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AMSELAMINE, A NEW SELECTIVE HISTAMINE H_2-RECEPTOR AGONIST#

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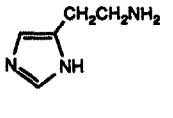
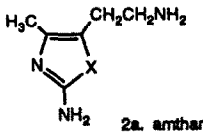
Abstract. The synthesis of amselamine (2-amino-5-(2-aminoethyl)-4-methyl-1,3-selenazole), a potent histamine H_2-agonist, has been described. At the guinea pig right atrium amselamine revealed to be slightly more active than its sulfur analogue amthamine and histamine. Moreover negligible effects on H_1 and H_3-receptors were obeserved.

Introduction

During long time the possibility of a tautomeric shift of the ligand, as can be very easily achieved in the imidazole structure of histamine (1), has been thought to be a structural requirement for the stimulation of the histamine H_2-receptor[1]. Although several authors questioned the necessity of a tautomeric shift[2], recently Eriks et al.[3] provided evidence that also non-tautomeric structures can be H_2-agonists. Examples are found in a series of thiazoles, with amthamine (2a) being the most active compound of the series.



1. histamine



2a. amthamine (X = S)
2b. amselamine (X = Se)

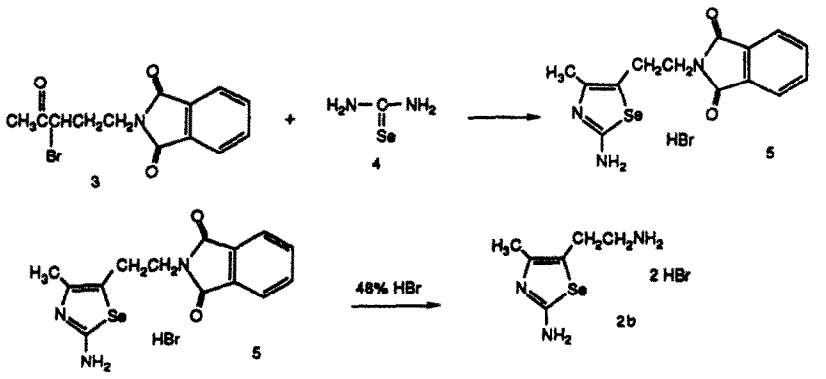
Since it has been shown that in these type of compounds the pK_a of the heterocyclic system is determining the affinity to the H_2-receptor, it is interesting to vary X in structure 2 in order to modify the pK_a of the ring system. Preliminary calculations revealed that the selenazole 2b might be expected to possess fairly high histamine H_2-agonistic activity. Therefore this compound was prepared and pharmacologically evaluated.

Chemistry

The selenazole 2b was prepared as indicated in scheme 1.The phthalimidobromopentanone[4] 3 was condensed with selenourea (4) in refluxing ethanol during 6 hrs. After cooling 2-amino-4-methyl-5-[2-(N-phthalimido)ethyl]-1,3-selenazole (5) was filtered off as the hydrobromide and crystallized from ethanol. Yield 95%, melting point 206.2 - 208.9°C.

To the memory of John Eriks who died October 26th, 1992.

Scheme 1



^{1}H-NMR (200 mHz) in d_6-DMSO: 1.90 ppm (singlet, CH_3), 2.94 ppm (triplet, J = 6.1 Hz, $ArCH_2$), 3.96 ppm (triplet, J = 6.1 Hz, NCH_2), 7.88 ppm (singlet, 4 x ArH), 9.36 ppm (broad singlet, NH_2), 12.52 ppm (broad singlet, ^+NH).

Subsequently the phthalimidoselenazole 5 was hydrolyzed in refluxing 48% HBr during 5 hrs. After evaporation to dryness the residue (2b) was crystallized three times from ethanol. Yield 56%, melting point 249.6 - 250.0°C.

^{1}H-NMR (200 mHz) in d_6-DMSO: 2.11 ppm (singlet, CH_3), 2.99 ppm (singlet, 2 x CH_2), 8.00 ppm (broad singlet, $^+NH_3$), 9.39 ppm (broad singlet, NH_2), 12.65 (broad singlet, ^+NH).

Mass spectrum (EI, 70 eV): found: m/e = 205.0129, calculated for $C_6H_{11}N_3{}^{80}Se$: 205.0118.

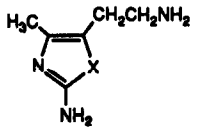
Titration with 0.1 N NaOH in water containing 0.162 M KNO_3 revealed that the equivalent weight of the sample prepared was 99.8% of the theoretical value. The pK_a values calculated from the titration curve are indicated in table 1. Results of elemental analysis were within 0.4 % of the theoretical value for C, H and N.

