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Synthesis of 6,7,8,9-tetrahydropyrido[2,3-*b*]indolizine and 3,4-dihydro-2*H*-pyrido[2′,3′:4,5]pyrrolo[2,1-*b*][1,3]oxazine derivatives as new melatonin receptor ligands

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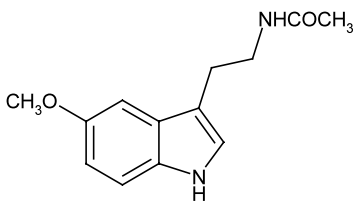
Abstract—The synthesis of new tricyclic azaindolic analogs of the hormone melatonin is described. Treatment of 1-(4-bromobutyl)pyrrolo[3,2-*b*]pyridine derivative with tributyltin hydride and AIBN results in radical cyclisation to give the 6,7,8,9-tetrahydropyrido[2,3-*b*]indolizine ring system. A new synthetic approach of pyridopyrrolo[2,1-*b*][1,3]oxazine moiety is shown to be accomplished readily from 1-(3-bromopropyl)-2-oxopyrrolopyridine derivative with sodium hydride in *N*,*N*-dimethylformamide.

Melatonin (*N*-acetyl-5-methoxytryptamine) is the principal hormone of the mammalian pineal gland and is released following a circadian rhythm with highest levels during the night.[1] In humans it has been suggested that melatonin have a variety of clinical uses in jet lag,[2] seasonal depression[3] and delayed sleep phase syndrome.[4] A number of reports have appeared describing effects of melatonin on the immune system[5] which suggests that melatonin has also immunomodulatory properties and might be useful as a coadjuvant in cancer therapy.[6]

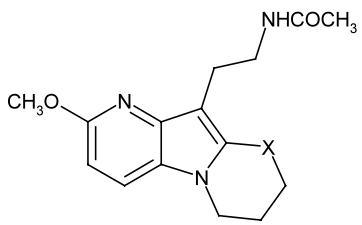
The important contribution for receptor binding by 2-substituents has been further investigated on the indole series and confirmed on a series of bioisosteric ligands.[7] Recently, in our research group, the synthesis of azaindole bioisoteres has been reported[8] and our efforts have now been directed towards the synthesis of tricyclic analogs obtained from azaindole moiety by introducing an alkyl or alkoxy chain in position 2 linked to *N*-1 position, while keeping the methoxy group and the ethylamido chain present in melatonin itself. We report here the synthesis of *N*-[2-(2-methoxy-6,7,8,9-tetrahydropyrido[2,3-*b*]indolizin-10-yl)ethyl]-acetamide **1a** and *N*-[2-(8-methoxy-3,4-dihydro-2*H*-pyrido-[2′,3′:4,5]pyrrolo[2,1-*b*][1,3]oxazin-10-yl)ethyl]-acetamide **1b**.

In view of our work on the synthesis of the tricyclic ring system, we were attracted by recent reports of radical cyclisations onto the indole 2-position.

5-Methoxy-1*H*-pyrrolo[3,2-*b*]pyridine **2** was prepared by the method of Makosza et al.,[9] which consists of the



