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Minireview

One-compound-multiple-targets strategy to combat Alzheimer's disease

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Abstract The present one-drug-one-target paradigm in drug discovery has been considered partially responsible for the more-funding-less-drug predicament in modern pharmaceutical industry. To hit the multiple targets implicated in complex diseases, two strategies, based on multicomponent or single-ingredient, are conceivable. Although the latter is more difficult to be fulfilled than the former, the recent progress made in the fight against Alzheimer's disease (AD) has brought us the first light of success of the latter strategy. In this review, both synthetic and natural multipotent agents are described, which hit two or more targets implicated in AD, e.g., acetylcholinesterase, monoamine oxidase, amyloid-β, τ protein, metal ions and reactive oxygen species. Nevertheless, due to the potential risks in safety, absorbability and pharmacokinetics of synthetic multipotent agents, natural counterparts seem more promising in the future development.

Keywords: Acetylcholinesterase; Amyloid-β aggregation; Metal ions; Monoamine oxidase; Multipotent agents; Reactive oxygen species

1. Introduction

Modern pharmaceutical industry is facing unprecedented challenges in drug development. The global research funding has doubled since 1991, but the approved new drugs have fallen by 50% [1]. Considering the fact that most human diseases, such as cancer, diabetes, heart disease, arthritis and neurodegenerative diseases, involve multiple pathogenetic factors, the more-funding-less-drug predicament is attributed in part to the limitations of the present one-drug-one-target paradigm in drug discovery [1,2]. Therefore, more and more effort is devoted to finding new therapeutics aiming at multiple targets [2], which is becoming a new paradigm in drug discovery.

To hit the multiple targets implicated in the complex diseases, two strategies are conceivable. One is called multicomponent therapeutic strategy, which incorporates two or more active ingredients in one drug [2]. In fact, this strategy has been successfully used in traditional medicine (in China and many other countries) for thousands of years and in current drug cocktails as well to suppress the spreading of HIV. The other attempts to employ one compound to hit the multiple targets, which can be termed as one-compound-multiple-targets strategy. Although the latter strategy seems more convenient than the former, it is more difficult to be fulfilled. Nevertheless, the accumulating experience gained in the battle against Alzheimer's disease (AD) displays the feasibility of the latter strategy.

AD, characterized by progressive memory loss, decline in language skills and other cognitive impairments, has been a major threat to ageing population [3,4]. Although the etiology of AD is not very clear, multiple factors, such as amyloid-β (Aβ) and τ protein aggregation, excessive metal ions (e.g., Cu^{2+}, Zn^{2+}, Fe^{3+}), oxidative stress and reduced acetylcholine (ACh) level, have been considered to play important roles in the pathogenesis of AD [3–6]. This provides diverse targets for screening AD-modifying drugs. Indeed, numerous synthetic or natural molecules have been screened to decrease Aβ production (e.g., β-secretase inhibitor), to prevent Aβ or τ aggregation, to chelate transition metals, to scavenge reactive oxygen species (ROS) or to inhibit acetylcholinesterase (AChE) or monoamine oxidase (MAO) [3–7]. However, the success of the one-drug-one-target strategy is limited, which has stimulated the search for more efficient combined weapons to combat AD.

2. Synthetic compounds as multipotent agents

Some pioneers resorted to incorporating two or more pharmacophores in one molecule to design multipotent agents to hit more than one target in AD. Several pioneering studies attempted to combine AChE and MAO inhibiting activity. Fink et al. [8] showed that hybrid of an AChE inhibitor (i.e., physostigmine) and an irreversible MAO inhibitor, such as L-deprenyl, resulted in dual AChE and MAO inhibitors. Furthermore, they found that a series of imino 1,2,3,4-tetrahydrocyclopent[b]indole carbamates (Fig. 1) are efficient dual AChE and irreversible MAO inhibitors too [8]. Brühlmann et al. [9] discovered that some coumarin and chromone derivatives (Fig. 1) can behave as inhibitors of both MAO (mainly MAO-B) and AChE. By incorporating two pharmacophores in inhibiting AChE and MAO-B, i.e., carbamate and propargyl group, into a single molecule scaffold, Sterling et al. [10] also gained novel dual inhibitors of AChE and MAO.

