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**ORIGINAL ARTICLE**

# Multi-Target Hybrid Drugs: A Promising Approach for Treating Alzheimer's, Neurological Diseases, Diabetes, and Cancer

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**KEYWORDS**

Acridine;
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**ABSTRACT:** Multi-target drugs are a class of hybrid compounds that can act on multiple targets and diseases simultaneously. These drugs have the potential to treat a range of disorders including Alzheimer's disease, diabetes, and cancer. This review aims to assess the efficacy of acridine- and tacrine-based multi-target hybrid drugs for the treatment of various diseases. In December 2022, a systematic literature search was conducted using "acridine," "tacrine," "multi-target agent, "and "multi-factorial diseases" along with their synonyms. According to the findings, acridine-based conjugates exhibited anti-cancer and anti-diabetic properties by directly inhibiting α-Glucosidase and α-Amylase, and by binding to DNA, topoisomerases, histone deacetylase, and poly (ADP-ribose) polymerase. The results suggest that acridine- and tacrine-based hybrid complexes have the potential to serve as promising multi-target agents for the treatment of Alzheimer's disease, neurological disorders, diabetes, and cancer. Overall, these compounds offer a new approach to drug development by targeting multiple disease pathways with a single agent. In conclusion, the use of multi-target drugs could potentially lead to improved therapeutic outcomes with fewer side effects, making them a promising area of research for the treatment of complex diseases. Keywords for this review include acridine, tacrine, multi-factorial diseases, and multi-target drugs.

## INTRODUCTION

Multi-target agents refer to biologically active molecules, which can simultaneously act on different biological targets. These molecules can be considered for treatment of multifactorial diseases such as prion disease, Alzheimer's disease, schizophrenia and cancer [1]. Multi-target drugs can also be used for synergetic or multi action on different targets. They can enhance the efficiency of treatment by providing interactions with

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multiple targets, and therefore, through multiple mechanism of action. Multi-target drugs are generally synthetic molecules that are synthesized by hybridization of two or more pharmacologically active units from different compounds, leading to owning several pharmacological properties [2]. One of these potential molecules is acridine derivatives, and most of these conjugated molecules are known as effective acetylcholinesterase (AChE) inhibitor. Acridine can bind to variety of molecule and macromolecules such as peptides, and nucleic acids. Finding has also demonstrated that acridine-metal complexes may have remarkable inhibitory potential on various tumors with negligible cytotoxic effect against human cells [3].

Acridine due to its unique chemical properties can interact with various coupling agents through substitution, and alkylation, or may undergo oxidation, reduction, and phosphorylation to produce new active derivatives. Many of acridine derivatives have shown biological activity including anticancer and anti-Alzheimer's disease [4]. Due to their planar structure, acridine derivatives can interact with the DNA through intercalation, which can lead to subsequent regulation of gene expression or inhibit of regulatory proteins such as topoisomerase enzymes [5]. Therefore, anticancer effects are mainly mediated via great affinity of acridine in binding to the DNA through the minor groove. Besides owning many promising pharmacological properties, clinical application of acridines is limited due to their high cytotoxic effects [5] .However, combining with another biologically active unit may enhance the efficiency and minimize the possible side effects of acridine derivatives.

Considering the above-described properties of acridine and its derivatives, in the present review, we aimed to systematically review available literature on efficiency and pharmaceutical value of multi-target acridine derivatives effective in the treatment of various diseases.

## MATERIALS AND METHODS

### *Study search and inclusion criteria*

In this study, a systematic search was performed in Web of Science, Scopus, PubMed, Embase, Ovid, Science Direct, and Google Scholar. The search terms used for this purpose include "acridine" "tacrine", and "multi-target agent" with all their equivalents and similar terms. For this purpose, PRISMA checklist 2009 that is a valid and standard protocol for systematic reviews was used for study design and article selection process [6].

## RESULTS

After literature search and considering the predefined inclusion criteria, a total of 481 articles were collected, of which 200 were from PubMed, 18 were in Scopus, 41 were in Google scholar, and 43 were in other databases. Additionally, and also, three articles were identified by screening the reference list of included articles. By limiting the records to the defined inclusion criteria, 245 articles were retrieved. After removal of irrelevant documents, 82 articles were selected for data synthesis. Selection process of articles is demonstrated in Figure 1.