Melatonin



1a, X = CH_2
1b, X = O

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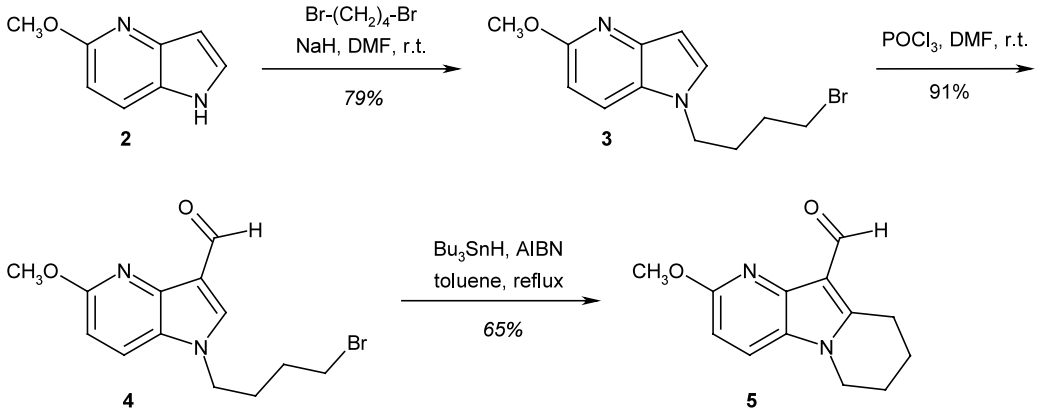
cyanomethylation of 5-nitro-2-methoxypyridine via vicarious nucleophilic substitution of hydrogen, followed by catalytic hydrogenation using palladium on charcoal. Alkylation of the 5-methoxy-1*H*-pyrrolo[3,2-*b*]-pyridine **2** with the 1,4-dibromobutane using sodium hydride in *N*,*N*-dimethylformamide gave the corresponding 1-(4-bromobutyl)-5-methoxy-1,3-dihydro-2*H*-pyrrolo[3,2-*b*]pyridin-2-one **3** in 79%. Formylation of the latter under Vilsmeier–Haack conditions provided the desired substrate for the radical cyclisation in 91%. The cyclisation reaction was carried out by slow addition of tributyltin hydride and azobisisobutyronitrile to compound **4** in refluxing toluene and furnished the expected tricyclic ring system in 65% yield. Moody and Norton[10] have shown radical cyclisation of alkyl radicals to the 2-position of indole-3-carbaldehydes. Our synthetic approach was based on the formation of the 6,7,8,9-tetrahydropyrido[3,2-*b*]indolizine moiety by intramolecular radical cyclisation from 5-methoxy-4-azaindole **2**, as shown in Scheme 1.

To develop new tricyclic melatonin analogs, we wanted to verify the effect on binding caused by incorporating the oxygen atom within a six-membered ring as in **7**. To our knowledge the only reported methods for the elaboration of the pyridopyrrolo[2,1-*b*][1,3]oxazine skeleton consists of the treatment of a pyrrolopyridine-3-carboxylate derivative with *N*-chlorosuccinimide and 3-bromopropanol in chloroform, followed by cyclisation with potassium carbonate in acetone without prior isolation of the intermediate halo ether.[11] We now describe a novel synthetic approach to the pyrido pyrrolo[2,1-*b*][1,3]oxazine ring system which was prepared by an intramolecular cyclisation via an *O*-alkylation of 1-(3-bromopropyl)-2-oxopyrrolopyridine **6** with sodium hydride in *N*,*N*-dimethylformamide (Scheme 2) to provide **7** in 75% yield.

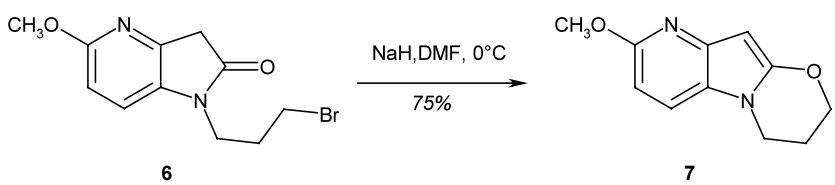
N-Alkylation of **2** with sodium hydride and 1-benzyloxy-3-bromopropane in *N*,*N*-dimethylformamide gave the required 1-[3-(benzyloxy)propyl]pyrrolopyridine **8** in 95% yield, which was then converted to the 2-oxopyrrolopyridine derivative. First, we focused on the oxidation of pyrrolo-[3,2-*b*]pyridine following the procedure described by Marfat[12] for the conversion of 7-azaindole to 7-azaoxindole. Unfortunately, treatment of **8** with 3–4 equivalents of pyridinium bromide perbromide (PBPB) in *tert*-butyl alcohol furnished only the dibromide **9** in 94%. A solution to this problem was achieved with the oxidative method reported by Robinson et al.[13] Oxidative bromination of **8** with 4 equivalents of bromine in *tert*-butyl alcohol and water provided 25% of dibromide **10** and 50% of tribromide **11** (Scheme 3).

