ARYL DIAZINYL KETOXIMES: SYNTHESIS AND CONFIGURATIONAL ASSIGNMENT

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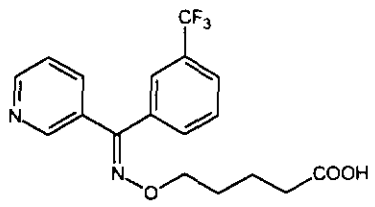
Abstract - Preparation of a series of new aryl diazinyl ketoximes (**7a,b - 12a,b**) required as synthetic building blocks is described. Separation of the E/Z-isomers obtained was achieved by means of chromatography, their configuration was assigned using nmr techniques. Moreover, procedures for the synthesis of the starting ketones (**1b - 6b**) are given.

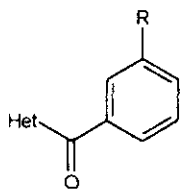
INTRODUCTION

Compounds acting as thromboxane A_2 synthetase inhibitors and simultaneously as thromboxane receptor antagonists represent an interesting class of novel antithrombotic agents.[2,3] Out of a series of aryl 3-pyridyl ketoxime derivatives exhibiting this dual mode of action, Ridogrel[4] (**A**) recently has been selected for clinical trials.[5] In the course of our ongoing studies towards the exploitation of the bioisosteric potential of diazines, we now became interested in ketoximes (**7a,b - 12a,b**) as synthetic building blocks for the preparation of pyridazine, pyrimidine, and pyrazine congeners of Ridogrel (Scheme 1). Here we report on the synthesis of these ketoximes and on the assignment of their configuration by means of nmr spectroscopy.

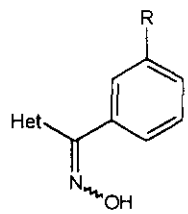
Scheme 1



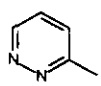
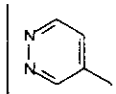
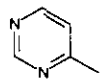
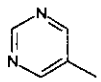
A (Ridogrel)



1a,b-6a,b



7a,b-12a,b

Het =						
R = H	**1a, 7a**	**2a, 8a**	**3a, 9a**	**4a, 10a**	**5a, 11a**	**6a, 12a**
R = CF_3	**1b, 7b**	**2b, 8b**	**3b, 9b**	**4b, 10b**	**5b, 11b**	**6b, 12b**

RESULTS AND DISCUSSION

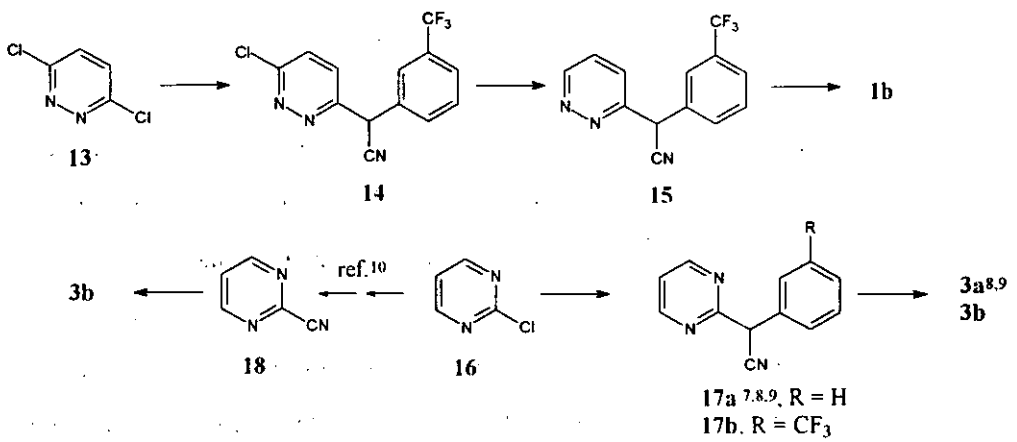
Syntheses

The required starting ketones (**1a,b - 6a,b**) were prepared as follows:

3-Pyridazinyl(3-trifluoromethylphenyl)methanone (**1b**) was obtained from 3,6-dichloropyridazine (**13**) and 3-trifluoromethylphenylacetonitrile *via* an oxidative decyanation route previously developed for the synthesis of **1a**.[6] A slight modification of the procedure given in ref.[7] was used for the synthesis of the 2-pyrimidinyl ketone (**3a**)[8,9] from 2-chloropyrimidine (**16**) and phenylacetonitrile (45% yield, Scheme 2). The trifluoromethyl congener (**3b**) under these conditions, however, resulted in only poor yield. In this case, better results (50% related to **16**) were obtained when 2-cyanopyrimidine (**18**) was reacted with 3-trifluoromethylphenylmagnesium bromide (Scheme 2). For the preparation of the 4-pyridazinyl ketone (**2b**) 4-pyridazinecarboxylic acid (**19**) was reacted with 3-trifluoromethylbenzoyl radicals under acidic conditions followed by thermally induced decarboxylation (Scheme 3). This methodology provides access also to the ketones (**2a**)[11] and (**6a**)[12], but gave only poor yields (< 10%) of **6b**. On the other hand, the 2-pyrazinyl ketone (**6b**) became accessible in 56% overall yield upon reaction of methyl

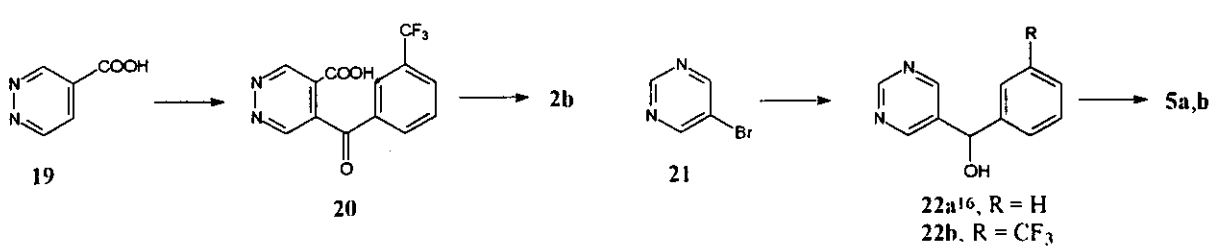
2-pyrazinecarboxylate with 3-trifluoromethylphenyllithium in analogy to ref.[13] Treatment of ethyl or methyl 4-pyrimidinecarboxylate[14,15] with phenylmagnesium chloride or 3-trifluoromethylphenyllithium afforded **4a**[9] and **4b**, respectively. High yields of the required 4-pyrimidinyl ketones can be obtained when the formation of tertiary alcohols is suppressed by addition of the organometallic reagent to the 4-pyrimidinecarboxylic acid ester at -80°C or -90°C, respectively.

Scheme 2



The reported convenient availability of the alcohol (**22a**)[16] from commercial 5-bromopyrimidine (**21**) prompted us to use the latter compound as educt in the preparation of the 5-pyrimidinyl ketones (**5a,b**) by halogen-lithium exchange followed by reaction with the appropriate aldehyde and subsequent oxidation with activated manganese dioxide. Under these conditions the ketones (**5a**)[17] and (**5b**) were obtained in high yields (Scheme 3).

Scheme 3



Treatment of the ketones (**1a,b - 6a,b**) with two equivalents of hydroxylamine hydrochloride in the presence of an excess of sodium acetate (in ethanolic solution) afforded E/Z mixtures of the target ketoximes (**7a**,[19] **7b**, **8a**,[20] **8b**, **9a,b - 11a,b**, **12a**,[21] and **12b**) in satisfactory yields. Separation of the isomers was achieved chromatographically.

Configurational Assignment

In view of the intended employment of the ketoximes (**7a,b - 12a,b**) as starting materials for systematic structural modifications of Ridogrel-type antithrombotics, unequivocal assignment of their stereochemistry became indispensible.

The utility of homonulear NOE difference spectroscopy for the rapid determination of the stereochemistry of compounds containing a C=N bond has been recently demonstrated.[22-24] NOE experiments with the isomerically pure ketoximes (**7a,b - 12a,b**) now revealed that with the faster eluting isomers, irridiation of the OH-resonance leads to significant enhancement of the signals due to protons of the heteroaromatic protons (except for 2-pyrimidinyl ketoximes (**9a,b**)). The aryl proton signals are not or only slightly affected. This gives a strong hint for Z-configuration of these ketoximes. In constrast, similar NOE difference experiments (irridiation of the OH-resonance) with the slower eluting isomers did not permit an unequivocal assignment of E-configuration. Here enhancements of signals of adjacent aryl proton signals as well as those of heteroaromatic protons are observed (for a typical example see Figure 1). However, there cannot be any doubt about the assumed E-configuration of the latter isomers considering the marked differences in the ^{13}C chemical shifts between the stereoisomers.