Besides hydrolyzing ACh, AChE also functions as a promoter of Aβ fibril formation, which is independent of its

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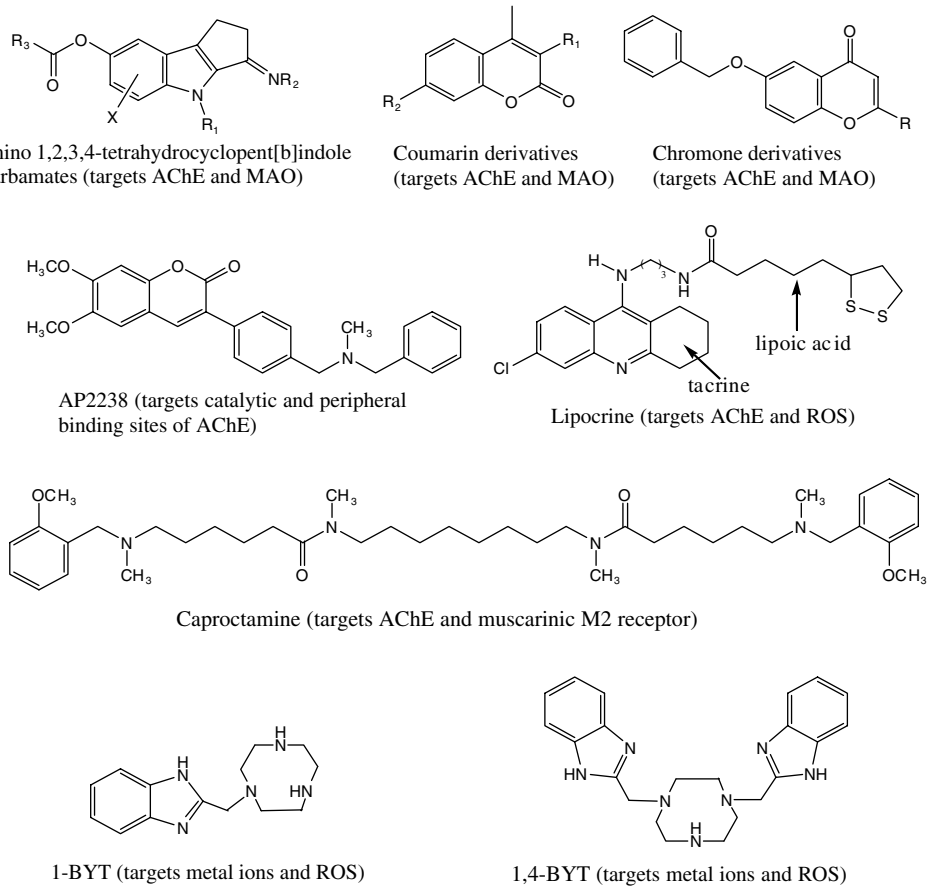

Fig. 1. Synthetic multipotent compounds to combat Alzheimer's disease. The targets for each molecule are indicated in the parentheses. A basic principle to design multipotent compounds is incorporating two or more pharmacophores in one molecule. Despite the in vitro success of these synthetic agents, the potential risks in safety, absorbability and pharmacokinetics is a big hurdle in their further development.

