Synthesis of *ortho*-Functionalized 4-Aminomethylpyridazines as Substrate-Like Semicarbazide-Sensitive Amine Oxidase Inhibitors

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A series of 4-aminomethylpyridazines and -pyridazin-3(2*H*)-ones ("diaza-benzylamines"), bearing alkylamino side chains in *ortho* position relative to the CH_2NH_2 unit, was synthesized by catalytic hydrogenation of the corresponding nitriles in strongly acidic medium. *N*-Benzyl protecting groups either at the pyridazinone ring nitrogen or at an exocyclic nitrogen were selectively removed hydrogenolytically or by treatment with a Lewis acid. The new compounds were tested *in vitro* for semicarbazide-sensitive amine oxidase (SSAO) inhibitory activity and 4-(aminomethyl)-*N*,*N*′-diethylpyridazine-3,5-diamine (22) was found to be the most active representative.

Key words 4-aminomethylpyridazine; diaza-benzylamine; selective debenzylation; semicarbazide-sensitive amine oxidase/vascular adhesion protein 1; semicarbazide-sensitive amine oxidase inhibitor

4-Aminomethylpyridines with one or two substituents of the type alkyl-X- (X=NH, O, S) at the C-3 and/or C-5 position have been reported by Bertini *et al.*[1,2] to exhibit significant inhibitory activity towards copper-containing amine oxidases. Obviously, these compounds can mimick benzylamine, which is a prototypical substrate of these enzymes, and thus these "aza-benzylamines" were classified as substrate-like amine oxidase inhibitors.[2] Among the copper-containing amine oxidases, the enzyme named "semicarbazide-sensitive amine oxidase" (SSAO), which is also known as "vascular adhesion protein 1" (VAP-1) has found particular attention and has been extensively investigated with respect to its role in various pathophysiological conditions.[3—5] Among other implications, both for its plasma-soluble and its tissue-bound forms, inflammatory processes and many of the well-known late-stage complications of type-2 diabetes (such as vascular damage and retinopathy) have been associated with increased levels of SSAO activity.[6,7] Thus, SSAO was recognized as an interesting target for new drug molecules which could open new possibilities in the prevention and treatment of such diseases. Although a large number of SSAO-inhibitory agents has been identified so far, a really effective and selective compound fulfilling all requirements for clinical application is still lacking, and the search for new lead structures is continuing. Among the various approaches, the development of 4-aminopyridines as substrate-like inhibitors (see above) deserves attention, as these compounds do not possess the frequently observed toxicity of classical carbonyl reagents such as hydrazine derivatives, which are known to irreversibly block the enzyme by forming a covalent bond with the topaquinone subunit of SSAO.[3,4] Starting from the structural motif of Bertini's 4aminomethylpyridines ("aza-benzylamines"),[2] we now took the aza-bioisosterism principle one step further, as we envisaged replacement of the pyridine ring by a pyridazine ring. It is well known that exchange of a pyridine by a diazine (and especially by a pyridazine) can significantly alter the physicochemical properties of a compound (lower basicity, higher dipole moment, increased water solubility), as demonstrated, for instance, with some aza analogues of the pyridocarbazole alkaloids.[8,9] Here, we wish to report on the synthesis and preliminary *in-vitro* biological evaluation of a series of new 4-aminomethylpyridazine derivatives ("diaza-benzylamines") with various alkylamino side chains located at one or both positions *ortho* to the CH_2NH_2 moiety.

Despite the close structural similarity between the envisaged 4-aminomethylpyridazines and the known 4-aminomethylpyridine lead compounds, we had to develop different synthetic strategies in order to make the target compounds accessible. As 2-aza analogues of the 4-aminomethyl-3-alkylaminopyridines,[2] we first prepared the corresponding 4-aminomethylpyridazines (**3a**—**d**) with C_1—C_4 alkylamino substituents at position C-3. As the starting material, we chose 3-chloro-4-pyridazinecarbonitrile[10] (**1**) which is easily accessible from commercial reagents in two steps.[10,11] First, the activated chloro substituent was replaced with the requisite alkylamino group by treatment with the appropriate amine in ethanolic solution at room temperature. After optimization of the reaction times (1—4 h, depending on the alkyl chain length), the 3-alkylamino-4-pyridazinecarbonitriles **2a**—**d** were obtained in yields between 76% and 92%. In a subsequent step, the cyano group was reduced to the desired aminomethyl group by catalytic hydrogenation in strongly acidic medium.

Extending the compound library towards 4-aminomethylpyridazines with heteroatom substituents both at C-3 and C-5, we developed a synthesis of pyridazin-3(2*H*)-one derivatives bearing a (cyclic) dialkylamino moiety at position C-5, next to the essential CH_2NH_2 group at position C-4. Starting from 4,5-dichloro-2-methylpyridazin-3(2*H*)-one[12] (**4**), we made use of the well-known regioselective nucleophilic displacement of the 5-chloro function by secondary amines in aqueous medium (apolar solvents would favor substitution at position C-4).[13] Reaction of **4** with pyrrolidine or morpho-

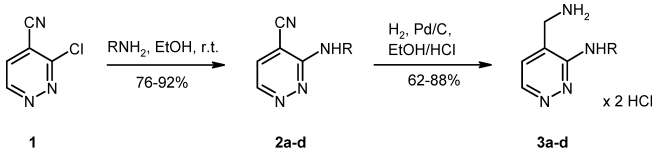

Chart 1

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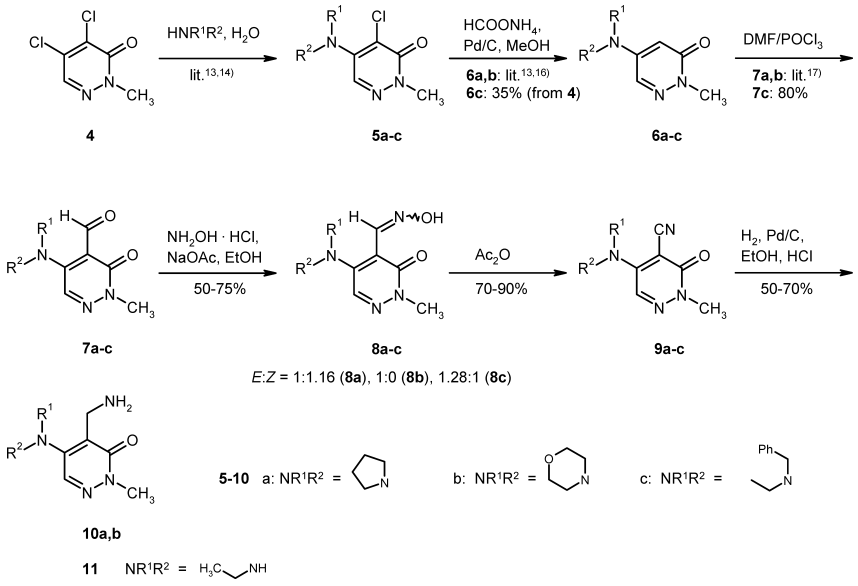

Chart 2

line gave the known 4-chloro-5-cycloaminopyridazinones **5a**[14] and **5b**,[13] respectively. Attempts to directly replace the 4-chloro substituent in compounds of type **5** with a cyano function by palladium-catalyzed cyanation[15] failed, so we decided to introduce the requisite carbon side chain at position C-4 by an electrophilic substitution reaction, after reductive removal of the halogen. Thus, catalytic transfer hydrogenation of **5a**, **b** with ammonium formate/palladium gave the known 5-cycloaminopyridazinones **6a**[16] and **6b**,[13] respectively. Vilsmeier–Haack formylation of these electron-rich pyridazinones then afforded the aldehydes **7a**, **b**.[17] Treatment of the crude aldehydes with hydroxylamine hydrochloride/sodium acetate in aqueous ethanol smoothly gave the corresponding oximes (**8**). These new compounds were obtained either as an *E*/*Z* mixture (in the case of **8a**) or as the pure *E*-configured isomer (in the case of **8b**), as determined by ^{1}H-NMR spectroscopy (nuclear Overhauser effect (NOE) between the aldehydic proton and the N-OH proton of the *E*-oxime; see Experimental). Dehydration of the oximes by heating in acetic anhydride led to the nitriles **9a**, **b**, which then were reduced to the target aminomethyl compounds **10a**, **b** by catalytic hydrogenation in ethanol in the presence of 2 N hydrochloric acid.