A well esthablished method for the discrimination of isomeric ketoximes and related compounds is based on the γ-effect: carbon atoms being in γ-position (α to C=N) to a *syn* located oxime-oxygen suffer an upfield shift of 3 - 6 ppm compared to the γ-atoms in *anti* position due to steric compression.[25] This method requires unequivocal assignment of the ^{13}C signals of the γ-carbon atoms (*ipso* carbon atoms of the benzene and hetarene ring). In most cases this could be achieved on the basis of ^{1}H broadband decoupled ^{13}C-nmr spectra in combination with DEPT spectra, since the *ipso* heteroaromatic carbon atoms showed chemical shifts about 10 to 30 ppm downfield compared to the *ipso* benzene carbon atoms (see Tables 1 and 2). Only for the 5-pyrimidinyl derivatives (**11a,b**) and 4-pyridazinyl derivatives (**8a,b**) both *ipso* carbon atom signals (benzene and hetarene) were within the range of 126 to 135 ppm. For an

unambigous assignment of these signals further experiments were performed such as gated decoupled ^{13}C nmr experiments, 2D (δ,δ) long-range HETCOR experiments,[26] or 1D long-range INEPT experiments with selective DANTE excitation.[27] The ^{13}C data which thus enable us to assign the configuration for all ketoximes (**7a,b - 12a,b**) unequivocally are listed in Tables 1 and 2.

Figure 1:

a) ^{1}H-nmr spectrum of **Z-12b** (DMSO-d_6), b) NOE-difference spectrum of **Z-12b** resulting from irridiation of N-OH (DMSO-d_6), c) ^{1}H-nmr spectrum of **E-12b** (DMSO-d_6), d) NOE-difference spectrum of **E-12b** resulting from irridiation of N-OH (DMSO-d_6)

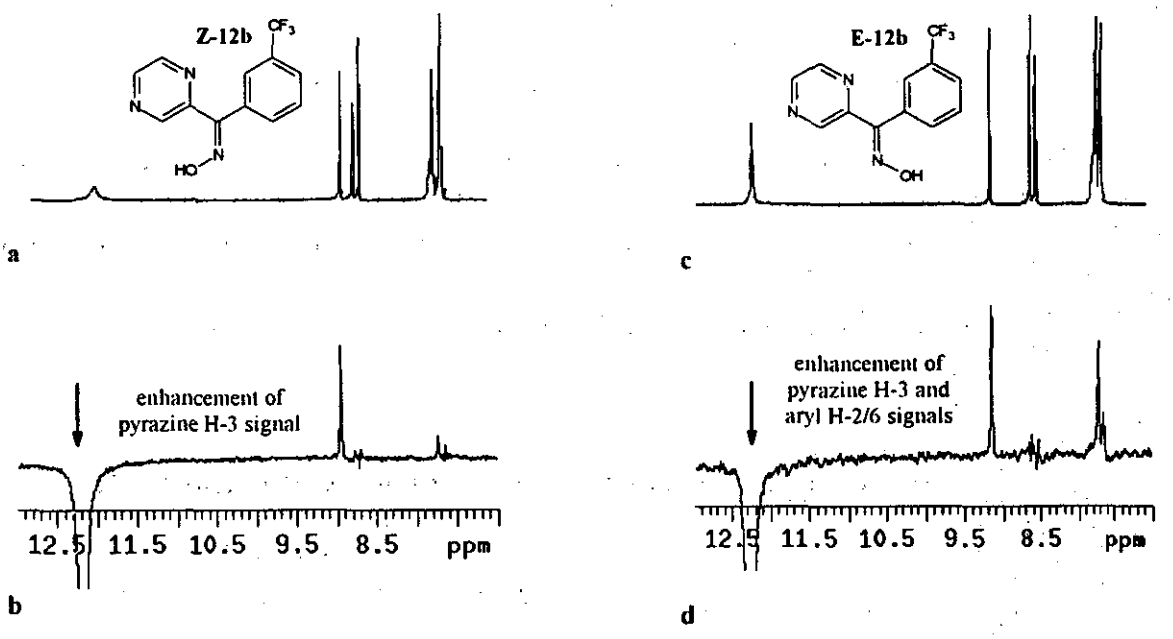


Table 1: ^{13}C Nmr chemical shifts (δ, ppm, in DMSO-d_6) of E- and Z-ketoximes (**7a - 12a**) (R = H)