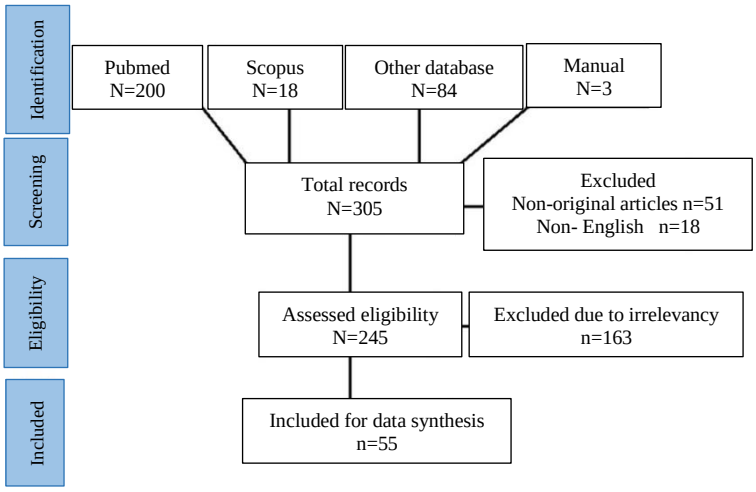


**Figure 1**. Selection process of articles.

Findings suggested that acridine derivatives as multi-targeted anticancer agents interfere with DNA synthesis and inhibit topoisomerases, histone deacetylase and poly (ADP-ribose) polymerase 1 (PARP1). Tacrine-coumarin hybrids were also shown to simultaneously inhibit both Aβ aggregation and β-secretase. These hybrid complexes also demonstrated potent inhibitory activity against cholinesterases (ChE), and monoamine oxidase (MAO); however, findings indicated that these complexes can penetrate the CNS and may show cell toxicity [7,8].

Some of anticancer complexes were also potential multi-target kinase inhibitors of Src, GSK-3α/β and MEK. Anti-Alzheimer's agents were found to inhibit ChE, including AChE and butyrylcholinesterase (BuChE). They could effectively inhibit the formation and either self- or AChE-induced aggregation of β-amyloid in the micromolar and even nanomolar range. Most of these complexes had also antioxidant activity and metal chelating properties. They also had potent neuroprotective effects against cell death with low cytotoxicity, which could cross the blood-brain barrier, emerging as an effective candidate for treating Alzheimer's disease. The detailed information of each complex is presented in Table 1.

Table 1. Physiochemical properties and the targets of multi-targeted agents.

| No | Conjugate part | Main target | Other targets | Inhibition value (IC50) | Reference |
|---|---|---|---|---|---|
| **1** | TAC- Quinuclidine | ChlE | Alpha 7 nicotinic receptor | AChE=15.2 nM<br>BuChE= 131 nM | [9] |
| **2** | TAC-Hydroxamate | ChlE | HDACs | AChE= 0.12 nM<br>BuChE= 361.52 nM<br>HDAC= 0.23 nM | [10] |
| **3** | TAC- Benzofuran | AChE | β-amyloid, metal chelating | AChE= 40 μM | [11] |
| **4** | AC- Givinostat | HDACs | AChE | HDACs = 0.57 μM<br>AChE= 0.72 μM | [12] |
| **5** | AC- Isatin Schiff base | ChlE | β-amyloid | AChE= 0.42 nM<br>BuChE= 79.66 nM | [13] |
| **6** | TAC- Tryptophan | ChlE | NOS | AChE= 6.3 nM<br>BuChE= 9.1 nM<br>NOS= 19 μM | [14] |
| **7** | C-Phenyl benzothiazole | AChE | β-amyloid | AChE= 0.06 μM | [15] |
| **8** | TAC-Valmerin | AChE | Kinases | AChE= 9.5 nM<br>GSK-3α/β = 7 nM | [16] |
| **9** | TAC-Isatin | ChlE | β-amyloid | AChE= 0.42 nM<br>BuChE= 0.11 nM | [17] |
| **10** | AC- dihydropyrimidin | ChlE | Calcium channel blockade | AChE= 3.05 μM<br>BuChE= 3.19 μM | [18] |
| **11** | TAC- cinnamic acid | AChE | β-amyloid | AChE= 10.2 nM | [19] |
| **12** | TAC- deferiprone | AChE | Metal chelating | AChE= 0.64 μM | [20] |
| **13** | TAC- quinoline | ChlE | β-amyloid | AChE= 0.32 μM<br>BuChE= 0.97 μM | [21] |
| **14** | TAC-hBIM | AChE | β-amyloid | AChE= 6 nM | [22] |
| **15** | TAC- Vilazodone | 5-HT | AChE, BuChE | 5-HT1A= 0.36 nM<br>AChE= 1.72 μM<br>BuChE= 0.34 μM | [23] |
| **16** | - Amido-benzimidazole | Top and PARP-1 | CYP450 | Top= 2.14 μM<br>PARP-1= 0.45 μM<br>CYP450= 2.2 μM | [24] |