In an analogous manner, the 5-ethylamino compound **11** was prepared, starting from **4** and *N*-ethylbenzylamine.[18] In this case, regioselectivity of the nucleophilic substitution reaction with the secondary amine was much lower, and the product (**5c**) was found to contain substantial amounts of the 4-dialkylamino-5-chloro isomer. Chromatographic separation turned out to be difficult, but could be achieved much more conveniently after the next reaction step, *i.e.* reductive dehalogenation, thus giving the 4-unsubstituted intermediate **6c** in high purity. The remaining steps in this sequence leading to **11** are analogous to those described for the synthesis of **10a**, **b**. The benzyl protecting group is removed during the final hydrogenation reaction, which requires slightly elevated pressure.

In order to find an access also to 4-aminomethylpyridazines bearing alkylamino groups both at the C-3 and the C-5 position, we had to further modify the synthetic pathway described above. Starting from a 4,5-dichloropyridazin-3(2*H*)-one precursor with a removable substituent at the pyridazine N-2 atom should offer this option. Thus, the 2-benzyl compound **12**[19] was reacted with *N*-ethylbenzylamine in water, which gave the 5-substitution product **13** along with its 4-isomer. Again, chromatographic isomer separation was successfully performed after the dehalogenation step, and the resulting 4-unsubstituted intermediate **14** was formylated to give the aldehyde **15**. Attempts to remove the benzyl protecting group from the ring nitrogen by treatment with a Lewis acid ($AlCl_3$) in toluene failed, so we decided to postpone this deprotection step. Transformation of the aldehyde **15** into the nitrile **17** was achieved smoothly *via* the oxime **16**, which was isolated as a 4 : 1 *E*/*Z* isomer mixture. Whereas catalytic hydrogenation of the nitrile **17** in acidic medium at 3.44 bar effected selective debenzylation at the tertiary amino group (together with reduction of the cyano group) to yield compound **18**, the 2-benzyl residue in **17** could be selectively removed with $AlCl_3$ in toluene (in analogy to lit.[20—26]), affording the 2-unsubstituted pyridazinone **19**. When the latter was heated in phosphorus oxychloride at 110 °C, the 3-chloropyridazine **20** was obtained in good yield. Treatment of this reactive intermediate with methanolic ethylamine then gave the 3-ethylamino-4-pyridazinecarbonitrile **21**. In the final step, the cyano group was reduced to the CH_2NH_2 moiety and the benzyl group was hydrogenolytically removed, again by catalytic hydrogenation at slightly elevated pressure in strongly acidic ethanol (which requires 6 N hydrochloric acid, in this case). Thus, the target 4-aminomethyl-*N*,*N*′-diethylpyridazine-3,5-diamine (**22**) was obtained in good yield as the corresponding dihydrochloride.

In a screening assay on recombinant human SSAO, the 3,4-disubstituted pyridazines **3a**—**d** showed only weak inhibitory activity (between 27% and 47% at a fixed sample concentration of 500 μM), with the methylamino compound **3a** as the most active representative (see Table 1). Among the pyridazin-3(2*H*)-one derivatives, only the morpholino-substituted compound **10b** was found to possess moderate activity,

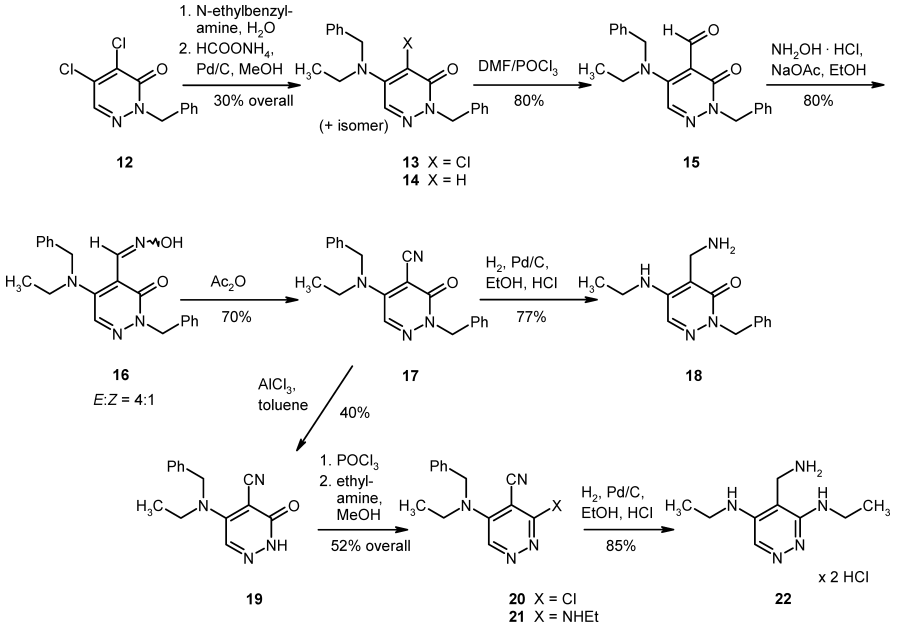

Chart 3

Table 1. Inhibitory Activity (% Inhibition) of Compounds **3a**—**d**, **10a**, **b**, **11**, **18** and **22** on Recombinant Human SSAO at a Fixed Sample Concentration of 500 μM

Compound	**3a**	**3b**	**3c**	**3d**	**10a**	**10b**	**11**	**18**	**22**
% inhibition	47	29	44	27	<10	93	13	<10	>99

with an IC_{50} value of >200 μM (93% inhibition at 500 μM sample concentration). The most significant SSAO inhibitory activity was observed with the triamine **22**, for which an IC_{50} value of 30 μM was found. The latter compound thus offers some potential for further investigation and derivatization. Structural modification, in this case, will be facilitated by our flexible synthetic pathway, principally permitting also the introduction of different alkylamino substituents at C-3 and C-5 of the pyridazine nucleus. Our results also indicate that isosteric replacement of the benzene ring of benzylamines might lead to SSAO inhibitors.

Experimental

Melting points (uncorrected) were determined on a Kofler hot-stage microscope (Reichert). ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Unity*Plus* 300 spectrometer (300, 75 MHz, respectively). IR spectra were recorded on a Perkin-Elmer 1605 FTIR or on a Perkin-Elmer Spectrum 1000 FTIR instrument. Mass spectra were recorded on a Shimadzu QP5050A spectrometer, high-resolution mass spectra were obtained on a Finnigan MAT 8230 instrument at the Institute of Organic Chemistry, University of Vienna. Elemental analyses were carried out at the Microanalytical Laboratory, Faculty of Chemistry, University of Vienna. Column chromatography was performed on Merck Kieselgel 60 (0.063—0.200 mm), unless stated otherwise. For TLC, Merck aluminium sheets pre-coated with Kieselgel 60 F_{254} were used. Compounds **1**,[10] **4**,[12] **5a**,[14] **5b**,[13] **6a**,[16] **6b**,[13] **7a**,[17] **7b**,[17] and **12**[19] were prepared by known procedures.

For determination of the SSAO inhibitory activity, the spectrophotometric assay described by Holt *et al.*[27] for monoamine oxidase and analogous enzymes was used, employing benzylamine as the substrate. Recombinant SSAO/VAP-1 enzyme was expressed in Chinese Hamster Ovary cells (CHO), these cells and cell cultures have been described earlier by Smith *et al.*[28]

3-(Methylamino)pyridazine-4-carbonitrile (2a) To a solution of 3-chloropyridazine-4-carbonitrile (**1**) (279 mg, 2 mmol) in absolute ethanol (4 ml) was added a 33% solution of methylamine in absolute ethanol (0.60 ml, 4.8 mmol), and the mixture was stirred at room temperature for 1 h. The volatile components were removed under reduced pressure, the residue was taken up in 2 M aqueous Na_2CO_3 (15 ml) and it was extracted several times with dichloromethane. The combined extracts were washed with water, dried, and evaporated. The residue was purified by column chromatography (eluent: dichloromethane/ethyl acetate, 4 : 1) to give compound **2a** (204 mg, 76%) as a pale yellow solid. Recrystallization from *tert*-butyl methyl ether afforded almost colorless crystals, mp 149—150 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.23 (3H, d, J=4.8 Hz, $NHC\underline{H}_3$), 5.45 (1H, br, $N\underline{H}CH_3$), 7.35 (1H, d, J=4.8 Hz, 5-H), 8.69 (1H, d, J=4.8 Hz, 6-H). ^{13}C-NMR ($CDCl_3$) δ: 28.9, 97.7, 114.1, 129.2, 141.8, 156.2. IR (KBr) cm^{-1}: 3392, 3261, 3137, 3059, 2225, 1589, 1505, 1387, 1296, 1137, 1036, 869, 837, 769, 599. MS *m*/*z* (rel. int.): 135 ([M+1]$^+$, 12%), 134 (M$^+$, 100), 106 (9), 91 (7), 80 (49), 79 (36), 65 (15), 64 (40), 55 (40), 52 (17). *Anal.* Calcd for $C_6H_6N_4$: C, 53.72; H, 4.51; N, 41.77. Found: C, 54.07; H, 4.56; N, 41.57.

