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Synthesis of novel imidazopyridines and their biological evaluation as potent anticancer agents: A promising candidate for glioblastoma

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ABSTRACT

Novel imidazopyridine derivatives were synthesized according to a very simple protocol and then subjected to cytotoxicity testing against LN-405 cells. Two of the compounds exhibited antiproliferative effects on LN-405 cells at 10 and 75 μM and were selected as lead compounds for further study. Safety experiment for lead compounds on WS1 was carried out and IC_{50} values were calculated as 480 and 844 μM. LN-405 cell line were incubated with the lead compounds and then tested for DNA damage by comet assay and effects on cell cycle using flow cytometry. The results of these two tests showed that both lead compounds affected the G0/G1 phase and did not allow the cells to reach the synthesis phase. The log BB (blood–brain barrier) and Caco-2 permeability of the synthesized molecules were calculated and it was shown that imidazopyridine derivatives taken orally are likely to pass through gastrointestinal membrane and the blood–brain barrier.

Imidazopyridine is one of the most important structural skeletons in the area of natural and pharmaceutical products owing to the broad biological activities of imidazopyridines, such as agents for lung,[1] prostate,[2,3] and breast cancer,[4] tuberculosis treatment,[5] or inhibitors of glycogen synthase kinase-3β (GSK-3)[6] and protein kinase B, which functions as a key signaling node in cell proliferation.[7] Furthermore, some clinically used drugs are based on an imidazopyridine scaffold, such as zolpidem, alpidem, olprinone, zolimidine, and necopidem (Fig. 1).

Gliomas account for approximately 30% of all central nervous system tumors, with glioblastoma being the most aggressive and common type of malignant brain tumor, accounting for approximately 50% of all gliomas.[8] The standard treatment for glioblastoma patients is currently surgical resection followed by radiotherapy and/or chemotherapy. Chemotherapy is clearly one of the most important treatments for glioblastoma and temozolomide is the most important chemotherapeutic agent. Although surgery, radiotherapy, and chemotherapy are applied widely, in people who suffer from glioblastoma, initial or acquired drug resistance can occur. The development of chemotherapeutic drug resistance in cancer therapy is an important point that should be considered in the development of new drugs. Other chemotherapeutic agents, such as carmustine and lomustine, are also used clinically. Despite treatment options involving chemotherapeutic agents and/or radiotherapy, glioblastoma remains an incurable cancer.[9,10] Thus, numerous investigations are underway to find a cure for glioblastoma.[11–13]

Despite advances in treatment strategies, novel imidazopyridine derivatives might make good candidates for alternative therapeutic

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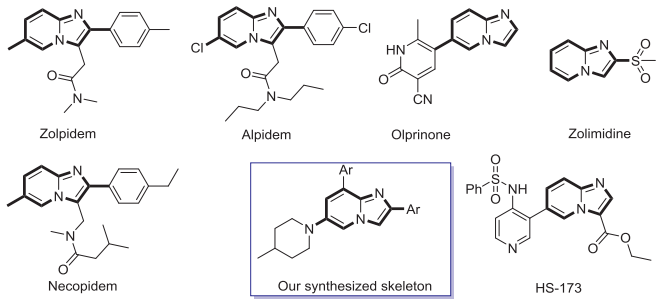
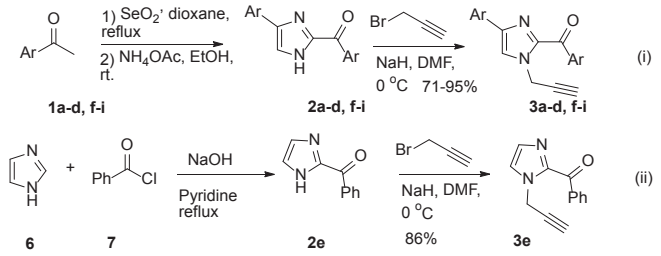
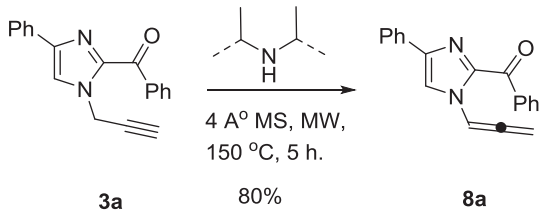


Fig. 1. Clinically used imidazopyridines and our synthesized skeleton.



