ANNISHA NOOR DIENNA

BAHASA INGGRIS

PROFESI

Research Gap?

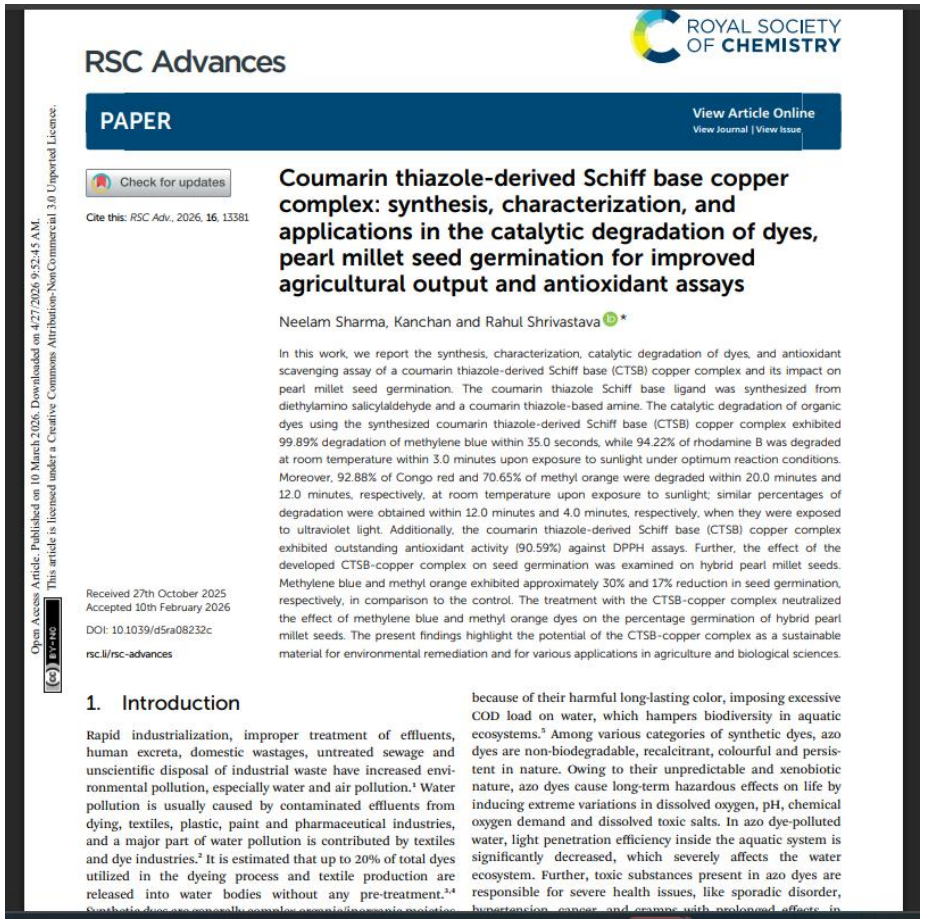
Kekosongan / keterbatasan dalam penelitian sebelumnya yang membuka peluang penelitian baru

Fungsinya adalah menjadi dasar kebaruan (novelty), menjamin orisinalitas penelitian, dan memberikan arah eksplorasi untuk pengembangan ilmu baru

METODE PRAKTIS

Step 1
Cari “Apa yang SUDAH ADA”

Identifikasi
•Penelitian sebelumnya fokus ke apa?



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Coumarin thiazole-derived Schiff base copper complex: synthesis, characterization, and applications in the catalytic degradation of dyes, pearl millet seed germination for improved agricultural output and antioxidant assays

Neelam Sharma, Kanchan and Rahul Shrivastava *

In this work, we report the synthesis, characterization, catalytic degradation of dyes, and antioxidant scavenging assay of a coumarin thiazole-derived Schiff base (CTSB) copper complex and its impact on pearl millet seed germination. The coumarin thiazole Schiff base ligand was synthesized from diethylamino salicylaldehyde and a coumarin thiazole-based amine. The catalytic degradation of organic dyes using the synthesized coumarin thiazole-derived Schiff base (CTSB) copper complex exhibited 99.89% degradation of methylene blue within 35.0 seconds, while 94.22% of rhodamine B was degraded at room temperature within 3.0 minutes upon exposure to sunlight under optimum reaction conditions. Moreover, 92.88% of Congo red and 70.65% of methyl orange were degraded within 20.0 minutes and 12.0 minutes, respectively, at room temperature upon exposure to sunlight; similar percentages of degradation were obtained within 12.0 minutes and 4.0 minutes, respectively, when they were exposed to ultraviolet light. Additionally, the coumarin thiazole-derived Schiff base (CTSB) copper complex exhibited outstanding antioxidant activity (90.59%) against DPPH assays. Further, the effect of the developed CTSB-copper complex on seed germination was examined on hybrid pearl millet seeds. Methylene blue and methyl orange exhibited approximately 30% and 17% reduction in seed germination, respectively, in comparison to the control. The treatment with the CTSB-copper complex neutralized the effect of methylene blue and methyl orange dyes on the percentage germination of hybrid pearl millet seeds. The present findings highlight the potential of the CTSB-copper complex as a sustainable material for environmental remediation and for various applications in agriculture and biological sciences.