3-(Ethylamino)pyridazine-4-carbonitrile (2b) To a solution of 3-chloropyridazine-4-carbonitrile (**1**) (279 mg, 2 mmol) in absolute ethanol (4 ml) was added a 2 M solution of ethylamine in methanol (2.2 ml, 4.4 mmol), and the mixture was stirred at room temperature for 2.5 h. Work-up and chromatographic purification were done exactly as described for **2a**, yielding compound **2b** (269 mg, 91%) as a pale yellow solid. Recrystallization from *tert*-butyl methyl ether/light petroleum afforded almost colorless crystals, mp 101—102 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7.2 Hz, $NHCH_2C\underline{H}_3$), 3.67—3.76 (2H, m, $NHC\underline{H}_2CH_3$), 5.29 (1H, br, $N\underline{H}CH_2CH_3$), 7.34 (1H, d, J=4.8 Hz, 5-H), 8.67 (1H, d, J=4.8 Hz, 6-H). ^{13}C-NMR ($CDCl_3$) δ: 14.4, 36.9, 97.4, 114.1, 129.1, 141.7, 155.7. IR (KBr) cm^{-1}: 3363, 3043, 2974, 2873, 2229, 1586, 1566, 1498, 1354, 1285, 1133, 1045, 858, 770, 599. MS *m*/*z* (rel. int.): 149 ([M+1]$^+$, 9%), 148 (M$^+$, 78), 133 (58), 120 (100), 106 (24), 95 (21), 79 (37), 66 (66), 65 (58), 64 (89), 52 (34). *Anal.* Calcd for $C_7H_8N_4$: C, 56.74; H, 5.44; N, 37.81. Found: C, 57.09; H, 5.29; N, 37.61.

3-(Propylamino)pyridazine-4-carbonitrile (2c) To a solution of 3-chloropyridazine-4-carbonitrile (**1**) (279 mg, 2 mmol) in absolute ethanol (6 ml) was added freshly distilled propylamine (260 mg, 4.4 mmol), and the mixture was stirred at room temperature for 3 h. Work-up and chromatographic purification were done exactly as described for **2a**, yielding compound **2c** (287 mg, 88%) as a yellow solid. Recrystallization from *tert*-butyl methyl ether/light petroleum afforded pale yellow crystals, mp 79—80 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, J=7.4 Hz, $NHCH_2CH_2C\underline{H}_3$), 1.67—1.80 (2H, m, $NHCH_2C\underline{H}_2CH_3$), 3.62—3.68 (2H, m, $NHC\underline{H}_2CH_2CH_3$), 5.26 (1H, br, $N\underline{H}CH_2CH_2CH_3$), 7.33 (1H, d, J=4.8 Hz, 5-H), 8.67 (1H, d, J=4.8 Hz, 6-H). ^{13}C-NMR ($CDCl_3$) δ: 11.2, 22.3, 43.6, 97.4, 114.1, 129.1, 141.6, 155.8. IR (KBr) cm^{-1}: 3232, 3127, 2964, 2875, 2229, 1582, 1502, 1370, 1298, 1146, 1101, 1049, 845, 599. MS *m*/*z* (rel. int.): 163 ([M+1]$^+$, 13%), 162 (M$^+$, 23), 147 (23), 135 (36), 133 (72), 120 (100), 106 (21), 92 (11), 79

(26), 66 (28), 65 (36), 64 (42), 52 (29). *Anal.* Calcd for $C_8H_{10}N_4$: C, 59.24; H, 6.21; N, 34.54. Found: C, 59.42; H, 6.20; N, 34.41.

3-(Butylamino)pyridazine-4-carbonitrile (2d) To a solution of 3-chloropyridazine-4-carbonitrile (**1**) (279 mg, 2 mmol) in absolute ethanol (6 ml) was added freshly distilled butylamine (322 mg, 4.4 mmol), and the mixture was stirred at room temperature for 4 h. Work-up and chromatographic purification were done exactly as described for **2a**, yielding compound **2d** (326 mg, 92%) as a tan solid. Recrystallization from light petroleum afforded almost colorless crystals, mp 34—35 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, t, J=7.5 Hz, $NHCH_2CH_2CH_2C\underline{H}_3$), 1.40—1.50 (2H, m, $NHCH_2CH_2C\underline{H}_2CH_3$), 1.65—1.74 (2H, m, $NHCH_2C\underline{H}_2CH_2CH_3$), 3.65—3.72 (2H, m, $NHC\underline{H}_2CH_2CH_2CH_3$), 5.22 (1H, br, $N\underline{H}CH_2CH_2CH_2CH_3$), 7.33 (1H, d, J=4.8 Hz, 5-H), 8.67 (1H, d, J=4.8 Hz, 6-H). ^{13}C-NMR ($CDCl_3$) δ: 13.7, 20.0, 31.2, 41.7, 97.4, 114.1, 129.0, 141.6, 155.8. IR (KBr) cm^{-1}: 3239, 3124, 2958, 2930, 2872, 2224, 1582, 1505, 1420, 1291, 1140, 1053, 844, 599. MS *m/z* (rel. int.): 177 ([M+1]$^+$, 8%), 176 (M$^+$, 48), 161 (10), 147 (50), 139 (45), 134 (71), 133 (93), 121 (31), 120 (100), 106 (19), 76 (92), 64 (30), 51 (22). *Anal.* Calcd for $C_9H_{12}N_4$: C, 61.34; H, 6.86; N, 31.79. Found: C, 61.37; H, 6.80; N, 31.77.

4-(Aminomethyl)-*N*-methylpyridazin-3-amine (3a) To a solution of the nitrile **2a** (204 mg, 1.52 mmol) in ethanol (29 ml) and 2 N HCl (2.3 ml) was added 10% Pd on carbon (60 mg), and the mixture was hydrogenated at normal pressure for 3 h. The catalyst was filtered off and the filtrate was evaporated under reduced pressure. The solid residue was triturated with a mixture of methanol and tetrahydrofuran (THF) (1 : 1), then it was kept in the refrigerator for 16 h. The solid material was collected by filtration, washed with THF and dried to afford the dihydrochloride-monohydrate of compound **3a** (200 mg, 67%) as almost colorless, hygroscopic crystals. ^{1}H-NMR (DMSO-d_6) δ: 2.99 (3H, s, $NHC\underline{H}_3$), 4.17 (2H, s, $ArC\underline{H}_2NH_2$), 7.95 (1H, d, J=4.8 Hz, 1H, 5-H), 8.69 (1H, d, J=4.8 Hz, 6-H), 9.00—9.40 (4H, br, NH). ^{13}C-NMR (DMSO-d_6) δ: 29.2, 36.9, 130.4, 130.4, 140.1, 153.5. IR (KBr) cm^{-1}: 3445, 3234, 2994, 2840, 2602, 1630, 1597, 1480, 1440, 1384, 1195, 1027, 856, 769, 613, 555. HR-MS *m/z*: 138.0907 (Calcd for $C_6H_{10}N_4$: 138.0905).

4-(Aminomethyl)-*N*-ethylpyridazin-3-amine (3b) To a solution of the nitrile **2b** (269 mg, 1.8 mmol) in ethanol (35 ml) and 2 N HCl (2.8 ml) was added 10% Pd on carbon (70 mg), and the mixture was hydrogenated at normal pressure for 2 h. The catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was taken up in aqueous satuarted Na_2CO_3 solution (10 ml) and it was exhaustively extracted with a mixture of chloroform and 2-propanol (9 : 1; 100 ml). The combined extracts were washed with brine (10 ml) and evaporated under reduced pressure at a temperature below 25 °C. The oily residue was purified by column chromatography on neutral alumina (eluent: dichloromethane/methanol/triethylamine, 9 : 1 : 0.1) to afford compound **3b** (240 mg, 88%) as a light-brown oil. The base was dissolved in dry toluene (10 ml) and treated with an excess of 1 M ethereal HCl to give the hydrochloride salt as almost colorless, very hygroscopic crystals. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, J=7.1 Hz, $NHCH_2C\underline{H}_3$), 3.48 (2H, q, unresolved, $NHC\underline{H}_2CH_3$), 4.16 (2H, s, $ArC\underline{H}_2NH_2$), 7.94 (1H, d, J=4.5 Hz, 5-H), 8.72 (1H, d, J=4.5 Hz, 6-H), 8.90—9.10 (3H, br, NH). ^{13}C-NMR (DMSO-d_6) δ: 13.0, 36.9, 37.1, 130.5, 130.7, 139.6, 153.1. IR (KBr) cm^{-1}: 3415, 3111, 2923, 2626, 1734, 1639, 1601, 1496, 1385, 1350, 1265, 1099, 851, 762, 598. HR-MS *m/z*: 152.1058 (Calcd for $C_7H_{12}N_4$: 152.1062).