normal hydrolyzing activity and is associated with the peripheral binding site of AChE [11]. This stimulated the interest to design hybrid molecules to inhibit AChE and AChE-induced Aβ aggregation simultaneously. Piazzi et al. [12] achieved this goal by linking a benzylamino group and a coumarin heterocycle through a phenyl ring. The combined molecule (AP2238) (Fig. 1) is able to contact both the catalytic and the peripheral binding sites of AChE at the same time. Moreover, Rosini et al. [13] rationally designed a novel compound (lipocrine) (Fig. 1) by linking tacrine, a AChE inhibitor, and lipoic acid, a universal antioxidant, and endowed the hybrid molecule with three functions, i.e., inhibiting the catalytic activity of AChE and AChE-induced Aβ aggregation and protecting against ROS. Melchiorre et al. [14] showed that a polyamine, caproctamine (Fig. 1), is well balanced between an AChE inhibitor and a competitive muscarinic M_2 receptor antagonist, which means that caproctamine will stimulate cholinergic activity in the brain by decreasing ACh hydrolysis rates and by enhancing ACh release in the synapse at the same time. More interestingly, caproctamine also has potential to prevent AChE-induced Aβ aggregation by interacting with the peripheral binding sites of AChE [14].

Considering the preliminary success of metal chelators (e.g., clioquinol) in treating AD [5,15] and the fact that some superoxide dismutase (SOD) mimetics are metal chelates, Ji et al. [16] proposed that better clinical effects than clioquinol can be expected for a SOD-mimetic ligand with metal-binding ability comparable with clioquinol, because the ligand bears metal–protein-attenuating ability and radical-scavenging potential in one structure. By means of quantum chemical calculation, two metal chelators, 1-BYT and 1,4-BYT (Fig. 1) were revealed to be qualified candidates to fulfill this strategy [16].

3. Natural products as multipotent agents

Despite the in vitro success of synthetic multifunctional agents, the potential risks in safety, absorbability and pharmacokinetics is a big hurdle in their further development [8]. Hence, it is exciting to note that some natural products also hold multiple functions, among which, curcumin (Fig. 2) is given the most attention. The beneficial effect of curcumin to prevent AD has been shown by transgenic mouse experiment [17] and epidemiologic investigation that AD prevalence is only 1% in people over age 65 of rural India, where turmeric is commonly used in food [18]. The AD-preventing mechanism of curcumin was naturally related to its well known antioxidant and anti-inflammatory activities [19,20]. However, recent in vitro and in vivo experiments revealed that curcumin can block Aβ aggregation with high efficiency ($IC_{50} < 1$ μM) [21,22]. In addition, curcumin is also a good metal chelator