Treatment of the mixture **10** and **11** with an excess of zinc in acetic acid followed by cleavage of the benzyl ether by hydrogenation gave the alcohol **14** in 61% from **8**. Transformation of **14** into the corresponding bromide[14] was then accomplished using carbon tetrabromide and 1,2-bis(diphenylphosphino)ethane (DIPHOS) in methylene chloride followed by treatment with sodium hydride in *N*,*N*-dimethylformamide to provide the pyrido[2′,3′:4,5]pyrrolo[2,1-*b*][1,3]oxazine ring system in 75% yield. Formylation of compound **7** was accomplished by reaction with phosphorus oxychloride in *N*,*N*-dimethylformamide to yield the desired aldehyde **15** in 86% (Scheme 4).

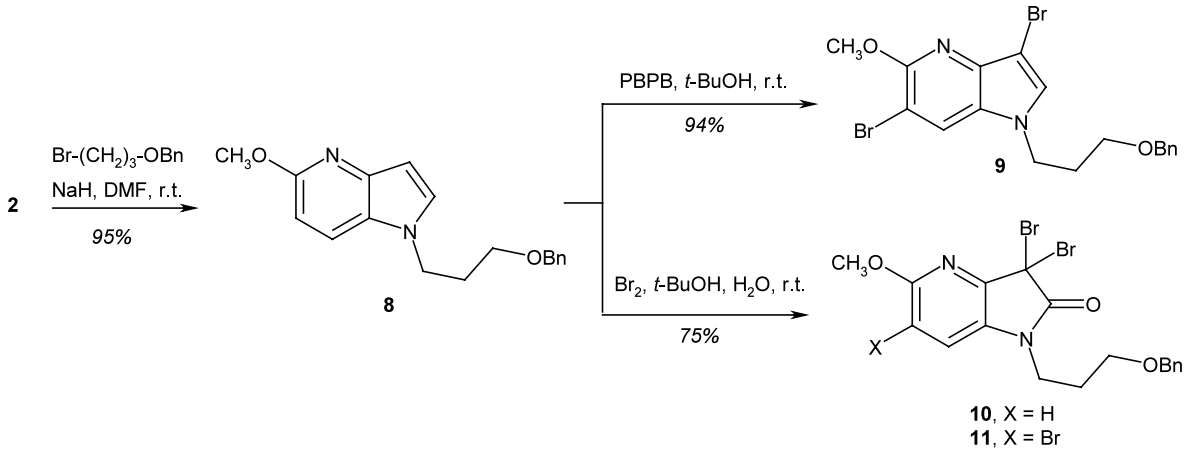
The target derivatives **1a** and **1b** were prepared according to the route shown in Scheme 5.[8] The formyl derivatives **5** and **15** were condensed with nitromethane in the presence of a catalytic amount of ammonium acetate to afford the expected nitrovinyl products **16a** and **16b** by a Henry reaction. Reduction of the α,β-



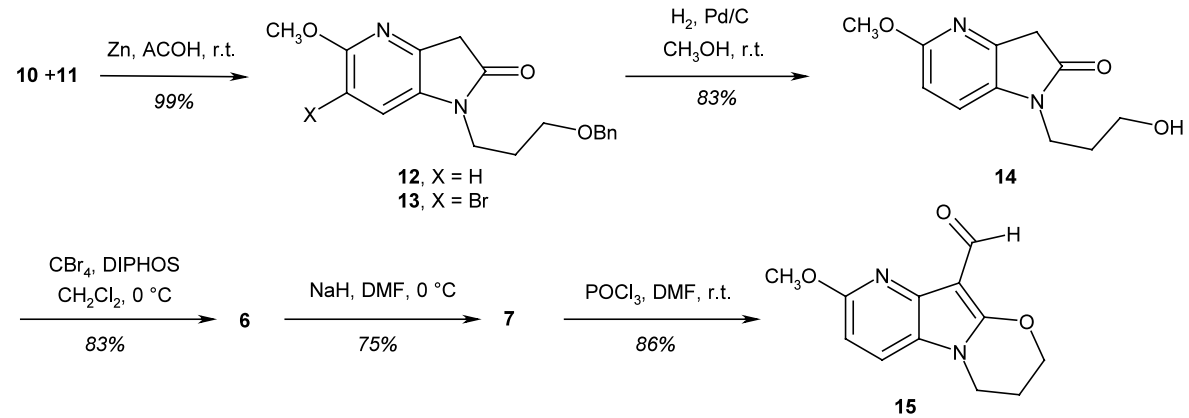
Scheme 1.