No.	Het	Diazine-C[a]					Phenyl-C[a]				C=N
		C-2	C-3	C-4	C-5	C-6	C-1	C-2(6)	C-3(5)	C-4	
E-7a		--	157.9	127.1	124.9	151.2	131.9	129.4	127.7	128.4	153.7
Z-7a		--	156.0	128.5	126.6	151.2	135.0	128.4	126.6	129.3	152.7
E-8a		--	148.3	134.5	123.7	151.6	130.8	128.5	128.9	129.2	151.5

No.	Het	Diazine-C[a]					Phenyl-C[a]				C=N
		C-2	C-3	C-4	C-5	C-6	C-1	C-2(6)	C-3(5)	C-4	
Z-8a		--	150.8	**132.0**	126.4	151.7	**134.5**	126.7	128.6	129.5	150.8
E-9a		**162.9**	--	157.3	120.6	157.3	**132.6**	129.2	127.7	128.3	154.2
Z-9a		**162.1**	--	157.6	120.7	157.6	**134.1**	128.5	126.0	129.1	153.5
E-10a		158.2	--	**161.7**	118.0	157.2	**131.2**	129.3	127.7	128.5	154.1
Z-10a		158.8	--	**160.1**	122.5	157.4	**134.2**	128.5	126.5	129.2	152.8
E-11a		158.0	--	155.5	**130.6**	155.5	**130.8**	128.9	128.7	129.8	152.4
Z-11a		158.2	--	157.4	**127.3**	157.4	**134.7**	128.7	127.5	130.7	151.8
E-12a		**150.7**	143.8	--	143.4	142.9	**131.7**	129.4	127.7	128.5	153.7
Z-12a		**148.3**	146.1	--	144.1	144.6	**135.1**	126.8	128.3	129.1	152.5

[a] ^{13}C Chemical shifts of the *ipso* carbon atoms of the diazinyl and phenyl ring are given in bold numbers.

Table 2: ^{13}C Nmr chemical shifts (δ, ppm, DMSO-d_6) of E- and Z-ketoxímes (**7b - 12b**) (R = CF_3)

No.	Het	Diazine-C[a]					3-CF_3-Phenyl-C[a,b]							C=N
		C-2	C-3	C-4	C-5	C-6	C-1	C-2	C-3	C-4	C-5	C-6	CF_3	
E-7b		--	**157.2**	127.2	124.7	151.4	**132.8**	125.1	128.6	125.9	128.9	133.5	--[c]	152.5
Z-7b		--	**155.0**	129.0	126.8	151.5	**136.1**	122.7	129.2	125.6	129.7	130.8	123.9	151.4
E-8b		--	148.1	**133.9**	123.7	151.6	**131.8**	125.7	129.3	126.0	129.7	133.1	123.9	150.4
Z-8b		--	151.8	**131.2**	126.5	150.8	**135.6**	122.6	129.5	126.0	130.0	130.9	123.9	149.7
E-9b		**162.0**	--	157.4	120.8	157.4	**133.7**	125.0	128.6	125.7	128.9	133.3	124.1	153.1
Z-9b		**161.2**	--	157.8	121.1	157.8	**135.2**	121.8	129.4	125.7	129.9	130.1	--[c]	152.2

No.	Het	Diazine-C[a]						3-CF_3-Phenyl-C[a,b]						C=N
		C-2	C-3	C-4	C-5	C-6	C-1	C-2	C-3	C-4	C-5	C-6	CF_3	
E-10b		158.2	--	**161.0**	117.7	157.3	**132.2**	125.2	128.6	125.9	128.9	133.5	124.1	152.9
Z-10b		158.8	--	**158.8**	122.9	157.5	**135.4**	122.7	129.3	125.7	129.7	130.8	123.9	151.5
E-11b		158.3	--	154.9	**130.3**	154.9	**132.4**	125.9	129.2	125.9	129.7	133.2	124.0	149.7
Z-11b		158.3	--	156.9	**126.7**	156.9	**136.4**	122.8	129.4	125.8	129.9	131.0	123.9	149.2
E-12b		**149.9**	144.0	--	143.4	142.7	**132.6**	125.2	128.7	125.9	128.9	133.5	124.1	152.5
Z-12b		**147.1**	146.6	--	144.5	144.6	**136.2**	123.0	129.2	125.5	129.6	131.0	123.9	151.2

[a] ^{13}C Chemical shifts of the *ipso* carbon atoms of the diazinyl and phenyl ring are given in bold numbers.

[b] $^{13}C,^{19}F$ Spin coupling constants (Hz): $^{1}J(C,F) = 271.2 - 273.3$, $^{2}J(C,F) = 32.3 - 33.7$, $^{3}J(C,F) = 3.3 - 4.6$.

