Microwave-assisted Synthesis of 4-imino-quinoxalin-3-amines

4-imino-quinoxalin-3-amines are versatile intermediates in the synthesis of [1,2,4]triazolo[1,5-\(c\)]quinazolin-2-amines. The common methods for the generation of 4-imino-quinoxalin-3-amines involve the reaction of imino-esters with hydrazine hydrate. These imino-esters can be envisaged as activated amides and are either generated by the reaction of 2-amino-arylnitriles with triethylamine tetrafluoroborate (Meerwein’s salt). Both methods have severe drawbacks: The first is limited by the poor availability of complex orthoesters, while the second is unreliable and involves the use of a highly cancerogenic reagent.

Our approach was to react hydrazine hydrate with non-activated N-acetylated 2-arylnitriles under microwave irradiation. The latter reagents are easily accessible by reacting 2-aminobenzonitrile with the corresponding acyl halogenides.

First experiments with benzoic acid derivatives (R = Ph, p-Br-Ph, p-F-Ph, and o-F-Ph) gave very encouraging results: After 10 minutes at 120°C under microwave irradiation with an 8-fold excess of hydrazine hydrate, the desired 4-imino-quinoxalin-3-amines could be isolated in 47-62% yield. If nitro groups were present, they were reduced to the corresponding amines, which could be isolated in low yields. Heteroatomically substituted 2-carboxamidobenzonitriles gave yields from 33 to 51%, except for R = 3-furyl, which was decomposed.

N-Acylated 2-aminobenzonitriles derived from alkyl acyl halogenides usually gave a mixture of 4-imino-quinoxalin-3-amines and their precursor N-(2-cyanophenyl)-alkyl-imidazolidinyl hydrazones. These mixtures did not need to be separated as these two substances give the same product in the subsequent reactions.

Our products were tested for affinity at rat A1 and A2A receptors. Aromatic substituents with the size of a phenyl ring showed high affinity to adenosine receptors. A fluorescent atom at the 3-position of the phenyl ring was well tolerated, while a fluorescent atom at the 4-position led to a 10-fold decrease in affinity. Bromine in the 4-position led to an even more dramatic loss of affinity. All heteroatomically substituted compounds showed high affinity. The thienyl derivatives had even higher \(K_i\) values than the benzene series. The 5-phenyl[1,2,4]triazolo[1,5-c]quinazolin-2-amine, 2-furyl was well tolerated, pyridine residues were less favorable. Receptor subtype selectivity was low. The lead compound, 5-phenyl[1,2,4]triazolo[1,5-c]quinazolin-2-amine, showed 9-fold selectivity for A2A over A1 (3-fold at human receptors), the 3-thienyl-derivative 3-fold (7-fold at human receptors). Selectivity of the other tested (hetero)aromatic substituents was even lower. This trend was also present in 5-aryl-substituted [1,2,4]triazolo[1,5-c]quinazolin-2-amines, which generally possessed lower affinity for adenosine receptors. In one case, namely the isopropyl derivative, there was even an 11-fold selectivity for A2A over A1 (5-fold at human receptors).

The 5-aminosubstituted [1,2,4]triazolo[1,5-c]quinazolin-2-amines were synthesized from thioisatoic anhydride. After reaction with aminoguanidine, cyclization was performed by heating in sulfolane to yield 2-amino[1,2,4]triazolo[1,5-c]quinazolin-2-thione. This compound could either be reacted with the corresponding amine, either alone or under oxidative conditions (H2O2, or be methylated to give 5-methylsulfanyl[1,2,4]triazolo[1,5-c]quinazolin-2-thione. This compound could either be reacted with the corresponding amine, either alone or under oxidative conditions (H2O2, or be methylated to give 5-methylsulfanyl[1,2,4]triazolo[1,5-c]quinazolin-2-amine as an activated intermediate, which could be reacted with an amine.

The affinity of the products was generally lower than for the compound described above, with small, lipophilic residues being most potent. Selectivity was generally low.

![Diagram](image.png)