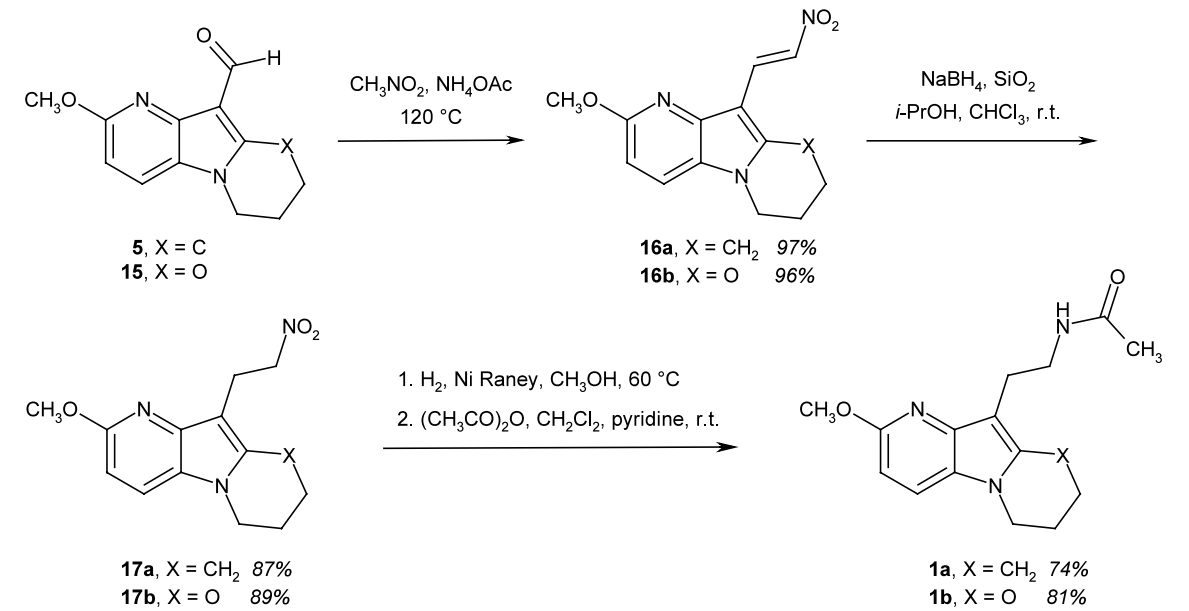
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

unsaturated nitroalkenes to the desired saturated amines was performed with sodium borohydride in a mixture of chloroform and isopropanol in the presence of silica gel, followed by hydrogenation over Raney nickel. The ethylamino function was acylated with acetic anhydride in a mixture of methylene chloride and pyridine to furnish the target compounds **1a**, **1b** in 74 and 81% yields, respectively.

In summary, two types of tricyclic azaindolic analogs of melatonin were investigated. Both reactions involved 5-methoxy-4-azaindole as common intermediates. The synthesis of 6,7,8,9-tetrahydro-pyrido[2,3-*b*]indolizine moiety was easily performed by intramolecular radical cyclisation. We have now developed a new procedure leading to the access of the pyridopyrrolo[2,1-*b*]-[1,3]oxazine skeleton.

Acknowledgements

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