| | | | | | |
|---|---|---|---|---|---|
| **17** | thoxyTAC- memantine | ChlE | β-secretase, NMDA | AChE= 10.5 μM<br>BuChE= 21 μM<br>β-secretase = 2 μM<br>NMDA= 1 μM | [25] |
| **18** | TAC- Vilazodone | AChE | 5-HT reuptake inhibition | AChE= 3.319 μM<br>5-HT= 76.3 nM | [26] |
| **19** | TAC- Resveratrol | AChE | β-amyloid | AChE= 10 μM | [27] |
| **20** | C- Fluorobenzoic acid | ChlE | β-amyloid | AChE= 41.37 nM<br>BuChE= 1.39 nM | [28] |
| **21** | AC- Benzylamino | Top II | - | Top= 100 μM | [29] |
| **22** | TAC-HBP | AChE | Radical scavenging | AChE= 0.57 μM | [30] |
| **23** | TAC-Benzofuran | AChE | β-secretase | AChE= 0.86 nM<br>β-secretase = 1.35 μM | [31] |
| **24** | TAC- Indole | 5-HT6 receptor | AChE, BuChE | $5\text{-HT}_6$= 27 nM<br>AChE= 12 nM<br>BuChE= 29 nM | [32] |
| **25** | TAC- Indole | ChlE | MAO-A | AChE= 1.5 μM<br>BuChE= 2.4 μM<br>MAO-A= 0.49 μM | [33] |
| **26** | C- multi-alkoxybenzene | AChE | - | AChE= 5.63 nM | [34] |
| **27** | AC- Phenyl-urea | Src and MEK kinase | - | Src 59.67%, MEK 43.23% at 10 μM | [35] |
| **28** | AC- Chromenone | AChE | β-secretase | AChE= 16.17 μM<br>β-secretase = 7.99 μM | [36] |
| **29** | TAC- Trolox | ChlE | - | AChE= 0.08 μM<br>BuChE= 0.54 μM | [37] |
| **30** | TAC-CUM | ChlE | MAO-B | AChE= 16.11 nM<br>BuChE= 112.72 nM<br>MAO-B= 0.24 μM | [8] |
| **31** | TAC- Ferulic acid | BuChE | β-amyloid | BuChE= 68.2 nM | [38] |
| **32** | TAC- Caffeic acid | ChlE | β-secretase | AChE= 0.15 μM<br>BuChE= 0.36 μM<br>β-secretase = 10 μM | [39] |
| **33** | idin-2-yl) methyl) acridin-9-amine | Top I | Cytotoxicity | Top I= 1 μM<br>Cytotoxicity on K562 and HepG-2 cells at 2.517 and 10.73 μM | [40] |
| **34** | TAC- β-carboline | ChlE | β-amyloid | AChE= 63.2 nM<br>BuChE= 39.8 nM | [41] |
| **35** | TAC- Rhein | ChlE | β-amyloid | AChE= 27.3 nM<br>BuChE= 200 nM | [42] |
| **36** | TAC-CUM | ChlE | β-secretase | AChE= 35.7 nM<br>BuChE= 8.7 nM | [43] |
| **37** | TAC-Flurbiprofen | ChlE | β-amyloid | AChE= 19.3 nM<br>BuChE= 3.7 nM | [44] |
| **38** | TAC- Benzothiazole | AChE | β-amyloid | AChE= 0.34 μM | [45] |
| **39** | TAC- Huprine | ChE | β-secretase | AChE= 2.04 μM<br>BuChE= 86.8 μM | [46] |