[c] Not detected due to low signal to noise ratio.

EXPERIMENTAL

Melting points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. The ir spectra (potassium bromide pellets or neat oils between sodium chloride discs) were recorded on a Mattson Galaxy Series FTIR 3000 spectrophotometer or on a Jasco IRA-1 spectrophotometer. Mass spectra were obtained on a Varian MAT 311A or on a Varian MAT 44/S instrument (both EI, 70eV). Nmr spectra were recorded on a Varian Gemini 200 spectrometer (200 MHz for ^{1}H, 50 MHz for ^{13}C), on a Bruker AC 80 (80 MHz for ^{1}H, 20 MHz for ^{13}C) or on a Bruker AM 300 spectrometer (300 MHz for ^{1}H, 75 MHz for ^{13}C). The center of the solvent signal (DMSO-d_6) or singlet ($CDCl_3$) was used as an internal standard, which was related to tetramethylsilane with δ 2.49 ppm or δ 7.24 ppm (^{1}H), and δ 39.5 ppm or δ 77.0 ppm (^{13}C), respectively. Reactions were monitored by tlc using Polygram SIL G/UV_{254} (Macherey-Nagel) plastic-packed plates (0.25 mm layer thickness) and visualized using an UV lamp or iodine vapour. Column chromatographic separations were performed on Merck Kieselgel 60 (230 - 400 mesh) and medium pressure liquid chromatography (mplc) was carried out on Merck LiChroprep Si 60 (230 - 400 mesh), detection at 280 nm. Preparative tlc separations were performed using Merck PSC-Fertigplatten (20 x 20 cm, Kieselgel 60 F_{254}). Chromatographic separation of E/Z-isomers was performed using

mixtures of dichloromethane - ethyl acetate at ratio resulting in R_f-values of about 0.25 for the faster eluted component (Z-isomer). Elemental analyses were carried out by Mikroanalytisches Laboratorium, Institute of Physical Chemistry, University of Vienna. Light petroleum refers to the fraction of bp 40-60°C. The yields given and separations of E/Z-isomers are not optimized. The following compounds were prepared according to reported procedures: **1a**,[6] **2a**,[11] **6a**,[12] **8a**.[20]

Preparation of ketones 1b, 2b, 3a,b - 5a,b, and 6b.

6-Chloro-3-pyridazinyl(3-trifluoromethylphenyl)acetonitrile (**14**)

To a stirred solution of 1.85 g (10 mmol) of 3-trifluoromethylphenylacetonitrile in 20 ml of dry toluene was added 0.78 g (20 mmol) of sodium amide powder in small portions at 0°C under a nitrogen atmosphere. After 10 min, 1.48 g (10 mmol) of 3,6-dichloropyridazine were added portionwise and the mixture was allowed to warm up to room temperature. Stirring was continued for 5 h, then the mixture was poured into 50 ml of ice-water and adjusted to pH 7 with 2N sulfuric acid. The organic layer was separated and the aqueous layer was extracted exhaustively with ether. The combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting dark brown oil was subjected to flash chromatography (eluent: dichloromethane) followed by recrystallisation from ethanol - water (addition of charcoal) to afford 1.49 g (50%) of **14** as orange needles, which were used for the subsequent reaction step without further purification. An analytically pure sample was obtained by a second recrystallisation step from diisopropyl ether - light petroleum affording colorless needles of mp 83-84°C; ^{1}H-nmr (300 MHz, $CDCl_3$): δ 7.70-7.35 (m, 6H, Ph-H, pyridazine H-4, pyridazine H-5), 5.71 (s, 1H, NC-CH); ir (KBr): cm^{-1} 2255 (C≡N); ms: m/z (%) 299/297 (M^+, 13/75), 298/296 (M^+-1, 45/100), 262 (32), 227 (23), 87 (27), 86 (27), 85 (40), 51 (31), 50 (38), 43 (45), 42 (32), 41 (25). *Anal.* Calcd for $C_{13}H_7N_3ClF_3$: C, 52.46; H, 2.37; N, 14.12. Found: C, 52.49; H, 2.07; N, 14.04.

