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An efficient method to access spiro pseudoindoxyl ketones: evaluation of indoxyl and their *N*-benzylated derivatives for inhibition of the activity of monoamine oxidases†

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A simple, metal-free approach was developed to obtain novel pseudoindoxyl derivatives. The reaction was mediated by *t*BuOK on tetrahydrocarbazole **8** in dimethyl sulfoxide (DMSO) at room temperature through the hydroxylation of the indole double bond and a subsequent pinacol-type rearrangement. Spiro pseudoindoxyl compounds and their *N*-benzylated derivatives were assessed for their inhibitory activities against monoamine oxidase (MAO) enzymes. Based on half-maximal inhibitory concentration (IC_{50}) values, 13 compounds were found to have higher inhibitory activity against MAO-B than against MAO-A. With regard to MAO-B inhibition, **11f** showed the best inhibitory activity, with an IC_{50} value of 1.44 μM, followed by **11h** (IC_{50} = 1.60 μM), **11j** (IC_{50} = 2.78 μM), **11d** (IC_{50} = 2.81 μM), and **11i** (IC_{50} = 3.02 μM). Compound **11f** was a competitive inhibitor with a K_i value of 0.51 ± 0.023 μM. In a reversibility experiment using dialysis, **11f** showed effective recovery of MAO-B inhibition similar to that of safinamide. These experiments suggested that **11f** was a potent, reversible, and competitive inhibitor of MAO-B activity.

Introduction

Many alkaloids and biologically active substances have spiro core heterocyclic structures.[1] Indole is an important heterocyclic core found in many natural products. The pseudoindoxyl sub-structural motif is a unique subgroup of the class of oxygenated indoles among the many alkaloids.[1] The pesudoindoxyl structure (especially one with a spiro quaternary C2 carbon center) is an essential skeleton of indole alkaloids. The pseudoindoxyl alkaloids are an excellent example of a 2,2-disubstitution of a pseudoindoxyl compound, which is a preferred entity because it is a vital part of many important chemical compounds.[2] Examples of characteristic natural products with different biological activities in these spiro pseudoindoxyl compounds include duocarmycin c1/b2, brevianamide A (**4**), (+)-aristotelone (**3**), and diketopiperazine (**7a**) (Fig. 1).[3]

Moreover, the extracts of leaves of *Mitragyna speciosa* and flowering plants of the Rubiaceae family contain alkaloids with diverse structural motifs such as indole, indolenine, and spiro pseudoindoxyl. The natural product mitragynine undergoes rearrangement into mitragynine pseudoinoxyl after oxidation at an indole site to form 7-hydroxymitragynine, and all of them show powerful pain-relieving (or analgesic) effects and opioid activity. The mitragynine pseudoindoxyl acts non-selectively on mu- and delta-opioid receptors.[2h,j] These opioids have shown neuroprotective effects against hypoxia–ischemia injury and have a modulatory effect on the regulation of neurotransmitter chemicals. Recently, the importance of opioids receptors in modulation of more complicated neurodegenerative diseases (*e.g.*, Alzheimer's disease (AD)) has been shown.[2j,k] The biological activity of these alkaloids has yet to be explored. Because of the affinity of these compounds with opioid receptors, we were interested in evaluating the role of the pseudoindoxyl core in neurodegenerative diseases by inhibiting some of their target enzymes, such as monoamine oxidases (MAOs).

Furthermore, in recent years, these compounds have been demonstrated to have fascinating roles in terms of bioactivity, materials research, and optoelectronic research (Fig. 1).[4–7] For example, the lipid droplets in the 3T3L1 cell line and fat deposits in zebrafish were strained using these pseudoindoxyl derivatives without apparent toxicity up to 100 mM.[4] Alkyne-linked 2,2-disubstituted pseudoindoxyl oligomers have been

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