10:15 Oral

Alkyl-nitroquipazine derivatives as serotonin transporter and 5-HT$_{1A}$ receptor ligands

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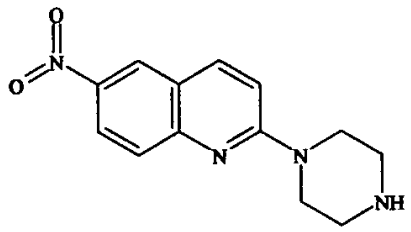
Inhibition of serotonin transporter (SERT) results in increased concentration of serotonin in the synaptic cleft. Drugs selectively inhibiting SERT have been used in many psychiatric disorders including depression, anxiety and obsessive compulsive disorder. 6-Nitroquipazine (**1**) is a potent SERT inhibitor with an affinity constant K_i = 0.17 nM [1] having higher affinity than clinically used inhibitors such as fluoxetine, fluvoxamine, paroxetine or sertraline [2].



1

Here we report the synthesis and pharmacological evaluation of a series of alkyl-nitroquipazine analogues as mixed 5-HT$_{1A}$ receptor/ SERT ligands. The compounds exhibited diversified 5-HT$_{1A}$ receptor and SERT affinity with saw-like affinity-alkyl chain length relationship. Some of them affected SERT functioning *in vitro* and *in vivo*.

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2. Lee B. S., Chu S., Lee B.-S., Chi D. Y., Chi D. Y., Song Y. S., Jin C. Synthesis and binding affinities of 6-nitroquipazine analogues for serotonin transporter. Part 2. Substituted 6-nitroquipazines. *Bioorg. Med. Chem. Lett.* **12** 811-815 (2002).

10:35 Oral

An efficient preparation of 3,5-bis(2-cyanoisopropyl) toluene-key intermediate in Anastrozole synthesis

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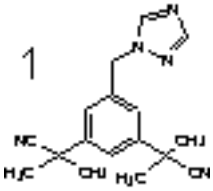
Anastrozole **1** is an anti-tumor drug for the treatment of breast cancer.

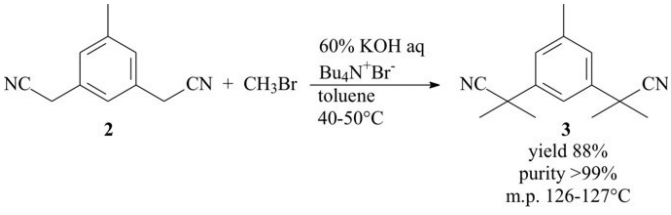
A key step in synthesis of **1** is exhaustive methylation of 3,5-bis(cyanomethyl)toluene **2**, whose elegant synthesis from commercially available 5-methylisophthalic acid was described recently[1].



Methylation of **2** was performed using sodium hydride in DMF as a base and methyl iodide[2] or methyl p-toluenesulphonate[1] as alkylating agents. Application of PTC (phase transfer catalysis, 50%NaOH in the presence of a catalyst - benzyltriethylammonium chloride) for this purpose was patented[3], however purity of product obtained precluded its use for synthesis of **1**[4]. This result is not surprising, because it is well known, that introduction of the second alkyl group to the 2-arylalkane nitriles under PTC conditions proceeds with difficulty.

We found recently, that PTC alkylation of phenylacetonitrile derivatives carried out in the presence of 60-75% aqueous KOH, instead of the typical 50% NaOH, provide substantial improvements in the overall yield and purity of products[5,6].

Application of such system to methylation of **2** (methyl bromide as an alkylating agent, 60% KOH aqueous solution as a base in the presence of 1 molar percent of tetrabutylammonium bromide, toluene as solvent) resulted in formation of tetramethylated product **3** in high isolated yield 88% and purity exceeding 99% after crystallization from ethanol.



2 **3**
yield 88%
purity >99%
m.p. 126-127°C