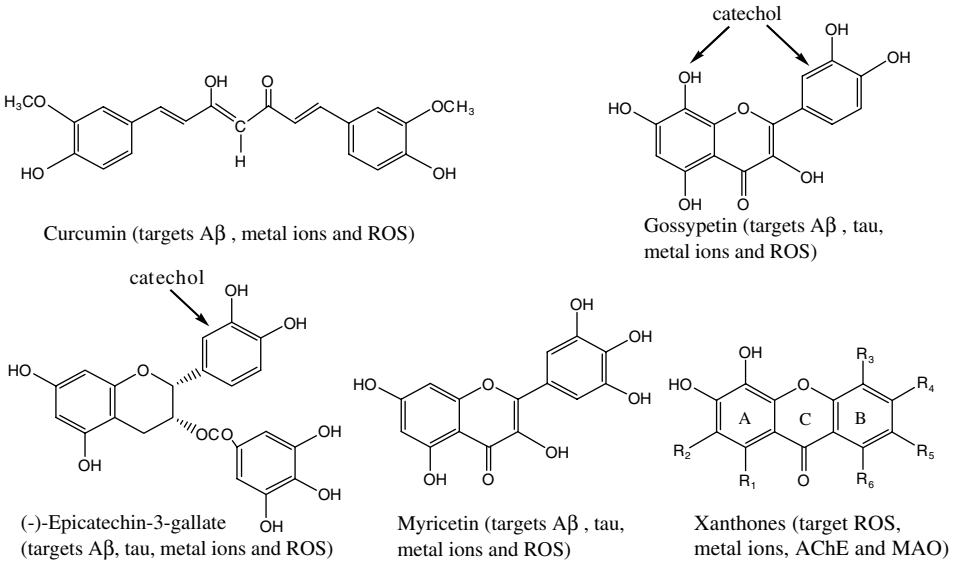

Fig. 2. Natural multipotent compounds to combat Alzheimer's disease (AD). The targets for each molecule are indicated in the parentheses. As catechol group serves as a metal ligand and a radical scavenger and is required in retarding Aβ aggregation, it is likely a multifunctional pharmacophore. Thus, catechol provides a good starting point for screening and designing AD-modifying drugs. To reduce the prooxidant danger of catechol, catechol-containing xanthones are recommended, because the perfect conjugation of rings A, B and electron-withdrawing ring C (1,4-pyrone) attenuates their electron-donating ability. More interestingly, some xanthones have been revealed as efficient AChE and MAO inhibitors.

[23]. Both experimental determination and theoretical calculation indicated that curcumin can efficiently sequester Cu^{2+} and the Cu^{2+}-curcumin complex gets more active than the parent curcumin in scavenging ROS by catalyzing the dismutation of superoxide anion radical [24] or by donating a proton or an electron [25]. Therefore, all of the evidence implies that curcumin is a very promising multipotent compound to treat AD.

Besides curcumin, flavonoids, such as gossypetin, (−)-epicatechin-3-gallate and myricetin (Fig. 2), are pleiotropic natural products too. They have long been known as excellent ROS scavengers endowed with high metal-chelating ability [26]. Moreover, Taniguchi et al. [27] revealed that these flavonoids hold Aβ- or τ-aggregation-inhibiting capability with IC_{50} lower than 5 μM. The different structures of curcumin and flavonoids suggest that the structural requirements to fulfill the multifunction are diverse and thus, it can be expected to find more candidates from natural product libraries. Considering the wide enzyme-inhibiting spectra of curcumin and flavonoids, it is challenging to investigate their effects on other AD-related proteins. Maybe, more AD-attenuating mechanisms can be revealed for both kinds of natural products.

As revealed by the structure–activity relationship study on flavonoids [26,28], catechol moiety is an active center to scavenge ROS or bind metal ions. On the other hand, catechol is also required, e.g., in apomorphine, to prevent Aβ aggregation [29]. Therefore, catechol likely plays a key role in exerting the multifunction of flavonoids and can be regarded as a multifunctional pharmacophore, which means that the multiple targets in AD can be hit not only by one compound but also by one pharmacophore. The feasibility of this new concept is further supported by an intriguing finding that there exist common peptide motifs in AD-related proteins. By bioinformatic analyses on 43 proteins implicated in AD, Stephenson et al. [30] identified BBXB and AXBBXB (where B is a basic residue, X represents any other amino acids and A refers to an acidic residue) as two common receptor motifs. BBXB motif occurs in 27 proteins, while AXBBXB motif is shared by 8 proteins and holds higher specificity. The common motifs will serve as the targets of multifunctional pharmacophores, which indeed boosts up the practicability of the one-compound- multiple-targets strategy in combating AD.

Although catechol is of great interest in AD-attenuating drug discovery, there is concern about its potential toxicity [31]. The toxicity of catechols may arise from its strong electron-donating ability, which will change the antioxidant to a prooxidant. In addition, the toxicity of catechols is likely associated with their quinone formation potential. It was revealed that the less quinone is formed, the safer the catechols [31]. These findings offer important clues to screening or designing catechol-based multipotent agents. For instance, catechol-containing xanthones (Fig. 2) may have more potential than flavonoids to act as pleiotropic agents to combat AD, because the perfect conjugation of rings A, B and electron-withdrawing ring C (1,4-pyrone) attenuates their electron-donating ability [32]. More interestingly, xanthones have really been revealed as efficient AChE and MAO inhibitors [33,34].

