ACS Medicinal Chemistry Letters

In This Issue

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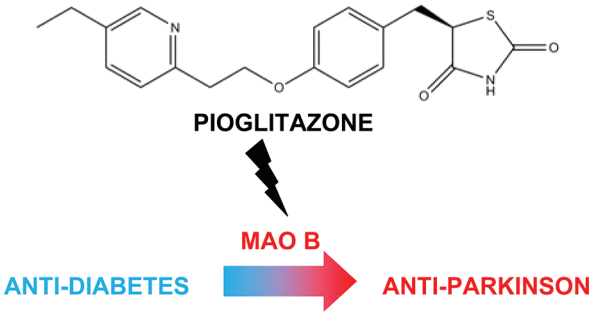
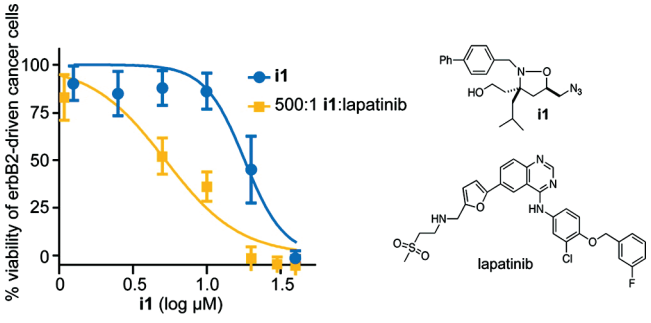
REPURPOSING ANTIDIABETIC DRUG FOR PARKINSON'S DISEASE



Neurodegenerative disease incidence has been on the rise, whereas there remains a dearth in approved therapies. In particular, Parkinson's disease continues to be a progressive disorder despite new targets, innovative clinical trial designs, and novel biomarkers for assessment. Currently, there are seven FDA-approved antimonoamine oxidase drugs for the treatment of depression and Parkinson's disease.

In this issue, Binda et al. (DOI: 10.1021/ml200196p) describe the mechanism of action of antidiabetic drug pioglitazone against human monoamine oxidase B to retard the progression of Parkinson's disease. The study shows pioglitazone to be a specific and reversible inhibitor with better selectivity than other glitazone inhibitors. This research further supports the emerging trend of "repurposing" known compounds for indications and diseases.

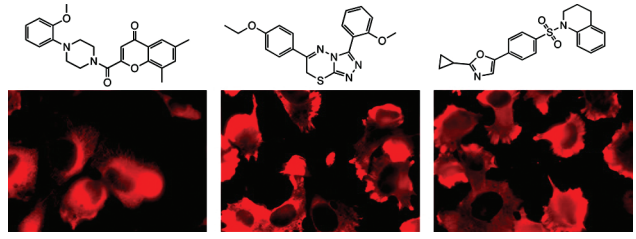
COMBINATION STRATEGY AGAINST CANCER CELLS



Abnormal functions of transcriptional activators are linked to the progression of cancer. However, while the transcription process provides numerous targets for intervention, direct transcriptional inhibitors suffer from modest potency and poor selectivity. One such target is ErbB2, a trans-membrane tyrosine kinase that can be overexpressed in breast cancers.

Here, Taylor et al. (DOI: 10.1021/ml200186r) present the combination of a transcriptional inhibitor with existing therapeutic agents that act upstream or downstream of the ErbB2 pathway in a multipronged attack on ErbB2-over-expressing cancer cells. This method synergistically increases the inhibitor activity to nanomolar levels and improves selectivity for cancer cells relative to healthy cells up to 35-fold. Significantly, this study highlights the combination strategy of using an enzyme inhibitor with a broadly toxic protein−protein interaction inhibitor.

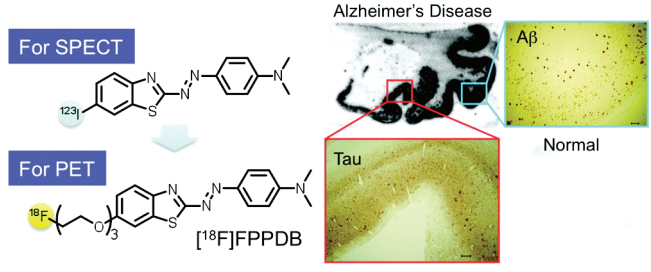
SYNTHETIC SMALL MOLECULES ANSWERING DRUG RESISTANCE QUESTIONS



Microtubules are validated targets for anticancer drug discovery. Eight natural product-derived microtubule inhibitors are currently in clinical use and are used in chemotherapy treatments. However, poor solubility, synthetic manageability, and serious side effects of natural product inhibitors remain a problem. Simple synthetic compounds can serve as invaluable scaffolds for lead discovery if they have sufficiently high potency, because they are more readily modified than complex natural products.

In this issue, Yang et al. (DOI: 10.1021/ml200195s) report the identification of three small organic molecules that are structurally simple but highly efficient in cancer cell killing and that target microtubules. One compound stabilizes microtubules, and another destabilizes them. The third compound neither stabilizes nor destabilizes microtubules, suggesting indirect association. Because these three modulators elicit cell death via different mechanisms, they might reveal additional factors that are related to drug resistance of microtubule inhibitors.

PROBING ALZHEIMER'S DISEASE BRAINS



Alzheimer's disease is the most common form of dementia, affecting more than 35 million people worldwide. To date, the pathogenesis of Alzheimer's disease is not yet fully understood, and there are no therapies available for this progressive brain disorder. In spite of recent developments, definite disease diagnosis can only be delivered postmortem based on histopathological examination. However, accumulation of amyloid plaques and neurofibrillary tangles is seen as the pathological trademarks of this disease.

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While significant effort has been devoted to the development of probes for in vivo imaging of senile plaque formation, there are currently only a few reports on selective detection probes for neurofibrillary tangles. In this issue, Matsumura et al. (DOI: 10.1021/ml200230e) describe the synthesis and evaluation of a compound probe for imaging neurofibrillary tangles in brains with Alzheimer's disease. Compound optimization could lead to a suitable imaging probe with selective affinity for neurofibrillary tangles, which may be useful in early diagnosis of the disease.

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