4-(Aminomethyl)-*N*-propylpyridazin-3-amine (3c) To a solution of the nitrile **2c** (287 mg, 1.77 mmol) in ethanol (34 ml) and 2 N HCl (2.7 ml) was added 10% Pd on carbon (70 mg), and the mixture was hydrogenated at normal pressure for 2 h. Work-up and chromatographic purification were done exactly as described for **3b**, yielding compound **3c** (183 mg, 62%) as a light-brown oil. The base was dissolved in dry toluene (10 ml) and treated with an excess of 1 M ethereal HCl to give the hydrochloride salt as almost colorless, very hygroscopic crystals. ^{1}H-NMR (DMSO-d_6) δ: 0.91 (3H, t, J=7.2 Hz, $NHCH_2CH_2C\underline{H}_3$), 1.64 (2H, m, $NHCH_2C\underline{H}_2CH_3$), 3.42 (2H, t, J=6.1 Hz, $NHC\underline{H}_2CH_2CH_3$), 4.19 (2H, s, $ArC\underline{H}_2NH_2$), 7.99 (1H, d, J=4.8 Hz, 5-H), 8.71 (1H, d, unresolved, 6-H), 8.90—9.30 (3H, br, NH). ^{13}C-NMR (DMSO-d_6) δ: 11.1, 20.5, 37.0, 43.6, 130.4, 130.6, 139.5, 153.2. IR (KBr) cm^{-1}: 3420, 3133, 2927, 2854, 2597, 2362, 1734, 1639, 1599, 1457, 1188, 902, 668, 571. HR-MS *m/z*: 166.1222 (Calcd for $C_8H_{14}N_4$: 166.1218).

4-(Aminomethyl)-*N*-butylpyridazin-3-amine (3d) To a solution of the nitrile **2d** (326 mg, 1.85 mmol) in ethanol (36 ml) and 2 N HCl (2.9 ml) was added 10% Pd on carbon (70 mg), and the mixture was hydrogenated at normal pressure for 2 h. Work-up and chromatographic purification were done exactly as described for **3b**, yielding compound **3d** (280 mg, 84%) as a light-brown oil. The base was dissolved in dry toluene (10 ml) and treated with an excess of 1 M ethereal HCl to give the hydrochloride salt as almost colorless, very hygroscopic crystals. ^{1}H-NMR (DMSO-d_6) δ: 0.90 (3H, t, J=7.2 Hz, $NHCH_2CH_2CH_2C\underline{H}_3$), 1.41 (2H, sext, J=7.2 Hz, $NHCH_2CH_2C\underline{H}_2CH_3$), 1.62 (2H, quint, J=7.2 Hz, $NHCH_2C\underline{H}_2CH_2CH_3$), 3.45 (2H, t, J=6.9 Hz, $NHC\underline{H}_2CH_2CH_2CH_3$), 4.17 (2H, s, $ArC\underline{H}_2NH_2$), 7.96 (1H, d, J=4.8 Hz, 5-H), 8.71 (1H, d, J=4.8 Hz, 6-H), 8.80—9.20 (3H, br, NH). ^{13}C-NMR (DMSO-d_6) δ: 13.6, 19.4, 29.3, 37.0, 41.8, 130.3, 130.6, 139.6, 153.4. IR (KBr) cm^{-1}: 3421, 3250, 2960, 2871, 2364, 2058, 1640, 1596, 1521, 1465, 1374, 1199, 881, 668, 598. HR-MS *m/z*: 180.1372 (Calcd for $C_9H_{16}N_4$: 180.1375).

5-[Benzyl(ethyl)amino]-2-methylpyridazin-3(2*H*)-one (6c) A mixture of 4,5-dichloro-2-methylpyridazin-3(2*H*)-one (**4**) (1.79 g, 10 mmol) and freshly distilled *N*-ethylbenzylamine (3.38 g, 25 mmol) in water (50 ml) was refluxed for 30 h. After cooling to room temperature, the mixture was made weakly acidic with 0.1 N HCl, then it was extracted with dichloromethane. The extract was dried and evaporated under reduced pressure to give crude 5-[benzyl(ethyl)amino]-4-chloro-2-methylpyridazin-3(2*H*)-one (**5c**) as a brown oil. This material was dissolved in methanol (60 ml). Ammonium formate (5.99 g, 95 mmol) and 10% Pd on carbon (1.0 g) were added, and the mixture was heated to 70 °C under an argon atmosphere until TLC (eluent: ethyl acetate) indicated completion of the reaction (approx. 3 h). The catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was taken up in water (100 ml) and it was extracted with dichloromethane. The extract was dried and evaporated, then the residue was subjected to column chromatography (eluent: dichloromethane/methanol, 19 : 1) to afford compound **6c** (850 mg, 35%) as a yellowish oil. ^{1}H-NMR (DMSO-d_6) δ: 1.10 (3H, t, J=7.1 Hz, $NCH_2C\underline{H}_3$), 3.47 (3H, s, NCH_3), 3.47 (2H, q, J=7.1 Hz, $NC\underline{H}_2CH_3$), 4.58 (2H, s, $NC\underline{H}_2Ph$), 5.55 (1H, d, J=3.0 Hz, 4-H), 7.36—7.17 (5H, m, phenyl-H), 7.76 (1H, d, J=3.0 Hz, 6-H). ^{13}C-NMR (DMSO-d_6) δ: 12.2, 38.1, 44.7, 52.1, 97.2, 126.4, 127.0, 128.1, 128.6, 137.3, 148.0, 160.4. IR (KBr) cm^{-1}: 3294, 2974, 1626, 1593, 1454, 1358, 1242, 1180, 974, 828, 712, 608. MS *m/z* (rel. int.): 244 (8%), 243 (M$^+$, 55), 228 (6), 214 (11), 153 (6), 136 (6), 121 (6), 91 (100), 81 (13), 69 (22), 65 (14). HR-MS *m/z*: 243.1378 (Calcd for $C_{14}H_{17}N_3O$: 243.1372).

5-[Benzyl(ethyl)amino]-2-methyl-3-oxo-2,3-dihydropyridazine-4-carbaldehyde (7c) To a solution of compound **6c** (1.21 g, 5 mmol) in dry *N*,*N*-dimethylformamide (DMF) (25 ml) was added dropwise at 5 °C a solution of phosphorus oxychloride (1.03 ml, 11 mmol) in dry DMF (5 ml). The mixture was stirred at room temperature for 15 min, then it was heated to 70 °C for 75 min. The volatile components were removed under reduced pressure, the residue was treated with crushed ice and it was stirred for 20 min. The mixture was made weakly alkaline (pH 8) with 40% aqueous NaOH, then it was extracted with ethyl acetate. The extract was washed with brine, dried, and evaporated to give the aldehyde **7c** (1.08 g, 80%) as a yellow oil which was used for the preparation of **8c** without further purification. ^{1}H-NMR (DMSO-d_6) δ: 1.13 (3H, t, J=7.0 Hz, $NCH_2C\underline{H}_3$), 3.44—3.52 (5H, m, $NC\underline{H}_2CH_3$, NCH_3), 4.70 (2H, s, $NC\underline{H}_2Ph$), 7.12—7.16 (2H, m, phenyl-H), 7.22—7.35 (3H, m, phenyl-H), 8.02 (1H, d, J=0.6 Hz, 6-H), 9.98 (1H, d, J=0.6 Hz, aldehyde-H). ^{13}C-NMR (DMSO-d_6) δ: 13.0, 38.2, 48.2, 55.0, 107.1, 127.3, 127.4, 128.5, 131.0, 136.0, 147.8, 161.5, 187.6. IR (KBr) cm^{-1}: 2974, 2935, 2868, 1662, 1627, 1511, 1451, 1348, 1304, 1125, 705. MS *m/z* (rel. int.): 272 (4%), 271 (M$^+$, 22), 242 (44), 214 (24), 180 (79), 162 (19), 152 (19), 129 (6), 110 (6), 91 (100), 81 (13), 69 (18), 65 (17). HR-MS *m/z*: 271.1331 (Calcd for $C_{15}H_{17}N_3O_2$: 271.1321).