Pharmacology

Histamine H_2-activity was determined on the isolated spontaneously beating guinea pig right atrium according to Sterk et al.[5] The pD_2 values were derived from the 50% level of the maximum response of the agonistic dose-response curves. Affinity to the H_2-receptor was determined on rat histamine H_2-receptors expressed in CHO cell as described by Traiffort et al.[6] using [^{125}I]-iodoaminopotentidine as the radioligand; the displacement curves were analysed with the program LIGAND[7].

Amselamine (2b) behaves as a full agonist with a pD_2 value of 6.41 which makes it slightly more potent than histamine and amthamine (2a). Its H_2-agonistic character was verified with cimetidine as antagonist. Cimetidine appeared to be a competitive antagonist with a pA_2 value of 6.41 ± 0.04 (3) with amselamine as agonist, which is in accordance with reported values using other agonists[2]. Dose-response curves are shown in fig.1.

Table 1 Pharmacological data and basicity of H_2-agonists.

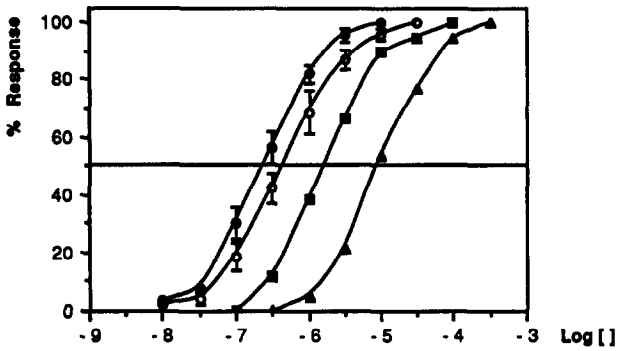


	X	$pD_2 \pm$ s.e.m.[a]	$pK_d \pm$ s.e.m.[b]	$pK_{a1} \pm$ s.e.m [c]	$pK_{a2} \pm$ s.e.m [d]
2b	Se	6.41 ± 0.08 (6)	5.01 ± 0.02 (3)	9.21 ± 0.01 (4)	5.78 ± 0.01 (4)
2a	S	6.21 ± 0.09 (7)	4.94 ± 0.06 (3)	9.15 ± 0.02 (6)	5.40 ± 0.01 (6)
histamine		6.14 ± 0.04 (22)	3.93 ± 0.06 (3)	9.32 ± 0.14 (3)	5.93 ± 0.14 (3)

a. Guinea pig right atrium; b. CHO rat H_2 cells; c. aliphatic amine; d. heterocyclic ring.

Amselamine shows very weak interactions with histamine H_1- and H_3-receptors. Thus concerning H_1-activity (guinea pig ileum) a pA_2-value of 3.85 ± 0.07 (4) against histamine was found, whereas in the test for H_3-activity (electrically stimulated guinea pig jejunum)[8] a pD_2-value of 4.44 ± 0.05 (3) was established. These results make amselamine a selective and relatively potent histamine H_2-agonist.

Fig. 1 Functional effects of amselamine on histamine H_2-receptors.
(Guinea pig right atrium, chronotropic effect)



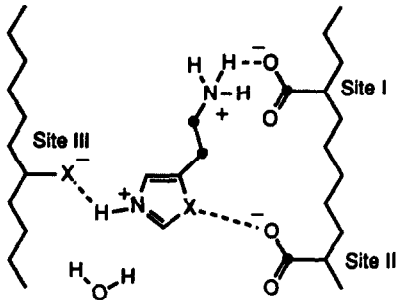
○ Histamine, ● Amselamine, ■ Amselamine + 10^{-6} M Cimetidine and
▲ Amselamine + 10^{-5} M Cimetidine.

Interaction with the H_2-receptor

Recently we provided evidence[3] that monocations of histamine, dimaprit and a number of thiazoles exert their interaction with the histamine H_2-receptor through H-bond formation with the primary ammonium group, protonation of the aromatic N-atom and H-bond formation (if X = NH) or electrostatic interaction (if X = S) as

shown in fig. 2.

Fig. 2 Binding to the histamine H_2-receptor



Since the selenazole ring of amselamine is somewhat more basic than the thiazole ring of amthamine (table 1), it may be expected that amselamine has a slightly higher affinity for the H_2-receptor than amthamine. However, since amthamine and amselamine exert almost equal affinities for the histamine H_2-receptor on CHO cells, such a statistically significant higher affinity was not established.

Conclusion

It appeared that the seleno analogue of the potent histamine H_2-agonist amthamine, which is designated as amselamine, behaves as a potent histamine H_2-agonist with a higher potency than histamine itself. Moreover amselamine exerts hardly any activity for histamine H_1- and H_3-receptors, which makes it selective for the histamine H_2-receptor.

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