3-Pyridazinyl(3-trifluoromethylphenyl)acetonitrile (**15**)

A mixture of 2.97 g (10 mmol) of **14**, 3.15 g (50 mmol) of ammonium formate, and 0.57 g of 10% palladium - charcoal in 50 ml of methanol was warmed up to 70°C under a nitrogen atmosphere until tlc indicated total consumption of **14**. After removal of the catalyst by filtration and evaporation of methanol *in vacuo*, the residue was taken up in dichloromethane and subjected to flash chromatography (eluents:

first dichloromethane, then ether). The etheral fraction was evaporated and the remaining crude **15** was recrystallized from diisopropyl ether - light petroleum to yield 1.08 g (41%) of **15** as orange needles with mp 67°C; ^{1}H-nmr (200 MHz, $CDCl_3$): δ 9.17 (dd, $J_{4,6}$ = 1.8 Hz, $J_{5,6}$ = 4.9 Hz, 1H, pyridazine H-6), 7.80-7.30 (m, 6H, Ph-H, pyridazine H-4, pyridazine H-5), 5.72 (s, 1H, NC-CH); ir (KBr): cm^{-1} 2249 (C≡N); ms: m/z (%) 263 (M^+, 55), 262 (100), 193 (42), 140 (22), 43 (24). *Anal.* Calcd for $C_{13}H_8N_3F_3$: C, 59.32; H, 3.06; N, 15.96. Found: C, 59.61; H, 2.87; N, 16.08.

3-Pyridazinyl(3-trifluoromethylphenyl)methanone (**1b**)

A 30% aqueous sodium hydroxide solution (3 ml, 22.5 mmol) was added dropwise to a stirred mixture of 2.63 g (10 mmol) of **15** and 0.11 g (0.5 mmol) of triethylbenzylammonium chloride in 50 ml of methanol. The solution was vigorously stirred at room temperature until the starting material was completely consumed (tlc monitoring). Then methanol was removed *in vacuo*, the residue was taken up in 150 ml of dichloromethane, and the organic layer was washed with water until the aqueous phase had pH 7. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed to give crude **1b**. Recrystallisation from diisopropyl ether - light petroleum afforded 1.92 g (76%) of **1b** as yellow needles with mp 62.5°C; ^{1}H-nmr (200 MHz, $CDCl_3$): δ 9.32 (dd, $J_{5,6}$ = 5.2 Hz, $J_{4,6}$ = 1.7 Hz, 1H, pyridazine H-6), 8.50-8.30 (m, 2H, Ph-H), 8.17 (dd, $J_{4,5}$ = 8.4 Hz, $J_{4,6}$ = 1.7 Hz, 1H, pyridazine H-4), 7.85-7.75 (m, 1H, Ph-H), 7.70 (dd, $J_{4,5}$ = 8.4 Hz, $J_{5,6}$ = 5.2 Hz, 1H, pyridazine H-5), 7.65-7.55 (m, 1H, Ph-H); ir (KBr): cm^{-1} 1672 (C=O); ms: m/z (%) 252 (M^+, 16), 224 (30), 183 (33), 173 (75), 145 (100), 95 (22), 75 (24), 43 (35). *Anal.* Calcd for $C_{12}H_7N_2OF_3$: C, 57.15; H, 2.80; N, 11.11. Found: C, 57.06; H, 2.50; N, 11.08.

5-(3-Trifluoromethylbenzoyl)pyridazine-4-carboxylic acid (**20**)

4-Pyridazinecarboxylic acid[11] (4.96 g, 40 mmol) and 3-trifluoromethylbenzaldehyde (20.89 g, 120 mmol) were dissolved in 80 ml of 6 N sulfuric acid at 5°C. Acetic acid was added to obtain a clear solution (about 100 ml). Then 15 ml (120 mmol) of *tert*-butyl hydroperoxide (80% solution in di-*tert*-butyl peroxide) and a saturated aqueous solution of 33.36 g (120 mmol) of iron(II)sulfate heptahydrate were added simultaneously while keeping the temperature below 10°C. After complete addition, stirring was continued for 1 h at room temperature. Then the reaction mixture was brought to a volume of 500 ml by addition of water, and was then exhaustively extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and evaporated *in*

vacuo. The resulting brown residue was recrystallized from water - ethanol (addition of charcoal) to yield 4.74 g (40%) of **20** as slightly brown powder with mp 180°C (decomp.); ^{1}H-nmr (300 MHz, DMSO-d_6): δ 9.69 (s, 1H, pyridazine H-6), 9.59 (s, 1H, pyridazine H-3), 8.15-7.65 (m, 4H, Ph-H); ir (KBr): cm^{-1} 1717 (COOH), 1682 (C=O) ; ms: m/z (%) 296 (M^+, 5), 173 (38), 145 (27), 44 (23), 43 (100). *Anal.* Calcd for $C_{13}H_7N_2O_3F_3$: C, 52.71; H, 2.38; N, 9.46. Found: C, 52.56; H, 2.24; N, 9.25.