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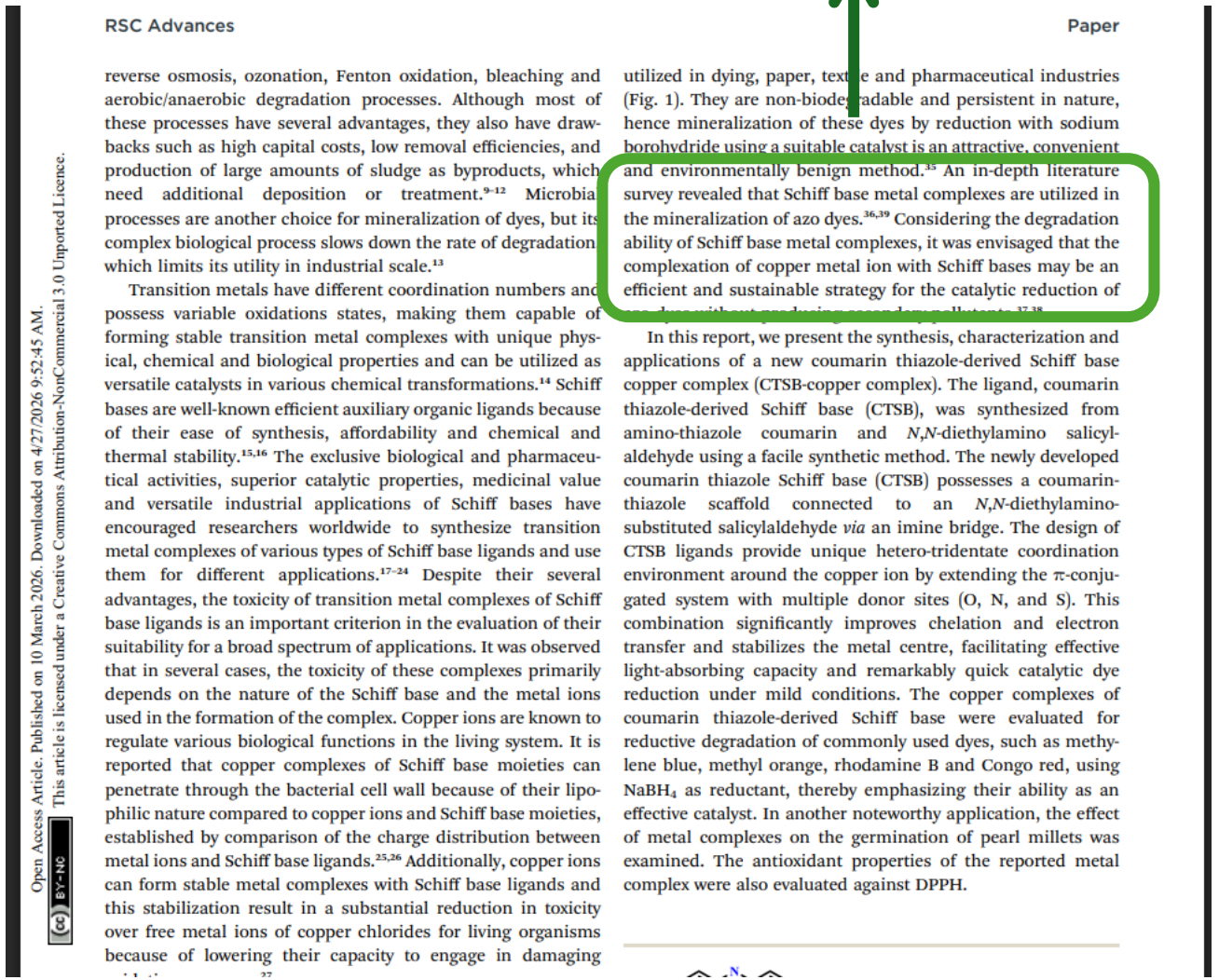
1. Introduction