4. Conclusion

Drug discovery paradigm is shifting from one-drug–one-target strategy to one-drug-multiple-targets strategy. The diverse targets can be hit not only by multiple components but also by one compound or even by a single pharmacophore. Thanks to the advancement in high throughput drug screening and computer-aided drug design, there is less and less technical hurdle in finding more multipotent agents to fulfill the new strategy. Especially, the recent progress made in fighting against AD has brought us the first light of success of the new concept, which also has important implications for treating other neurodegenerative diseases [35], because similar multiple pathogenetic factors, such as protein aggregation, excessive ROS and

metals, are involved [5,6] and different types of soluble amyloid oligomers bear a common structure [36].

Note. Following the acceptance of the review, two interesting papers appeared [37,38], in which Youdim and coworkers reported that some designed iron chelators hold MAO-AB inhibitory activity and antioxidant effect, thus can serve as multipotent agents to combat AD and Parkinson's disease. In addition, from the references of both papers, I found a pioneering review on multifunctional drugs to treat neurodegenerative disorders [39], which is very helpful to the researchers in this area.

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References

[1] Buehler, L.K. (2004) Advancing drug discovery-beyond design. PharmaGenomics 4, 24–26.
[2] Keith, C.T., Borisy, A.A. and Stockwell, B.R. (2005) Multicomponent therapeutics for networked systems. Nat. Rev. Drug Discov. 4, 71–78.
[3] Mattson, M.P. (2004) Pathways towards and away from Alzheimer's disease. Nature 430, 631–639.
[4] Cummings, J.L. (2004) Alzheimer's Disease. N. Engl. J. Med. 351, 56–67.
[5] Barnham, K.J., Masters, C.L. and Bush, A.I. (2004) Neurodegenerative diseases and oxidative stress. Nat. Rev. Drug Discov. 3, 205–214.
[6] Brown, D.R. and Kozlowski, H. (2004) Biological inorganic and bioinorganic chemistry of neurodegeneration based on prion and Alzheimer diseases. Dalton Trans. 13, 1907–1917.
[7] Citron, M. (2004) Strategies for disease modification in Alzheimer's disease. Nat. Rev. Neurosci. 5, 677–685.
[8] Fink, D.M., Palermo, M.G., Bores, G.M., Huger, F.P., Kurys, B.E., Merriman, M.C., Olsen, G.E., Petko, W. and O'Malley, G.J. (1996) Imino 1,2,3,4-tetrahydrocyclopent[b]indole carbamates as dual inhibitors of acetylcholinesterase and monoamine oxidase. Bioorg. Med. Chem. Lett. 6, 625–630.
[9] Brühlmann, C., Ooms, F., Carrupt, P.-A., Testa, B., Catto, M., Leonetti, F., Altomare, C. and Carotti, A. (2001) Coumarins derivatives as dual inhibitors of acetylcholinesterase and monoamine oxidase. J. Med. Chem. 44, 3195–3198.
[10] Sterling, J., Herzig, Y., Goren, T., Finkelstein, N., Lerner, D., Goldenberg, W., Miskolczi, I., Molnar, S., Rantal, F., Tamas, T., Toth, G., Zagyva, A., Zekany, A., Lavian, G., Gross, A., Friedman, R., Razin, M., Huang, W., Krais, B., Chorev, M., Youdim, M.B. and Weinstock, M. (2002) Novel dual inhibitors of AChE and MAO derived from hydroxy aminoindan and phenethylamine as potential treatment for Alzheimer's disease. J. Med. Chem. 45, 5260–5279.
[11] De Ferrari, G.V., Canales, M.A., Shin, I., Weiner, L.M., Silman, I. and Inestrosa, N.C. (2001) A structural motif of acetylcholinesterase that promotes amyloid β-peptide fibril formation. Biochemistry 40, 10447–10457.
[12] Piazzi, L., Rampa, A., Bisi, A., Gobbi, S., Belluti, F., Cavalli, A., Bartolini, M., Andrisano, V., Valenti, P. and Recanatini, M. (2003) 3-(4-[Benzyl(methyl)amino]methylphenyl)-6,7-dimethoxy-2H-2-chromenone (AP2238) inhibits both acetylcholinesterase and acetylcholinesterase-induced β-amyloid aggregation: a dual function lead for Alzheimer's disease therapy. J. Med. Chem. 46, 2279–2282.
[13] Rosini, M., Andrisano, V., Bartolini, M., Bolognesi, M.L., Hrelia, P., Minarini, A., Tarozzi, A. and Melchiorre, C. (2005) Rational approach to discover multipotent anti-Alzheimer drugs. J. Med. Chem. 48, 360–363.
[14] Melchiorre, C., Andrisano, V., Bolognesi, M.L., Budriesi, R., Cavalli, A., Cavrini, V., Rosini, M., Tumiatti, V. and Recanatini, M. (1998) Acetylcholinesterase noncovalent inhibitors based on a polyamine backbone for potential use against Alzheimer's disease. J. Med. Chem. 41, 4186–4189.