4-[(*E*,*Z*)-(Hydroxyimino)methyl]-2-methyl-5-(pyrrolidin-1-yl)pyridazin-3(2*H*)-one (8a) To a suspension of the aldehyde **7a** (207 mg, 1 mmol) in ethanol (5 ml) was added hydroxylamine hydrochloride (90 mg, 1.3 mmol) and a solution of sodium acetate (106 mg, 1.3 mmol) in water (2 ml). The mixture was refluxed and the reaction progress was monitored by TLC (eluent: ethyl acetate/methanol, 19 : 1). After completion of the reaction (approx. 3 h), the solvent was removed under reduced pressure, the residue was taken up in water (10 ml) and it was extracted with dichloromethane. The extract was dried and evaporated, then the residue was recrystallized from ethanol to give the oxime **8a** (111 mg, 50%) as colorless crystals, mp 168—169 °C. ^{1}H-NMR (DMSO-d_6), isomer ratio *E* : *Z*=1 : 1.16; δ: 1.80—1.88, (4H, m, pyrrolidine-H). 3.20—3.29 (4H, m, pyrrolidine-H), 3.49 (3H, s, CH_3, *Z* isomer), 3.51 (3H, s, CH_3, *E* isomer), 7.50 (1H, s, oxime-C$\underline{H}$, *Z* isomer), 7.74 (1H, s, 6-H, *Z* isomer), 7.78 (1H, s, 6-H, *E* isomer), 8.11 (1H, s, oxime-C$\underline{H}$, *E* isomer), 10.90 (1H, s, N–OH, *Z* isomer), 10.97 (1H, s, N–OH, *E* isomer; shows positive NOE on irradiation at 8.11 ppm). ^{13}C-NMR (DMSO-d_6) δ: 24.9, 25.0, 38.3, 38.5, 48.8, 51.0, 100.0, 101.3, 129.4, 129.9, 143.5, 143.8, 144.4, 144.9, 159.4, 160.5. IR (KBr) cm^{-1}: 3244, 2975, 2872, 1624, 1576, 1515, 1441, 1406, 1349, 1285, 1100, 960, 850, 760, 655, 565. MS *m/z* (rel. int.): 222 (M$^+$, 4%), 205 (100), 188 (27), 176 (6), 160 (6), 149 (5), 131 (15), 120

(5), 104 (12), 93 (5), 68 (6). *Anal.* Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found: C, 54.04; H, 6.44; N, 25.02.

4-[(*E*)-(Hydroxyimino)methyl]-2-methyl-5-(morpholin-4-yl)pyridazin-3(2*H*)-one (8b) To a suspension of the aldehyde **7b** (223 mg, 1 mmol) in ethanol (5 ml) was added hydroxylamine hydrochloride (90 mg, 1.3 mmol) and a solution of sodium acetate (106 mg, 1.3 mmol) in water (2 ml). The mixture was refluxed and the reaction progress was monitored by TLC (eluent: ethyl acetate/methanol, 19 : 1). After completion of the reaction (approx. 3 h), the solvent was removed under reduced pressure, the residue was taken up in water (10 ml) and it was extracted with dichloromethane. The extract was dried and evaporated, then the residue was recrystallized from ethanol to give the *E*-oxime **8b** (155 mg, 65%) as colorless crystals, mp 179—180 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.22, (4H, t, J=4.7 Hz, morpholine-H), 3.56 (3H, s, CH_3), 3.66 (4H, t, J=4.7 Hz, morpholine-H), 7.91 (1H, s, 6-H), 8.17 (1H, s, oxime-C<u>H</u>; shows positive NOE on irradiation at 11.35 ppm), 11.35 (1H, s, N–OH). ^{13}C-NMR (DMSO-d_6) δ: 39.2, 49.9, 65.8, 109.1, 131.5, 143.5, 147.3, 159.9. IR (KBr) cm^{-1}: 3260, 2866, 1635, 1616, 1575, 1394, 1256, 1106, 964, 888, 771, 579. MS *m*/*z* (rel. int.): 239 (4%), 238 (M^+, 4%), 221 (100), 176 (51), 163 (24), 150 (17), 133 (26), 105 (16), 92 (17), 65 (14), 43 (19). *Anal.* Calcd for $C_{10}H_{14}N_4O_3$: C, 50.41; H, 5.92; N, 23.52. Found: C, 50.70; H, 5.95; N, 23.30.

5-[Benzyl(ethyl)amino]-4-[(*E*,*Z*)-(hydroxyimino)methyl]-2-methylpyridazin-3(2*H*)-one (8c) To a solution of the aldehyde **7c** (814 mg, 3 mmol) in ethanol (10 ml) was added hydroxylamine hydrochloride (417 mg, 6 mmol) and a solution of sodium acetate (312 mg, 3.8 mmol) in water (3 ml). The mixture was heated to 65 °C for 2 h, then it was evaporated. The residue was taken up in water (20 ml) and it was extracted with dichloromethane. The extract was dried and evaporated and the residue was subjected to column chromatography (eluent: dichloromethane/methanol, 19 : 1) to afford an *E*/*Z* isomer mixture of the oxime **8c** (643 mg, 75%) as a yellow oil. ^{1}H-NMR (DMSO-d_6), isomer ratio E : Z=1.28 : 1; δ: 1.05, 1.07 (each 3H, t, J=7.2 Hz, $NCH_2C\underline{H}_3$), 3.34–3.44 (2×2H, m, $NC\underline{H}_2CH_3$), 3.47 (3H, s, NCH_3, *Z* isomer), 3.48 (3H, s, NCH_3, *E* isomer), 4.51 (2H, s, $NC\underline{H}_2Ph$, *Z* isomer), 4.59 (2H, s, $NC\underline{H}_2Ph$, *E* isomer), 7.14—7.33 (2×5H, m, phenyl-H), 7.41 (1H, s, oxime-C<u>H</u>, *Z* isomer), 7.76 (1H, s, 6-H, *Z* isomer), 7.83 (1H, s, 6-H, *E* isomer), 7.96 (1H, s, oxime-C<u>H</u>, *E* isomer; shows positive NOE on irradiation at 11.25—11.27 ppm), 11.25, 11.27 (each 1H, s, N–OH). ^{13}C-NMR (DMSO-d_6) δ: 12.6, 13.0, 38.4, 38.7, 45.5, 47.1, 53.1, 53.7, 103.2, 106.8, 126.9, 127.0, 127.05, 127.1, 128.4 (2), 130.3, 131.5, 137.2, 137.6, 143.1, 144.0, 145.8, 146.3, 159.2, 160.0. IR (KBr) cm^{-1}: 3262, 2977, 1593, 1437, 1348, 973, 739. MS *m*/*z* (rel. int.): 286 (M^+, 2%), 270 (8), 269 (43), 268 (6), 254 (4), 228 (3), 191 (7), 166 (41), 138 (6), 92 (7), 91 (100), 65 (11). HR-MS *m*/*z*: 286.1422 (Calcd for $C_{15}H_{18}N_4O_2$: 286.1430).

2-Methyl-3-oxo-5-(pyrrolidin-1-yl)-2,3-dihydropyridazine-4-carbonitrile (9a) A solution of the oxime **8a** (555 mg, 2.5 mmol) in acetic anhydride (20 ml) was refluxed for 30 min. After cooling, the mixture was poured onto ice, adjusted to pH 8 with 10% aqueous NaOH, and extracted with dichloromethane. The extract was washed with water, dried, and evaporated. The residue was recrystallized from ethanol to afford the nitrile **9a** (357 mg, 70%) as colorless crystals, mp 171—172 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.90—1.95 (4H, m, pyrrolidine-H), 3.55—3.80 (4H, m, pyrrolidine-H), 7.75 (1H, s, 6-H). ^{13}C-NMR (DMSO-d_6) δ: 24.6, 38.7, 49.7, 80.5, 117.1, 129.0, 148.0, 159.0. IR (KBr) cm^{-1}: 2980, 2878, 2207, 1639, 1597, 1541, 1457, 1356, 1306, 1225, 1096, 919, 878, 856, 754, 577, 558. MS *m*/*z* (rel. int.): 205 (15%), 204 (M^+, 100), 176 (37), 149 (30), 133 (54), 91 (21), 77 (13), 55 (12), 43 (21), 41 (15). *Anal.* Calcd for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found: C, 59.09; H, 5.75; N, 27.39.