4-Pyridazinyl(3-trifluoromethylphenyl)methanone (**2b**)

A mixture of 0.50 g (1.69 mmol) of **20** and 0.50 g of copper powder were triturated and heated in a kugelrohr apparatus at 200°C under reduced pressure (0.01 mm Hg). The dark brown distillate was purified by mplc (eluent: dichloromethane - ethyl acetate) to yield 277 mg (65%) of **2b** as yellow oil; ^{1}H-nmr (200 MHz, $CDCl_3$): δ 9.47 (dd, $J_{3,6}$ = 1.4 Hz, $J_{5,6}$ = 5.2 Hz, 1H, pyridazine H-6), 9.45 (dd, $J_{3,6}$ = 1.4 Hz, $J_{3,5}$ = 2.2 Hz, 1H, pyridazine H-3), 8.10-7.60 (m, 4H, Ph-H), 7.72 (dd, $J_{3,5}$ = 2.2 Hz, $J_{5,6}$ = 5.2 Hz, 1H, pyridazine H-5); ir (NaCl): cm^{-1} 1672 (C=O); ms: m/z (%) 252 (M^+, 96), 173 (100), 145 (58), 51 (29). *Anal.* Calcd for $C_{12}H_7N_2OF_3$: C, 57.15; H, 2.80; N, 11.11 Found: C, 57.17; H, 2.95; N, 10.87.

2-Pyrimidinylphenylacetonitrile (**17a**)[7,8,9]

Sodium hydride (4.00 g of a 60% suspension in paraffine oil, 100 mmol)) was added to a solution of 11.7 g (100 mmol) of phenylacetonitrile in 100 ml of dry tetrahydrofuran at -5°C under a nitrogen atmosphere. After stirring for 10 min, 4.58 g (40 mmol) of 2-chloropyrimidine (Fluka, recrystallized from n-hexane) were added portionwise. Stirring was continued for 30 min at -5°C and then for another 6 h at room temperature. Then the solution was poured into 150 ml of ice-water and adjusted to pH 7 with 6N sulfuric acid. The organic layer was separated and the aqueous layer was extracted exhaustively with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting oil was extracted with cold light petroleum to remove the paraffine oil and then the excess of phenylacetonitrile was removed by distillation in a kugelrohr apparatus (50°C, 0.005 mm Hg). The resulting residue was recrystallized from diisopropyl ether - light petroleum to yield 5.08 g (52%) of **17a** as slightly yellow needles with mp 92°C (lit.,[7] bp 170°C, 2 mm Hg).

2-Pyrimidinylphenylmethanone (3a)[8,9]

Compound (**3a**) was prepared starting from 1.95 g (10 mmol) of **17a** according to the procedure given for the synthesis of **1b**. Crude **3a** was recrystallized from diisopropyl ether - n-hexane to give 1.60 g (87%) of **3a** as yellow needles of mp 87-88°C (lit.,[8] mp 85-85.5°C).

2-Pyrimidinyl(3-trifluoromethylphenyl)acetonitrile (17b)

To a solution of 1.15 g (10 mmol) of 2-chloropyrimidine (Fluka, recrystallized from n-hexane) in 50 ml of dry tetrahydrofuran was added 0.40 g (10 mmol) of sodium hydride (60% suspension in paraffine oil) portionwise at 0°C under nitrogen atmosphere. Then 1.85 g (10 mmol) of 3-trifluoromethylphenylacetonitrile in 10 ml of dry tetrahydrofuran were added dropwise. After stirring for 4 h at room temperature, the solution was heated to 50°C for another 2 h. Then the solution was poured into 150 ml of ice-water and adjusted to pH 7 with 2N sulfuric acid. The organic layer was separated and the aqueous layer was extracted exhaustively with ether. The combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The resulting red oil was distilled in a kugelrohr apparatus (110°C, 0.005 mm Hg). The oily residue was purified by mplc (eluent: dichloromethane) to obtain 0.51 g (19%) of **17b** as an orange oil; ^{1}H-nmr (200 MHz, $CDCl_3$): δ 8.73 (d, $J_{4/6,5}$ = 4.9 Hz, 2H, pyrimidine H-4/6), 7.90-7.40 (m, 4H, Ph-H), 7.26 (t, $J_{4/6,5}$ = 4.9 Hz, 1H, pyrimidine H-5), 5.48 (s, 1H, NC-CH); ir (NaCl): cm^{-1} 2253 (C≡N); ms: m/z (%) 263 (M^+, 91), 262 (77), 252 (57), 237 (41), 236 (68), 224 (28), 193 (22), 173 (100), 145 (85), 43 (87). *Anal.* Calcd for $C_{13}H_8N_3F_3$: C, 59.32; H, 3.06; N, 15.96. Found: C, 59.51; H, 3.16; N, 15.98.