[15] Ritchie, C.W., Bush, A.I., Mackinnon, A., Macfarlane, S., Mastwyk, M., MacGregor, L., Kiers, L., Cherny, R., Li, Q.X., Tammer, A., Carrington, D., Mavros, C., Volitakis, I., Xilinas, M., Ames, D., Davis, S., Beyreuther, K., Tanzi, R.E. and Masters, C.L. (2003) Metal-protein attenuation with iodochlorhydroxyquin (clioquinol) targeting Aβ amyloid deposition and toxicity in Alzheimer disease: a pilot phase 2 clinical trial. Arch. Neurol. 60, 1685–1691.
[16] Ji, H.-F. and Zhang, H.-Y. (2005) A new strategy to combat Alzheimer's disease. Combining radical-scavenging potential with metal–protein-attenuating ability in one molecule. Bioorg. Med. Chem. Lett. 15, 21–24.
[17] Lim, G.P., Chu, T., Yang, F., Beech, W., Frautschy, S.A. and Cole, G.M. (2001) The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse. J. Neurosci. 21, 8370–8377.
[18] Chandra, V., Ganguli, M., Pandav, R., Johnston, J., Belle, S. and DeKosky, S.T. (1998) Prevalence of Alzheimer's disease and other dementias in rural India: the Indo-US study. Neurology 51, 1000–1008.
[19] Frautschy, S.A., Hu, W., Kim, P., Miller, S.A., Chu, T., Harris-White, M.E. and Cole, G.M. (2001) Phenolic anti-inflammatory antioxidant reversal of Abeta-induced cognitive deficits and neuropathology. Neurobiol. Aging 22, 993–1005.
[20] Aisen, P.S. (2002) Development of antiinflammatory therapy for Alzheimer's disease. Drug Develop. Res. 56, 421–427.
[21] Ono, K., Hasegawa, K., Naiki, H. and Yamada, M. (2004) Curcumin has potent anti-amyloidogenic effects for Alzheimer's β-amyloid fibrils in vitro. J. Neurosci. Res. 75, 742–750.
[22] Yang, F., Lim, G.P., Begum, A.N., Ubeda, O.J., Simmons, M.R., Ambegaokar, S.S., Chen, P.P., Kayed, R., Glabe, C.G., Frautschy, S.A. and Cole, G.M. (2005) Curcumin inhibits formation of amyloid β oligomers and fibrils, binds plaques, and reduces amyloid in vivo. J. Biol. Chem. 280, 5892–5901.
[23] Baum, L. and Ng, A. (2004) Curcumin interaction with copper and iron suggests one possible mechanism of action in Alzheimer's disease animal models. J. Alzheimer Dis. 6, 367–377.
[24] Barik, A., Mishra, B., Shen, L., Mohan, H., Kadam, R.M., Dutta, S., Zhang, H.-Y. and Priyadarsini, K.I. (2005) Evaluation of new copper-curcumin complex as superoxide dismutase mimic and its free radical reactions. Free Radic. Biol. Med. 39, 811–822.
[25] Shen, L., Zhang, H.-Y. and Ji, H.-F. (2005) A theoretical study on Cu(II)-chelating properties of curcumin and its implications for curcumin as a multipotent agent to combat Alzheimer's disease. J. Mol. Struct. (Theochem.), in press.
[26] Rice-Evans, C.A., Miller, N.J. and Paganga, G. (1996) Structure–antioxidant activity relationships of flavonoids and phenolic acids. Free Radic. Biol. Med. 20, 933–956.
[27] Taniguchi, S., Suzuki, N., Masuda, M., Hisanaga, S.-i., Iwatsubo, T., Goedert, M. and Hasegawa, M. (2005) Inhibition of heparin-induced tau filament formation by phenothiazines, polyphenols, and porphyrins. J. Biol. Chem. 280, 7614–7623.
[28] Zhang, H.-Y. (2005) Structure–activity relationships and rational design strategies for radical-scavenging antioxidants. Curr. Comput. Aided Drug Des. 1, 257–273.
[29] Lashuel, H.A., Hartley, D.M., Balakhaneh, D., Aggarwal, A., Teichberg, S. and Callaway, D.J.E. (2002) New class of inhibitors of amyloid-β fibril formation. Implications for the mechanism of pathogenesis in Alzheimer's disease. J. Biol. Chem. 277, 42881–42890.
[30] Stephenson, V.C., Heyding, R.A. and Weaver, D.F. (2005) The "promiscuous drug concept" with applications to Alzheimer's disease. FEBS Lett. 579, 1338–1342.
[31] Chichirau, A., Flueraru, M., Chepelev, L.L., Wright, J.S., Willmore, W.G., Durst, T., Hussainc, H.H. and Charron, M. (2005) Mechanism of cytotoxicity of catechols and a naphthalenediol in PC12-AC cells: the connection between extracellular autoxidation and molecular electronic structure. Free Radic. Biol. Med. 38, 344–355.
[32] Ji, H.-F., Tang, G.-Y. and Zhang, H.-Y. (2005) Theoretical elucidation on structure–activity relationships of antioxidant xanthones. QSAR Combin. Sci. 24, 826–830.