| | | | | | |
|---|---|---|---|---|---|
| **40** | TAC-Caffeic acid | ChlE | β-amyloid | AChE= 0.3 nM<br>BuChE= 29.5 nM | [47] |
| **41** | TAC- Huprine | M1 muscarinic receptors | - | M1 receptor= 4.4 µM | [48] |
| **42** | TAC- Cystamine | ChlE | β-amyloid | AChE= 5 nM<br>BuChE= 4.23 nM | [49] |
| **43** | TAC- Nimodipine | ChlE | $Ca^{2+}$ channel | AChE= 5 µM<br>BuChE= 1 µM | [50] |
| **44** | TAC-TAC | ChlE | β-secretase | AChE= 16.5 nM<br>BuChE= 14.7 nM<br>β-secretase = 0.4 µM | [51] |
| **45** | TAC multimers | AChE | β-amyloid | AChE= 63 nM | [52] |
| **46** | 9-Aminoacridine | VEGFR-2 and Src | - | VEGFR-2 and Src at inhibition rates of 44% and 8% at 50 µM | [53] |
| **47** | AC- Oxoisoaporphine | ChE | β-amyloid | AChE= 3.4 nM<br>BuChE= 110 nM | [54] |
| **48** | TAC- Melatonin | ChE | - | AChE= 0.008 µM<br>BuChE= 7.8 µM | [55] |
| **49** | Tetra-AC | Top II | Proteasome | Top II= 0.2 µM | [56] |
| **50** | Bis (7)- TAC | ChlE | - | AChE= 0.81 nM<br>BuChE= 5.66 nM | [57] |
| **51** | TAC- Huprine | ChlE | - | AChE= 0.29 µM<br>BuChE= 31.1 µM | [58] |
| **52** | AC-Thiadiazolidinone | AChE | - | AChE= 0.12 µM | [59] |
| **53** | Aminoacridine | AChE | β-amyloid | AChE= 20 pM | [60] |
| **54** | AC-carboxamide | Top I & II | - | Top I & II= 17 nM | [61] |

Complexes: TAC: Tacrine, CUM: Coumarin, AC: Acridine, hBIM: Hydroxyphenylbenzimidazole, BQCA: Benzyl quinolone carboxylic acid, HBP: Hydroxybenzoyl-pyridone.
Targets: HDACs: Histone deacetylase, Top II: Topoisomerase II, MAO-B: Monoamine oxidase B, GSK3α/β: Glycogen synthase kinase 3α/β, NOS: Nitric oxide synthase, ChlE: Cholinesterases, AChE: Acetylcholinesterase, BuChE: Butyrylcholinesterase, α-Gls: α-Glucosidase, α-Amy: α-Amylase, CYP450: Cytochrome P450.
Receptors: NMDA: N-methyl-d-aspartate receptors, EGFR: Epidermal growth factor receptor, VEGFR: Vascular endothelial growth factor receptors.
Diseases: AD, Alzheimer's disease, PD: Prion diseases.

## DISCUSSION

Multi-target drugs are typically known as compounds that are designed to interact with multiple targets of a specific disease or multiple active sites of a single target, leading to maximum selectivity for a single target. Therefore, a complex that simultaneously binds to the catalytic and the peripheral site of a target enzyme is also defined as multi-target agent. The main aim of designing such agents is to enhance the efficacy and potency of a drug against a specific target and to minimize the side effects.

