine bromide	R3=CH3	2	0.048±0.003	2.46+0.141	-	NMR, LC/MS
71	9-O-[3-(3-Methyl pyridinium bromide)propyl]-berberine bromide	R3=CH3	3	0.152+0.016	15.8+0.986	-	NMR, LC/MS
72	1,2-Di(berberine-9-O-yl)ethane dibromide	-	2	0.320±0.022	1.11±0.050	-	NMR, LC/MS
73	1,3-Di(berberine-9-O-yl)ethane dibromide	-	3	0.226±0.006	0.531±0.026	-	NMR, LC/MS
74	1,4-Di(berberine-9-O-yl)ethane dibromide	-	4	0.176±0.014	0.231±0.023	-	NMR, LC/MS
75	9-O-{3-{4-[(2-Methoxycarbonyl-pyrrolidin-1-yl)methyl]1H-1,2,3-triazol-1-yl}propyl}berberine bromide	Proline methyl ester	3	0.785±0.023	5.30±0.106	-	NMR, LC/MS
76	9-O-{3-{4-[(2-Methoxycarbonyl-pyrrolidin-1-yl)methyl]1H-1,2,3-triazol-1-yl}butyl}berberine bromide	Proline methyl ester	4	0.903±0.047	5.27±0.378	63.5	NMR, LC/MS, HRMS
77	9-O-{3-{4-[(2-Ethoxycarbonyl-pyrrolidin-1-yl)methyl]1H-1,2,3-triazol-1-yl}propyl}berberine bromide	Proline ethyl ester	3	0.601±0.147	2.40±0.258	-	NMR, LC/MS, HRMS
78	9-O-{3-{4-[(2-Ethoxycarbonyl-pyrrolidin-1-yl)methyl]1H-1,2,3-triazol-1-yl}butyl}berberine bromide	Proline ethyl ester	4	0.606±0.052	2.32±0.304	76.6	NMR, LC/MS, HRMS
79	9-O-{3-{4-[(Piperidin-1-yl)methyl]-1H-1,2,3-triazol-1yl}propyl} berberine bromide	piperidine	3	0.108±0.001	4.24±0.071	-	NMR, LC/MS, HRMS
80	9-O-{3-{4-[(Piperidin-1-yl)methyl]-1H-1,2,3-triazol-1yl}butyl} berberine bromide	piperidine	4	0.274±0.011	5.73±0.09	63.7	NMR, LC/MS, HRMS
81	9-O-{3-{4-[(N,N-Dibutyl-amino)methyl]-1H-1,2,3-triazol1-yl}propyl}berberine bromide	N(n-Bu)2	3	0.243±0.006	2.06±0.106	-	NMR, LC/MS, HRMS
82	9-O-{3-{4-[(N,N-Dibutyl-amino)methyl]-1H-1,2,3-triazol1-yl}butyl} berberine bromide	N(n-Bu)2	4	0.469±0.040	5.46±0.106	71.7	NMR, LC/MS, HRMS
83	9-O-{3-{4-[(N,N-Dipropyl-amino)methyl]1H-1,2,3-triazol1-yl} propyl}berberine bromide	N(n-Pr)2	3	0.140±0.011	1.58±0.099	-	NMR, LC/MS, HRMS

84	9-O-{3-{4-[(N,N-Dipropyl-amino)methyl]-1H-1,2,3triazol-1-yl}butyl}berberine bromide	N(n-Pr)2	4	0.270±0.018	4.77±0.148	62.5	NMR, LC/MS, HRMS
85	9-O-{3-{4-[(N,N-Di-isopropyl-amino)methyl]-1H-1,2,3triazol-1-yl}propyl}berberine bromide	N(i-Pr)2	3	0.067±0.003	2.86±0.396	-	NMR, HRMS
86	9-O-{3-{4-[(N,N-Di-isopropyl-amino)methyl]-1H-1,2,3triazol-1-yl}butyl}berberine bromide	N(i-Pr)2	4	0.044±0.001	6.21±0.127	52.8	NMR, HRMS
87	9-O-{3-[4-(Benzyl)-1H-1,2,3-triazol-1-yl]proyl}berberine bromide	Phenyl	3	0.310±0.029	2.21±0.138	-	NMR, LC/MS, HRMS
88	9-O-{3-[4-(Benzyl)-1H-1,2,3-triazol-1-yl]butyl}berberine bromide	Phenyl	4	1.32±0.196	1.50±0.131	60.6	NMR, LC/MS, HRMS
89	9-O-{3-[4-(Butyl)-1H-1,2,3-triazol-1-yl]propyl}berberine bromide	(CH2)2CH3	3	0.165±0.015	4.06±0.250	-	NMR, LC/MS, HRMS
90	9-O-{3-[4-(Butyl)-1H-1,2,3-triazol-1-yl]butyl}berberine bromide	(CH2)2CH3	4	0.201±0.017	2.02±0.500	77.9	NMR, LC/MS, HRMS