2-Methyl-5-(morpholin-4-yl)-3-oxo-2,3-dihydropyridazine-4-carbonitrile (9b) A solution of the oxime **8b** (500 mg, 2.1 mmol) in acetic anhydride (18 ml) was refluxed for 30 min. After cooling, the mixture was poured onto ice, adjusted to pH 8 with 10% aqueous NaOH, and extracted with dichloromethane. The extract was washed with water, dried, and evaporated. The residue was recrystallized from ethanol to afford the nitrile **9b** (416 mg, 90%) as colorless crystals, mp 165—166 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.52 (3H, s, CH_3), 3.69–3.73 (4H, m, morpholine-H), 3.75—3.79 (4H, m, morpholine-H), 8.02 (1H, s, 6-H). ^{13}C-NMR (DMSO-d_6) δ: 38.8, 48.4, 65.8, 84.0, 116.2, 129.4, 151.5, 158.7. IR (KBr) cm^{-1}: 2868, 2209, 1635, 1585, 1527, 1411, 1318, 1274, 1110, 1035, 891, 755, 594. MS *m*/*z* (rel. int.): 221 (17%), 220 (M^+, 100), 191 (9), 163 (33), 162 (32), 161 (27), 149 (20), 134 (55), 91 (31), 64 (17), 57 (19). *Anal.* Calcd for $C_{10}H_{12}N_4O_2 \cdot 0.2C_2H_5OH$: C, 54.44; H, 5.80; N, 24.42. Found: C, 54.17; H, 5.84; N, 24.29. HR-MS *m*/*z*: 220.0956 (Calcd for $C_{10}H_{12}N_4O_2$: 220.0960).

5-[Benzyl(ethyl)amino]-2-methyl-3-oxo-2,3-dihydropyridazine-4-carbonitrile (9c) A solution of the oxime **8c** (716 mg, 2.5 mmol) in acetic anhydride (20 ml) was refluxed for 30 min. After cooling, the mixture was poured onto ice, adjusted to pH 8 with 10% aqueous NaOH, and extracted with dichloromethane. The extract was washed with water, dried, and evaporated. The residue was subjected to column chromatography (eluent: dichloromethane/methanol, 9 : 1) to afford the nitrile **9c** (536 mg, 80%) as a yellow oil. ^{1}H-NMR (DMSO-d_6) δ: 1.24 (3H, t, J=7.0 Hz, $NCH_2C\underline{H}_3$), 3.50 (3H, s, NCH_3), 3.73 (2H, q, J=7.0 Hz, $NC\underline{H}_2CH_3$), 4.94 (2H, s, $NC\underline{H}_2Ph$), 7.22—7.40 (5H, m, phenyl-H), 7.79 (1H, s, 6-H). ^{13}C-NMR (DMSO-d_6) δ: 13.6, 38.9, 46.5, 53.3, 81.8, 116.4, 126.4, 127.4, 128.3, 128.7, 136.4, 149.8, 158.9. IR (KBr) cm^{-1}: 2981, 2936, 2210, 1635, 1591, 1533, 1450, 1357, 1028, 735. MS *m*/*z* (rel. int.): 269 (10%), 268 (M^+, 14), 253 (4), 239 (4), 178 (11), 106 (17), 91 (100), 65 (12). HR-MS *m*/*z*: 268.1332 (Calcd for $C_{15}H_{16}N_4O$: 268.1324).

4-(Aminomethyl)-2-methyl-5-(pyrrolidin-1-yl)pyridazin-3(2*H*)-one (10a) To a suspension of the nitrile **9a** (306 mg, 1.5 mmol) in ethanol (29 ml) were added 2 N HCl (2.3 ml) and 10% Pd on carbon (60 mg). The mixture was hydrogenated for 70 h at normal pressure, then the catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was taken up in water (20 ml) and extracted with dichloromethane in order to remove any unreacted starting material. Then, the pH of the aqueous phase was adjusted to 9 with conc. ammonia and it was extracted again with dichloromethane. The extract was washed with brine, dried and evaporated. Recrystallization of the residue from ethyl acetate/light petroleum afforded compound **10a** (187 mg, 60%) as colorless crystals, mp 111—112 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.83—1.88 (4H, m, pyrrolidine-H), 3.28 (2H, br s, NH_2), 3.52 (3H, s, CH_3), 3.52—3.60 (4H, m, pyrrolidine-H), 3.63 (2H, s, $C\underline{H}_2NH_2$), 7.64 (1H, s, 6-H). ^{13}C-NMR (DMSO-d_6) δ: 25.2, 36.9, 38.8, 50.0, 112.3, 129.9, 144.5, 161.5. IR (KBr) cm^{-1}: 3415, 3301, 2963, 2872, 1603, 1528, 1437, 1408, 1303, 1165, 1017, 854, 767, 559. MS *m*/*z* (rel. int.): 208 (M^+, 2%), 191 (100), 163 (29), 162 (44), 148 (19), 120 (27), 108 (22), 80 (17), 70 (26), 66 (23). HR-MS *m*/*z*: 208.1319 (Calcd for $C_{10}H_{16}N_4O$: 208.1324). *Anal.* Calcd for $C_{10}H_{16}N_4O \cdot 0.1H_2O$: C, 57.18; H, 7.77; N, 26.67. Found: C, 57.22; H, 7.82; N, 26.46.

4-(Aminomethyl)-2-methyl-5-(morpholin-4-yl)pyridazin-3(2*H*)-one (10b) To a suspension of the nitrile **9b** (330 mg, 1.5 mmol) in ethanol (29 ml) were added 2 N HCl (2.3 ml) and 10% Pd on carbon (60 mg). The mixture was hydrogenated for 65 h at normal pressure, then the catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was taken up in water (20 ml) and extracted with dichloromethane in order to remove any unreacted starting material. Then, the pH of the aqueous phase was adjusted to 9 with conc. ammonia and it was extracted again with dichloromethane. The extract was washed with brine, dried and evaporated. Recrystallization of the residue from ethyl acetate/light petroleum afforded compound **10b** (235 mg, 70%) as colorless crystals, mp 93—94 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.19 (4H, t, J=4.7 Hz, morpholine-H), 3.32 (2H, br s, NH_2), 3.52 (2H, s, $C\underline{H}_2NH_2$), 3.58 (3H, s, CH_3), 3.68 (4H, t, J=4.7 Hz, morpholine-H), 7.82 (1H, s, 6-H). ^{13}C-NMR (DMSO-d_6) δ: 37.7, 39.2, 50.7, 66.2, 124.7, 131.7, 148.8, 161.3. IR (KBr) cm^{-1}: 2964, 2854, 1622, 1437, 1265, 1209, 1112, 1021, 927, 897, 686, 617. MS *m*/*z* (rel. int.): 224 (M^+, 9%), 207 (100), 176 (17), 165 (18), 150 (33), 149 (44), 134 (23), 121 (34), 94 (15), 66 (20), 54 (23). *Anal.* Calcd for $C_{10}H_{16}N_4O_2$: C, 53.56; H, 7.19; N, 24.98. Found: C, 53.57; H, 7.25; N, 24.76.

4-(Aminomethyl)-5-(ethylamino)-2-methylpyridazin-3(2*H*)-one (11) To a solution of the nitrile **9c** (536 mg, 2 mmol) in ethanol (20 ml) were added 2 N HCl (3 ml) and 10% Pd on carbon (77 mg). The mixture was hydrogenated for 72 h in a Parr apparatus at a pressure of 3.44 bar, then the catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was taken up in water (20 ml) and extracted with dichloromethane in order to remove any unreacted starting material. Then, the pH of the aqueous phase was adjusted to 9 with conc. ammonia and it was extracted again with dichloromethane. The extract was washed with brine, dried and evaporated. Recrystallization of the residue from ethyl acetate afforded compound **11** (182 mg, 50%) as colorless crystals, mp 98—99 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.12 (3H, t, J=4.8 Hz, $NCH_2C\underline{H}_3$), 2.50—2.90 (2H, br s, NH_2), 3.24 (2H, q, unresolved, $NC\underline{H}_2CH_3$), 3.50 (3H, s, NCH_3), 3.59 (2H, s, $C\underline{H}_2NH_2$), 6.84 (1H, br s, NH), 7.67 (1H, s, 6-H). ^{13}C-NMR (DMSO-d_6) δ: 15.2, 35.2, 36.8, 38.9, 110.2, 127.3, 145.6, 160.2. IR (KBr) cm^{-1}: 3378, 2973, 2940, 1618, 1456, 1349, 1268, 1177, 769. MS *m*/*z* (rel. int.): 183 (9%), 182 (M^+, 74), 165 (100), 153 (91), 150 (72), 136 (34), 124 (51), 123 (62), 109 (24), 93 (20), 82 (28), 68 (26), 54 (31). HR-MS *m*/*z*: 182.1171 (Calcd for $C_8H_{14}N_4O$: 182.1168).