### *Acridine hybrid complexes*

Acridine and its derivatives are one of the oldest classes of biologically active agents, which have been widely used with potential therapeutic effects in the treatment of a number of diseases including cancer, Alzheimer's and bacterial and protozoan infections [62]. Mechanism of their activity is mainly attributed to interaction with DNA and subsequent effects on related enzymes such as topoisomerases and other DNA-related biological processes [63]. Acridine drugs have a unique chemical property in which they can combine with various biologically active agents to acquire multifunctional properties, leading to improved functional outcomes. Although acridine alone (as monomer or multimers) or

its hybrid conjugates such as acridine- dimethyl-aminobenzoic acid, acridine- iodobenzoic acid, and acridine- dichloronicotinic acid can act as cholinesterase inhibitors, as part of their anti-Alzheimer's activity, its hybrid complexes such as acridine - amido-benzimidazole can also bind to topoisomerase and poly [ADP-ribose] polymerase 1 (PARP-1) for anticancer activity [19, 64]. Findings of the present review demonstrated that dual activity of multi-target acridine complexes could provide a potent anticancer agent towards certain forms of tumor resistance, which are typically interfere with DNA synthesis and related enzymes such as inhibit topoisomerases and histone deacetylase [55].

***Tacrine derivatives***

Tacrine and its hybrid complexes are centrally acting AChE inhibitors that have been used as a respiratory stimulant, and for the treatment of mild to moderate symptoms of Alzheimer's disease and other central nervous system disorders [54]. The mechanism of action of tacrine is not fully understood, but it is suggested that tacrine with anti-ChE activity binds to ChE, leading to reversibly inactivation of this enzyme, which further inhibits the hydrolysis of acetylcholine, resulting in the accumulation of acetylcholine at cholinergic synapses [3۲]. In the present review, it was found that derivatization of tacrine with amine-containing drugs, oxoisoaporphine, donepezil, and hydroxyphenylbenzimidazole may more effectively inhibit AchE, which may be partly due to the enhanced efficiency of blood-brain barrier penetration. Evidence also suggests that abnormal intracellular $Ca^{2+}$ concentrations may be involved in Alzheimer's disease [٦5]. Therefore, the use of calcium blockers in conjugation with tacrine can play a vital role in prevention of its excessive entry and the cell survival. In this respect, Nimodipine in conjugation with tacrine can cross the blood-brain barrier and showed $Ca^{2+}$ channel blocking effect at submicromolar concentration [61,57].

## CONCLUSIONS

Findings showed that these hybrid complexes could inhibit AChE, BuChE, monoamine oxidase, and amyloid-β aggregation that is important for treatment of Alzheimer's. Also, acridine-based complexes most commonly showed anticancer effect through directly binding to DNA or enzymes such as topoisomerases. Also, some of them demonstrated kinase inhibitory effect, leading to anticancer effect. Findings suggested that development of multi-target drugs can be a potential approach for treatment of several multi-factorial diseases.

The findings of the study revealed that these hybrid complexes have the ability to inhibit several enzymes and processes that are crucial for the treatment of Alzheimer's disease. Specifically, they showed inhibitory effects on acetylcholinesterase (AChE), butyrylcholinesterase (BuChE), monoamine oxidase, and amyloid-β aggregation. This is significant as these targets are closely associated with the pathology and progression of Alzheimer's disease.

Furthermore, acridine-based complexes, in particular, demonstrated notable anticancer effects. They achieved this by directly binding to DNA or enzymes such as topoisomerases. Additionally, some of these complexes exhibited kinase inhibitory effects, leading to their anticancer properties. This highlights their potential as therapeutic agents for cancer treatment.

Overall, these findings suggest that the development of multi-target drugs could be a promising approach for the treatment of complex and multifactorial diseases. By targeting multiple pathways and processes simultaneously, these drugs may offer more effective treatment options compared to single-target therapies.

Looking towards the future, further research and development in this field may lead to the design and synthesis of more potent and selective hybrid complexes with enhanced therapeutic efficacy. The exploration of their mechanisms of action and optimization of their pharmacokinetic properties could pave the way for the development of novel drugs for Alzheimer's disease, cancer, and other challenging diseases.

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***Conflicts of Interest***

The authors declare no conflicts of interest.

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