Scheme 1. Synthesis of intermediates (synthesis of **3e** was carried out using a slightly modified method, as detailed in the Supporting Information).



Scheme 3. Reaction between *N*-propargyl imidazole and acyclic amine.

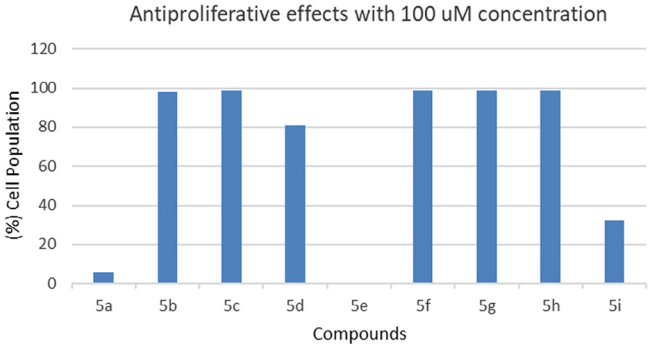
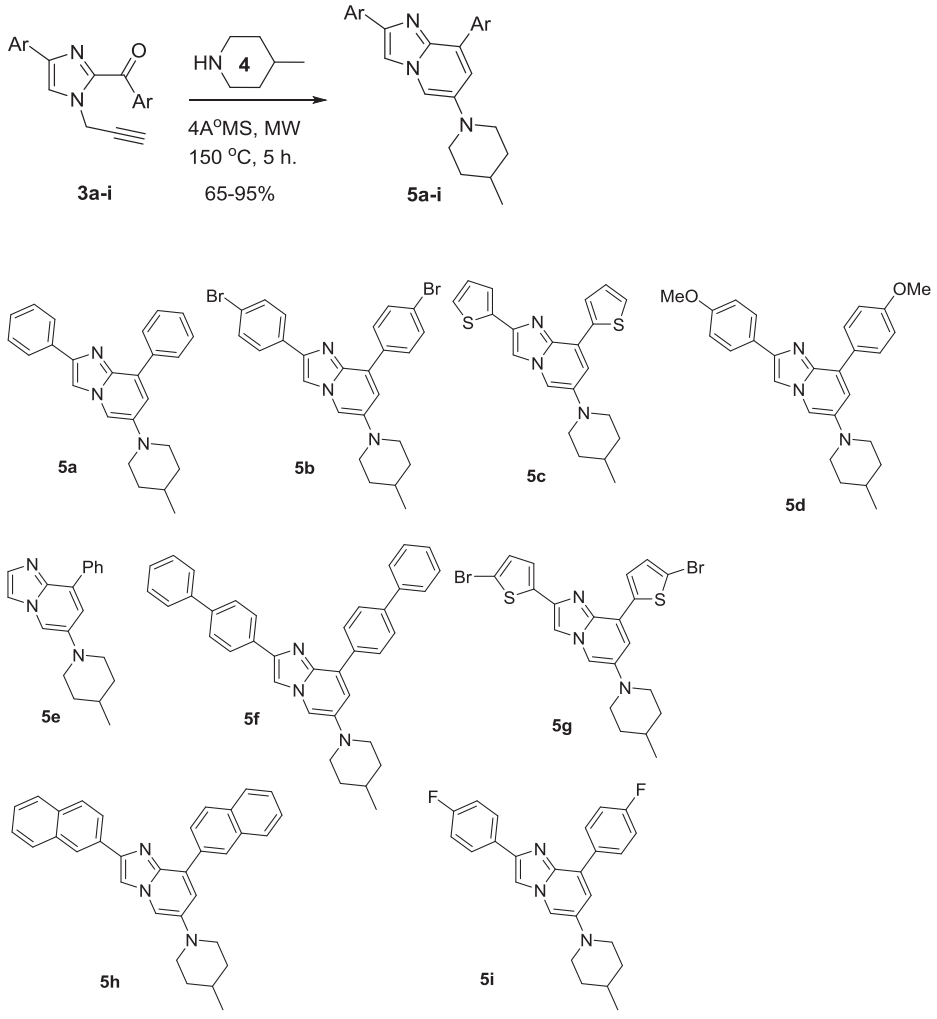


Fig. 2. Cell viability after incubating LN-405 cell lines with 100 μM concentrations of compounds **5a–i**.



Scheme 2. Synthesis of cyclic products.