Rapid industrialization, improper treatment of effluents, human excreta, domestic wastages, untreated sewage and unscientific disposal of industrial waste have increased environmental pollution, especially water and air pollution.[1] Water pollution is usually caused by contaminated effluents from dying, textiles, plastic, paint and pharmaceutical industries, and a major part of water pollution is contributed by textiles and dye industries.[2] It is estimated that up to 20% of total dyes utilized in the dyeing process and textile production are released into water bodies without any pre-treatment.[3,4] Synthetic dyes are generally considered as xenobiotic organic aromatic compounds because of their harmful long-lasting color, imposing excessive COD load on water, which hampers biodiversity in aquatic ecosystems.[5] Among various categories of synthetic dyes, azo dyes are non-biodegradable, recalcitrant, colourful and persistent in nature. Owing to their unpredictable and xenobiotic nature, azo dyes cause long-term hazardous effects on life by inducing extreme variations in dissolved oxygen, pH, chemical oxygen demand and dissolved toxic salts. In azo dye-polluted water, light penetration efficiency inside the aquatic system is significantly decreased, which severely affects the water ecosystem. Further, toxic substances present in azo dyes are responsible for severe health issues, like sporadic disorder, hypertension, cancer and cramps with prolonged effects in

Sudah ada → katalis degradasi dye



reverse osmosis, ozonation, Fenton oxidation, bleaching and aerobic/anaerobic degradation processes. Although most of these processes have several advantages, they also have drawbacks such as high capital costs, low removal efficiencies, and production of large amounts of sludge as byproducts, which need additional deposition or treatment.[9–12] Microbial processes are another choice for mineralization of dyes, but its complex biological process slows down the rate of degradation which limits its utility in industrial scale.[13]

Transition metals have different coordination numbers and possess variable oxidations states, making them capable of forming stable transition metal complexes with unique physical, chemical and biological properties and can be utilized as versatile catalysts in various chemical transformations.[14] Schiff bases are well-known efficient auxiliary organic ligands because of their ease of synthesis, affordability and chemical and thermal stability.[15,16] The exclusive biological and pharmaceutical activities, superior catalytic properties, medicinal value and versatile industrial applications of Schiff bases have encouraged researchers worldwide to synthesize transition metal complexes of various types of Schiff base ligands and use them for different applications.[17–24] Despite their several advantages, the toxicity of transition metal complexes of Schiff base ligands is an important criterion in the evaluation of their suitability for a broad spectrum of applications. It was observed that in several cases, the toxicity of these complexes primarily depends on the nature of the Schiff base and the metal ions used in the formation of the complex. Copper ions are known to regulate various biological functions in the living system. It is reported that copper complexes of Schiff base moieties can penetrate through the bacterial cell wall because of their lipophilic nature compared to copper ions and Schiff base moieties, established by comparison of the charge distribution between metal ions and Schiff base ligands.[25,26] Additionally, copper ions can form stable metal complexes with Schiff base ligands and this stabilization result in a substantial reduction in toxicity over free metal ions of copper chlorides for living organisms because of lowering their capacity to engage in damaging

utilized in dying, paper, textile and pharmaceutical industries (Fig. 1). They are non-biodegradable and persistent in nature, hence mineralization of these dyes by reduction with sodium borohydride using a suitable catalyst is an attractive, convenient and environmentally benign method.[35] An in-depth literature survey revealed that Schiff base metal complexes are utilized in the mineralization of azo dyes.[36,39] Considering the degradation ability of Schiff base metal complexes, it was envisaged that the complexation of copper metal ion with Schiff bases may be an efficient and sustainable strategy for the catalytic reduction of