[33] Brühlmann, C., Marston, A., Hostettmann, K., Carrupt, P.-A. and Testa, B. (2004) Screening of non-alkaloidal natural compounds as acetylcholinesterase inhibitors. Chem. Biodivers. 1, 819–829.
[34] Nunez, M.B., Maguna, F.P., Okulik, N.B. and Castro, E.A. (2004) QSAR modeling of the MAO inhibitory activity of xanthones derivatives. Bioorg. Med. Chem. Lett. 14, 5611–5617.
[35] Ji, H.-F., Tang, G.-Y. and Zhang, H.-Y. (2005) β-Lactam antibiotics are multipotent agents to combat neurological diseases. Biochem. Biophys. Res. Commun. 333, 661–663.
[36] Kayed, R., Head, E., Thompson, J.L., McIntire, T.M., Milton, S.C., Cotman, C.W. and Glabe, C.G. (2003) Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis. Science 300, 486–489.
[37] Zheng, H., Gal, S., Weiner, L.M., Bar-Am, O., Warshawsky, A., Fridkin, M. and Youdim, M.B.H. (2005) Novel multifunctional neuroprotective iron chelator-monoamine oxidase inhibitor drugs for neurodegenerative diseases: in vitro studies on antioxidant activity, prevention of lipid peroxide formation and monoamine oxidase inhibition. J. Neurochem. 95, 68–78.
[38] Gal, S., Zheng, H., Fridkin, M. and Youdim, M.B.H. (2005) Novel multifunctional neuroprotective iron chelator-monoamine oxidase inhibitor drugs for neurodegenerative diseases. In vivo selective brain monoamine oxidase inhibition and prevention of MPTP-induced striatal dopamine depletion. J. Neurochem. 95, 79–88.
[39] Youdim, M.B.H. and Buccafusco, J. (2005) Multi-functional drugs for various CNS targets in the treatment of neurodegenerative disorders. Trends Pharmacol. Sci. 26, 27–35.