Synthesis of Some New Linear and Chiral Macrocyclic Pyridine Carbazides as Analgesic and Anticonvulsant Agents

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A series of 2,6-disubstituted pyridine derivatives were prepared from 2,6-diacetylpyridine or 2,6-dicarbonyl pyridine dichloride as starting materials. Reaction of 2,6-diacetylpyridine **1** with hydroxylamine hydrochloride or different aromatic aldehydes afforded the corresponding 2,6-diacetylpyridine dioxime and 2,6-*bis*-[β-(2-thienyl)acryloyl]pyridine derivatives **2** and **3**, respectively. Additionally, $N^2,N^{2'}$-(pyridine-2,6-dicarbonyl)-L-amino acid hydrazides **5** were prepared starting from 2,6-dicarbonyl pyridine dichloride *via* the corresponding esters **4**. Compound **3** was reacted with hydroxylamine hydrochloride to afford the 2,6-*bis*-[β-(2-thienyl)acryloyl-oxime]-pyridine derivative **6**. Treatment of compounds **2** or **6** with phenyl isocyanate or phenyl isothiocyanate in refluxing dioxane gave the corresponding semicarbazide or thiosemicarbazide derivatives **7** and **8**, respectively. Their treatment with toluene-3,5-diisocyanate afforded the macrocyclic semicarbzides **9** and **10**, respectively. The chiral thiosemicarbazides **11a,b** were however, prepared by treating compounds **5a,b** with phenyl isothiocyanate followed by cyclization with sodium hydroxide (2N) yielding the triazoles **12a,b**. Finally, the hydrazides **5a,b** were treated with toluene-3,5-diisocyanate to afford the chiral macrocyclic tetrapeptide semicarbazides **13a,b** in reasonable yields, while the expected cyclic dipeptide **14** was not formed. The structure assignments of the new compounds were based on chemical and spectroscopic evidence.

The pharmacological screening showed that many of these compounds have good analgesic and anticonvulsant activities comparable to Voltarine® and Carbamazapine® used as reference drugs.

Key words: 2,6-Disubstituted Pyridine, Semicarbazides, Thiosemicarbazides, Chiral Macrocyclics, Anticonvulsants, Analgesics