2-Benzyl-5-[benzyl(ethyl)amino]pyridazin-3(2*H*)-one (14) A mixture of 2-benzyl-4,5-dichloropyridazin-3(2*H*)-one (**12**) (2.55 g, 10 mmol) and *N*-ethylbenzylamine (3.38 g, 25 mmol) in water (50 ml) was refluxed for

40 h. The mixture was made weakly acidic with 0.1 N HCl, then it was extracted with dichloromethane. The extract was washed with brine, dried and evaporated to give a brown, sticky oil (compound **13**), which was dissolved in methanol (60 ml). After addition of 10% Pd on carbon (1.0 g) and ammonium formate (5.99 g, 95 mmol), the mixture was heated to 70 °C under an argon atmosphere. The reaction was monitored by TLC (eluent: ethyl acetate), and further portions of ammonium formate were added as required. After completion of the reaction (approx. 3 h), the catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was taken up in water (50 ml) and it was extracted with dichloromethane. The extract was washed with brine, dried and evaporated. The residue was purified by column chromatography (eluent: dichloromethane/methanol, 99 : 1) to give compound **14** (958 mg, 30%) as a yellow oil. ^{1}H-NMR (DMSO-d_6) δ: 1.10 (3H, t, J=7.1 Hz, $NCH_2C\underline{H}_3$), 3.47 (2H, q, J=7.1 Hz, $NC\underline{H}_2CH_3$), 4.59 (2H, s, NCH_2Ph), 5.09 (2H, s, NCH_2Ph), 5.58 (1H, d, J=3.0 Hz, 4-H), 7.18—7.37 (10H, m, phenyl-H), 7.82 (1H, d, J=3.0 Hz, 6-H). ^{13}C-NMR (DMSO-d_6) δ: 12.2, 44.7, 52.1, 52.6, 97.2, 126.4, 127.1, 127.2, 127.7, 128.3, 128.6, 137.2, 137.6, 147.9, 160.0. IR (KBr) cm^{-1}: 3029, 2973, 1630, 1594, 1452, 1358, 1241, 822, 733. MS *m*/*z* (rel. int.): 320 (11%), 319 (M^+, 47), 214 (18), 213 (13), 199 (9), 172 (8), 137 (21), 106 (56), 91 (100), 65 (14). HR-MS *m*/*z*: 319.1680 (Calcd for $C_{20}H_{21}N_3O$: 319.1685).

2-Benzyl-5-[benzyl(ethyl)amino]-3-oxo-2,3-dihydropyridazine-4-carbaldehyde (15) To a solution of compound **14** (1.60 g, 5 mmol) in dry DMF (25 ml) was added dropwise at 5 °C a solution of phosphorus oxychloride (1.03 ml, 11 mmol) in dry DMF (5 ml). The mixture was stirred at room temperature for 15 min, then it was heated to 70 °C for 2.5 h. The volatile components were removed under reduced pressure, the residue was treated with crushed ice and it was stirred for 20 min. The mixture was made weakly alkaline (pH 8) with 40% aqueous NaOH, then it was extracted with ethyl acetate. The extract was washed with brine, dried, and evaporated to give the aldehyde **15** (1.39 g, 80%) as a yellow oil which was used for the preparation of **16** without further purification. ^{1}H-NMR (DMSO-d_6) δ: 1.14 (3H, t, J=7.1 Hz, $NCH_2C\underline{H}_3$), 3.49 (2H, q, J=7.1 Hz, $NC\underline{H}_2CH_3$), 4.71 (2H, s, NCH_2Ph), 5.11 (2H, s, NCH_2Ph), 7.13—7.35 (10H, m, phenyl-H), 8.08 (1H, d, J=0.9 Hz, 6-H), 9.99 (1H, d, J=0.9 Hz, aldehyde-H). ^{13}C-NMR (DMSO-d_6) δ: 13.0, 48.3, 52.8, 54.9, 107.2, 127.3, 127.5, 127.7, 128.3, 128.4, 128.5, 131.7, 135.8, 137.1, 147.7, 161.3, 187.7. IR (KBr) cm^{-1}: 3029, 2934, 1663, 1628, 1507, 1453, 1297, 1070, 702. MS *m*/*z* (rel. int.): 348 (1%), 347 (M^+, 2), 318 (4), 256 (6), 115 (3), 104 (4), 92 (8), 91 (100), 89 (5), 77 (5), 65 (24). HR-MS *m*/*z*: 347.1637 (Calcd for $C_{21}H_{21}N_3O_2$: 347.1634).

2-Benzyl-5-[benzyl(ethyl)amino]-4-[(*E*,*Z*)-(hydroxyimino)methyl]pyridazin-3(2*H*)-one (16) To a solution of the aldehyde **15** (1.04 g, 3 mmol) in ethanol (10 ml) was added hydroxylamine hydrochloride (417 mg, 6 mmol) and a solution of sodium acetate (312 mg, 3.8 mmol) in water (3 ml). The mixture was heated to 65 °C for 2 h, then it was evaporated. The residue was taken up in water (20 ml) and it was extracted with dichloromethane. The extract was dried and evaporated to afford an *E*/*Z* isomer mixture (approx. 4 : 1) of the oxime **16** (870 mg, 80%) as a yellow oil. ^{1}H-NMR (DMSO-d_6), signals of major isomer, δ: 1.02—1.10 (3H, m, $NCH_2C\underline{H}_3$), 3.39—3.47 (2H, m, $NC\underline{H}_2CH_3$), 4.61 (2H, s, NCH_2Ph), 5.09 (2H, s, NCH_2Ph), 7.13—7.34 (10H, m, phenyl-H), 7.90 (1H, s, 6-H), 7.94 (1H, s, oxime-C$\underline{H}$), 11.25 (1H, br s, N–OH); selected signals of minor isomer, δ: 4.51 (2H, s, NCH_2Ph), 5.07 (2H, s, NCH_2Ph), 7.42 (1H, s, oxime-C$\underline{H}$), 7.83 (1H, s, 6-H), 11.27 (1H, s, N–OH). ^{13}C-NMR (DMSO-d_6), signals of major isomer, δ: 12.6, 47.0, 53.2, 53.7, 106.4, 127.0, 127.1, 127.3, 127.7, 128.3, 128.4, 132.1, 137.0, 137.2, 144.1, 145.6, 159.8. IR (KBr) cm^{-1}: 3268, 3030, 2975, 1593, 1453, 1346, 1271, 1073, 949, 698. MS *m*/*z* (rel. int.): 363 (1%), 362 (M^+, 1), 346 (5), 345 (21), 319 (2), 267 (3), 242 (12), 106 (7), 92 (8), 91 (100), 77 (4), 65 (20), 51 (4). HR-MS *m*/*z*: 362.1747 (Calcd for $C_{21}H_{22}N_4O_2$: 362.1743).

2-Benzyl-5-[benzyl(ethyl)amino]-3-oxo-2,3-dihydropyridazine-4-carbonitrile (17) A solution of the oxime **16** (906 mg, 2.5 mmol) in acetic anhydride (15 ml) was refluxed for 30 min. After cooling, the mixture was poured onto ice, adjusted to pH 8 with 10% aqueous NaOH, and extracted with dichloromethane. The extract was washed with water, dried, and evaporated. The residue was purified by column chromatography (eluent: dichloromethane/methanol, 19 : 1) to afford the nitrile **17** (603 mg, 70%) as a yellow oil. ^{1}H-NMR (DMSO-d_6) δ: 1.24 (3H, t, J=7.0 Hz, $NCH_2C\underline{H}_3$), 3.73 (2H, q, J=7.0 Hz, $NC\underline{H}_2CH_3$), 4.95 (2H, s, NCH_2Ph), 5.10 (2H, s, NCH_2Ph), 7.23—7.39 (10H, m, phenyl-H), 7.85 (1H, s, 6-H). ^{13}C-NMR (DMSO-d_6) δ: 13.5, 46.5, 53.3, 53.5, 81.8, 116.3, 126.4, 127.4, 127.5, 127.9, 128.4, 128.7, 129.0, 136.3, 136.6, 149.7, 158.8. IR (KBr) cm^{-1}: 3030, 2979, 2934, 2209, 1635, 1590, 1533, 1452, 1357, 1322, 1070, 732. MS *m*/*z* (rel. int.): 345 (5%), 344 (M^+, 19), 253 (4), 239 (12), 224 (5), 162 (9), 121 (10), 106 (17), 92 (8), 91 (100), 65 (19). HR-MS *m*/*z*: 344.1632 (Calcd for $C_{21}H_{20}N_4O$: 344.1637).