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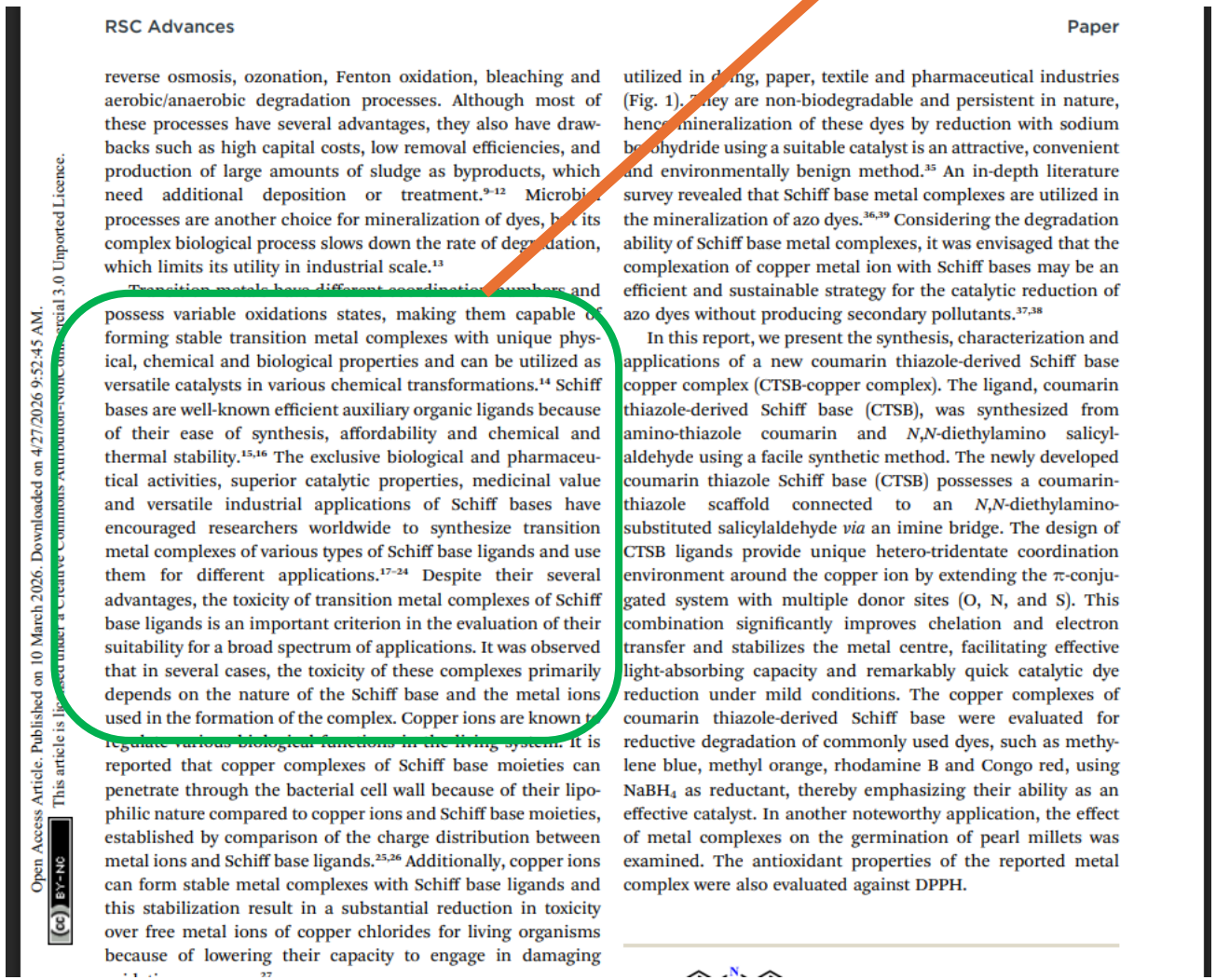
Step 2
“Cari fungsi lain yang disebut”

“biological and pharmaceutical activities…”

“Selain fungsi utama, senyawa ini bisa ngapain lagi?”



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Untuk MENEMUKAN POTENSI yang belum dimanfaatkan

Artinya:

Kita ingin melihat apakah suatu sistem/senyawa punya **kemampuan lain** yang belum dijadikan fokus utama penelitian.

1. Menemukan peluang penelitian baru
2. Melihat peluang integrasi
3. Jadi sumber research gap

Step 3
Cek apakah sudah DIGABUNG

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Fungsi KATALITIK

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Fungsi antioksidan

sistem ini punya multi-potensi, tetapi Tidak ada kalimat yang mengatakan kedua fungsi ini dirancang sebagai satu sistem terpadu”

***Research Gap*?**

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Penelitian ini mengevaluasi beberapa fungsi dari satu material, namun belum mengintegrasikannya secara konseptual

BUKAN:

“Penelitian ini mengintegrasikan fungsi katalitik dan biologis”

Analogi

- Satu alat:
  - bisa motong kayu
  - bisa buka botol

Tapi:

- tidak dirancang sebagai multi tool
- hanya diuji satu-satu

Maka gap:

“Integrasi fungsi katalitik dan biologis masih terbatas”

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Discovery of novel hybrids of coumarin and quinoline as potential anti-Alzheimer's disease agent

Shun Li [1], Xinrui Li [1], Shuanglong Li, Daoyuan Chen [*], Chunli Xia [*]

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ARTICLE INFO

Keywords:
Alzheimer's disease
Multi-target-directed ligands
Coumarin-quinoline hybrid
Amyloid-β protein
β-secretase 1

ABSTRACT

The multifaceted nature of Alzheimer's disease (AD) spurred growing interest in developing multi-target-directed ligands (MTDLs) for its prevention and treatment. Coumarin and quinoline scaffolds, recognized for their broad spectrum of AD-related biological activities including amyloid-β (Aβ) aggregation regulation, cholinesterase (ChE) inhibition, β-secretase 1 (BACE1) inhibition and neuroprotection, were identified as potential building blocks. Here in this study, 24 novel coumarin-quinoline hybrid compounds were rationally designed and synthesized. Inhibition studies targeting Aβ, ChE and BACE1 identified compound **B8** as a promising lead compound. **B8** exhibited effective binding to Aβ, and significantly attenuated Aβ-induced SH-SY5Y cell death by lowering oxidative stress and decreasing cellular apoptosis. Crucially, **B8** demonstrated excellent blood-brain barrier (BBB) permeability, and intragastric administration of **B8** to 7-month-old APP/PS1 transgenic mice resulted in improved cognitive function. This improvement was supported by the protection of hippocampal and cortical neurons from necrosis, attenuation of oxidative stress and inflammation in these brain regions, as well as a reduction in Aβ deposition. These findings highlight the potential of coumarin-quinoline hybrids as a novel class

Apa yang SUDAH ADA

1. Introduction

Alzheimer's disease (AD), characterized by progressive neurodegeneration, stands as the predominant cause of dementia among the elderly population. Pathological mechanisms of AD involve several key factors: abnormal accumulation of amyloid-beta (Aβ), disturbances in cholinergic neurotransmission, oxidative stress, and neuroinflammation.[1–4] Crucially, these factors are interconnected within a self-perpetuating neurotoxic cascade. For example, β-site amyloid precursor protein-cleaving enzyme 1 (BACE1)-mediated amyloid precursor protein (APP) cleavage increases the formation of soluble Aβ oligomers and fibrils, thereby promoting Aβ deposition and exacerbating neurotoxicity linked to oxidative stress. Excess reactive oxygen species (ROS), in turn upregulate BACE1 activity and accelerate abnormal tau phosphorylation and aggregation. Concurrently, hyperactive cholinesterases (ChEs) reduce synaptic acetylcholine (ACh) level, weakening cholinergic anti-inflammatory and neuroprotective regulation while also promoting Aβ aggregation, thus forming a vicious cycle.[5–8] Conventional pharmacological interventions focusing on singular pathological aspects, such as acetylcholinesterase inhibitors or *N*-methyl-D-aspartate (NMDA) receptor antagonists, have exhibited constrained clinical effectiveness, attributed to multifactorial etiology of the disease.[9] This has spurred an growing interest in the development of multi-target-directed ligands (MTDLs) as a more holistic therapeutic strategy.[10,11]

The persistent lack of effective therapeutic interventions for AD has driven extensive investigation into various natural and synthetic scaffolds.[12] Among these, coumarin and quinoline have emerged as promising scaffold for AD drug discovery. Derivatives of both scaffolds display a broad spectrum of AD-related biological activities, including inhibition of Aβ aggregation, modulation of ChEs activity, and suppression of BACE1 and monoamine oxidase (MAO-A/B). Representative reported bioactive coumarins include AP2238 and S-14b,[13–16] and quinoline-based agents like tacrine, clioquinol (CQ), and tacrine-8-hydroxyquinoline hybrids (Fig. 1).[17–20] Additionally, both coumarin and quinoline scaffolds offer high synthetic tunability: the facile introduction of diverse substituents or linkers allows fine-tuning of lipophilicity, conformation, and interactions with target proteins, thereby enabling optimization of compounds' activity, selectivity, and

Penelitian sebelumnya:

- fokus **single-target**
- contoh: AChE inhibitor, NMDA, dll

Fungsi lain yang disebut

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Ada fungsi lain = **multi-target biological activities (Aβ, ChE, BACE1, neuroprotection)**

Apakah sudah DIGABUNG?