4-(Aminomethyl)-2-benzyl-5-(ethylamino)pyridazin-3(2*H*)-one (18) To a solution of the nitrile **17** (688 mg, 2 mmol) in ethanol (20 ml) were added 2 N HCl (3 ml) and 10% Pd on carbon (77 mg). The mixture was hydrogenated for 72 h in a Parr apparatus at a pressure of 3.44 bar, then the catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was taken up in water (20 ml) and extracted with dichloromethane in order to remove any unreacted starting material. Then, the pH of the aqueous phase was adjusted to 9 with conc. ammonia and it was extracted again with dichloromethane. The extract was washed with brine, dried and evaporated. Recrystallization of the residue from ethyl acetate afforded compound **18** (397 mg, 77%) as colorless crystals, mp 134—136 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.15 (3H, t, J=6.9 Hz, $NCH_2C\underline{H}_3$), 3.27 (2H, q, J=6.9 Hz, $NC\underline{H}_2CH_3$), 3.74 (2H, s, $C\underline{H}_2NH_2$), 4.60—5.10 (2H, br s, NH_2), 5.14 (2H, s, NCH_2Ph), 7.12 (1H, br s, NH), 7.21—7.32 (5H, m, phenyl-H), 7.80 (1H, s, 6-H). ^{13}C-NMR (DMSO-d_6) δ: 15.1, 33.9, 36.9, 53.2, 106.0, 127.2, 127.7, 128.0, 128.3, 137.6, 145.9, 160.0. IR (KBr) cm^{-1}: 3351, 3263, 3031, 2969, 1616, 1454, 1333, 1240, 946, 817, 736, 695. MS *m*/*z* (rel. int.): 259 (4%), 258 (M^+, 20), 241 (13), 229 (10), 200 (7), 187 (26), 167 (13), 150 (12), 120 (12), 109 (17), 106 (16), 91 (100), 65 (19). HR-MS *m*/*z*: 258.1475 (Calcd for $C_{14}H_{18}N_4O$: 258.1481).

5-[Benzyl(ethyl)amino]-3-oxo-2,3-dihydropyridazine-4-carbonitrile (19) To a suspension of $AlCl_3$ (2.13 g, 16 mmol) in dry toluene (60 ml) was added a solution of the nitrile **17** (689 mg, 2 mmol) in dry toluene (5 ml), and the mixture was heated to 80 °C for 1 h. After cooling, the solvent was removed under reduced pressure and the residue was taken up in water (30 ml) and extracted with dichloromethane. The extract was washed with water, dried, and evaporated. The residue was purified by column chromatography (eluent: toluene/ethyl acetate, 3 : 2), followed by recrystallization from ethyl acetate to give the nitrile **19** (203 mg, 40%) as colorless crystals, mp 196—197 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.24 (3H, t, J=7.0 Hz, $NCH_2C\underline{H}_3$), 3.73 (2H, q, J=7.0 Hz, $NC\underline{H}_2CH_3$), 4.94 (2H, s, NCH_2Ph), 7.21—7.41 (5H, m, phenyl-H), 7.76 (1H, s, 6-H), 12.64 (1H, s, NH). ^{13}C-NMR (DMSO-d_6) δ: 13.6, 46.6, 53.4, 81.6, 116.3, 126.4, 127.4, 128.7, 129.0, 136.4, 150.1, 160.2. IR (KBr) cm^{-1}: 3282, 3145, 2985, 2892, 2209, 1645, 1584, 1549, 1458, 1355, 1332, 1081, 858, 811, 739, 633. MS *m*/*z* (rel. int.): 255 (3%), 254 (M^+, 20), 252 (5), 237 (5), 163 (5), 92 (9), 91 (100), 65 (10). *Anal.* Calcd for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 66.08; H, 5.66; N, 21.76.

5-[Benzyl(ethyl)amino]-3-chloropyridazine-4-carbonitrile (20) A mixture of compound **19** (508 mg, 2 mmol) and phosphorus oxychloride (8 ml) was heated to 110 °C for 3 h. The volatile components were removed under reduced pressure and the residue was treated with crushed ice. The mixture was made weakly alkaline with aqueous $NaHCO_3$, then it was extracted with dichloromethane. The extract was washed with water, dried, and evaporated to afford the chloro compound **20** (457 mg, 84%) as a brownish oil which was used for the following transformation without any further purification. ^{1}H-NMR (DMSO-d_6) δ: 1.27 (3H, t, J=7.0 Hz, $NCH_2C\underline{H}_3$), 3.79 (2H, q, J=7.0 Hz, $NC\underline{H}_2CH_3$), 5.00 (2H, s, NCH_2Ph), 7.24—7.40 (5H, m, phenyl-H), 8.84 (1H, s, 6-H). ^{13}C-NMR (DMSO-d_6) δ: 13.1, 46.5, 53.3, 89.9, 115.1, 126.4, 127.4, 128.7, 135.6, 141.1, 146.3, 155.2. HR-MS *m*/*z*: 272.0827 (Calcd for $C_{14}H_{13}ClN_4$: 272.0829).

5-[Benzyl(ethyl)amino]-3-(ethylamino)pyridazine-4-carbonitrile (21) To a solution of the chloropyridazine **20** (350 mg, 1.3 mmol) in absolute ethanol (5 ml) was added a 2 M methanolic solution of ethylamine (6.6 ml, 13.2 mmol), and the mixture was stirred in a closed vessel at 50 °C for 45 h. The volatile components were removed under reduced pressure and the residue was taken up in 2 M aqueous Na_2CO_3 and extracted with dichloromethane. The extract was washed with water, dried, and evaporated. The oily residue was subjected to column chromatography (eluent: toluene/ethyl acetate, 3 : 2) to afford compound **21** (226 mg, 62%) as yellow crystals, mp 93–95 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.12 (3H, t, J=7.2 Hz, $HNCH_2C\underline{H}_3$), 1.23 (3H, t, J=7.0 Hz, $NCH_2C\underline{H}_3$), 3.39—3.45 (2H, m, $HNC\underline{H}_2CH_3$), 3.69 (2H, q, J=7.0 Hz, $NC\underline{H}_2CH_3$), 4.86 (2H, s, NCH_2Ph), 7.19—7.39 (5H, m, phenyl-H), 8.19 (1H, s, 6-H). ^{13}C-NMR (DMSO-d_6) δ: 13.4, 14.6, 36.0, 46.0, 52.8, 74.3, 116.5, 126.3, 127.2, 128.7, 132.7, 136.8, 145.5, 156.8. IR (KBr) cm^{-1}: 3368, 2970, 2929, 2199, 1560, 1512, 1326, 1237, 1148, 1061, 738. MS *m*/*z* (rel. int.): 282 (2%), 281 (M^+, 11), 266 (17), 252 (7), 238 (9), 190 (32), 163 (7), 149 (5), 92 (12), 91 (100), 65 (24). HR-MS *m*/*z*: 281.1645 (Calcd for $C_{16}H_{19}N_5$: 281.1640).

4-(Aminomethyl)-*N*,*N*′-diethylpyridazine-3,5-diamine (22) To a solu-

tion of the nitrile **21** (315 mg, 1.12 mmol) in ethanol (50 ml) were added 6 N HCl (3 ml) and 10% Pd on carbon (42 mg). The mixture was hydrogenated for 48 h in a Parr apparatus at a pressure of 3.44 bar, then the catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was taken up in water (20 ml) and extracted with dichloromethane in order to remove any unreacted starting material. The aqueous layer was evaporated to dryness under reduced pressure and the crystalline residue was dried. It was then dissolved in ethanol (3 ml) and the product was precipitated by addition of diethyl ether to afford the dihydrochloride-monohydrate of compound **22** (278 mg, 85%) as pale yellow crystals, mp >190 °C (decomp.). ^{1}H-NMR (DMSO-d_6) δ: 1.00—1.23 (6H, m, $HNCH_2C\underline{H}_3$), 3.34—3.52 (4H, m, $HNC\underline{H}_2CH_3$), 4.12 (2H, s, $C\underline{H}_2NH_2$), 8.33 (1H, s, 6-H), 8.43, 8.44 (together 5H, br, NH), 13.60—13.80 (1H, br, NH). ^{13}C-NMR (DMSO-d_6) δ: 14.0, 14.8, 31.1, 37.3, 37.7, 95.6, 133.2, 146.8, 150.7. IR (KBr) cm^{-1}: 3232, 3139, 3050, 2979, 1595, 1508, 1410, 1332, 1191, 1130, 872, 837. *Anal.* Calcd for $C_9H_{17}N_5 \cdot 2.10HCl \cdot 1.10H_2O$: C, 37.06; H, 7.36; N, 24.01; Cl, 25.53. Found: C, 36.98; H, 6.90; N, 23.93; Cl, 25.61.

Acknowledgements The authors are grateful to Biotie Therapies Corp. (Turku, Finland) for performing the *in-vitro* evaluation of SSAO inhibitory activity. We also want to thank Mr. P. Unteregger (Institute of Organic Chemistry, University of Vienna) for measuring the high-resolution mass spectra. One of us, P.M., thanks the Hungarian Scientific Research Fund for financial support (K73389).

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