1. Introduction

Alzheimer's disease (AD), characterized by progressive neurodegeneration, stands as the predominant cause of dementia among the elderly population. Pathological mechanisms of AD involve several key factors: abnormal accumulation of amyloid-beta (Aβ), disturbances in cholinergic neurotransmission, oxidative stress, and neuroinflammation.[1–4] Crucially, these factors are interconnected within a self-perpetuating neurotoxic cascade. For example, β-site amyloid precursor protein-cleaving enzyme 1 (BACE1)-mediated amyloid precursor protein (APP) cleavage increases the formation of soluble Aβ oligomers and fibrils, thereby promoting Aβ deposition and exacerbating neurotoxicity linked to oxidative stress. Excess reactive oxygen species (ROS), in turn upregulate BACE1 activity and accelerate abnormal tau phosphorylation and aggregation. Concurrently, hyperactive cholinesterases (ChEs) reduce synaptic acetylcholine (ACh) level, weakening cholinergic anti-inflammatory and neuroprotective regulation while also promoting Aβ aggregation, thus forming a vicious cycle.[5–8]Conventional pharmacological interventions focusing on singular pathological aspects, such as acetylcholinesterase inhibitors or *N*-methyl-D-aspartate (NMDA) receptor antagonists, have exhibited constrained clinical effectiveness, attributed to multifactorial etiology of the disease.[9] This has spurred an growing interest in the development of multi-target-directed ligands (MTDLs) as a more holistic therapeutic strategy.[10,11]

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Considering the potential synergistic benefits of coupling coumarin and quinoline, here we undertook the rational design of a series of coumarin-quinoline hybrids, varying the linker length and sites between the two pharmacophores. This hybridization strategy aimed to develop MTDLs capable of simultaneously modulating multiple pathological hallmarks of AD (Fig. 2). A total of 24 coumarin-quinoline hybrids were synthesized via a streamlined two-step route and were then subjected to comprehensive in vitro inhibition evaluation against Aβ, ChE, and BACE1, alongside assessment of their BBB permeability using Parallel Artificial Membrane Permeation Assay (PAMPA). An optimal candidate, termed as **B8**, was selected for further mechanistic studies: its interaction with Aβ and its ability to protect SH-SY5Y cells from Aβ-induced cytotoxicity were examined. Finally, the in vivo efficacy of **B8** was assessed by behavioral testing and histopathological analysis of hippocampal neurons in an APP/PS1 transgenic AD mouse model.

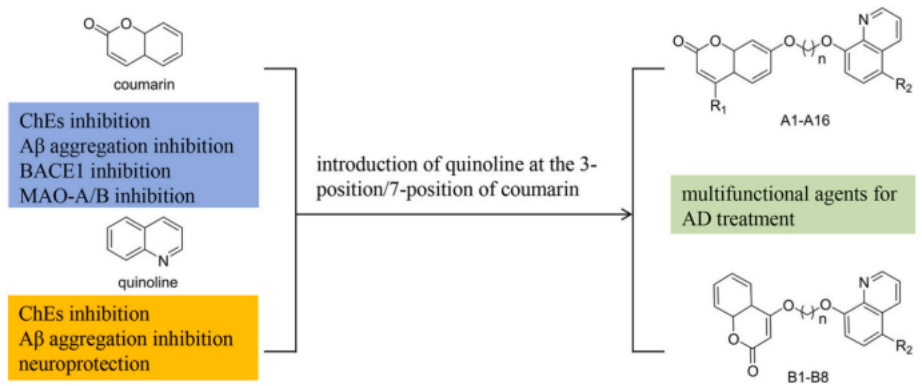

Fig. 2. Design strategies for new compounds **A1–A16** and **B1–B8.**

- **memang dirancang dari awal untuk digabung**
- bukan sekadar diuji terpisah

- SUDAH DIGABUNG (secara konsep dan desain → MTDL)

Research gap:

Strategi hybrid coumarin–quinoline sebagai multi-target masih belum banyak dieksplorasi dan belum optimal

TUGAS
CARI RESEARCH GAP DARI JURNAL BERIKUT
NO ABSEN 1-5 JURNAL 1
ABSEN 6-10 JURNAL 2
ABSEN 11-15 JURNAL 3
ABSEN 16-20 JURNAL 4
ABSEN 21-25 JURNAL 5
ABSEN 26-30 JURNAL 7
ABSEN 31-43 JURNAL 8