2-Pyrimidinyl(3-trifluoromethylphenyl)methanone (3b)

Compound (**3b**) was prepared starting from 2.63 g (10 mmol) of **17b** according to the procedure given for the synthesis of **1b**. Crude **3b** was recrystallized from diisopropyl ether - light petroleum (addition of charcoal) to give 1.99 g (79%) of **3b** as slightly yellow needles of mp 51°C; ^{1}H-nmr (200 MHz, $CDCl_3$): δ 8.95 (d, $J_{4/6,5}$ = 4.9 Hz, 2H, pyrimidine H-4/6), 8.40-8.20 (m, 2H, Ph-H), 7.90-7.80 (m, 1H, Ph-H), 7.70-7.55 (m, 1H, Ph-H), 7.50 (t, $J_{4/6,5}$ = 4.9 Hz, 1H, pyrimidine H-5); ir (KBr): cm^{-1} 1719 (C=O); ms: m/z (%) 252 (M^+, 32), 173 (70), 145 (100), 95 (23). *Anal.* Calcd for $C_{12}H_7N_2OF_3$: C, 57.15; H, 2.80; N 11.11. Found: C, 56.99; H, 2.68; N, 10.94.

2-Pyrimidinyl(3-trifluoromethylphenyl)methanone (**3b**)

To a solution of 2.10 g (20 mmol) of 2-pyrimidinecarbonitrile[10] in 40 ml of dry ether was added a solution of 3-trifluoromethylphenylmagnesium bromide [(prepared from 0.58 g (24 mmol) of magnesium and 5.40 g (24 mmol) of 3-trifluoromethylbromobenzene in 40 ml of dry diethylether)] dropwise at -15°C under a nitrogen atmosphere. Then the reaction mixture was allowed to warm up to room temperature while stirring overnight. After addition of 40 ml of 2 N hydrochloric acid, stirring was continued for 1 h. The solution was then made alkaline by addition of saturated sodium bicarbonate solution. After exhaustive extraction of the aqueous phase with ether, the combined organic layers were dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was recrystallized from diisopropyl ether - light petroleum (addition of charcoal) to give 3.69 g (73%) of **3b** as slightly yellow needles with mp 51°C.

Phenyl(4-pyrimidinyl)methanone (**4a**)[9]

To a cooled solution (-80°C) of 1.52 g (10 mmol) of ethyl 4-pyrimidinecarboxylate[14] in 20ml of tetrahydrofuran were added rapidly 6.57 ml (12 mmol) of phenylmagnesium chloride (25% solution in tetrahydrofuran). Then the reaction mixture was allowed to slowly warm up to room temperature. After addition of 20 ml of saturated aqueous ammonium chloride solution, the organic layer was separated and the aqueous phase was exhaustively extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by mplc (eluent: dichloromethane - ethyl acetate) to yield 1.44 g (80%) of **4a** as colorless needles with mp 98-100°C (lit.,[9] mp 104-106°C).

4-Pyrimidinyl(3-trifluoromethylphenyl)methanone (**4b**)

To a cooled solution (-80°C) of 3.75 g (15 mmol) of 3-trifluoromethylbromobenzene in 40 ml of a 1 : 1 mixture of dry ether and dry tetrahydrofuran was added 7 ml (15 mmol) of a 1.6 M solution of n-butyllithium in n-hexane under a nitrogen atmosphere during 45 min. After additional stirring for 1 h at -80°C the lithium salt suspension was added *via* syringe to 1.93 g (14 mmol) of methyl 4-pyrimidinecarboxylate[15] dissolved in 80 ml of a 1 : 3 mixture of dry ether and dry tetrahydrofuran at -90°C. Then the reaction mixture was allowed to slowly warm up to room temperature overnight. After addition of 20 ml of saturated aqueous ammonium chloride solution, the organic layer was separated and the aqueous phase was exhaustively extracted with dichloromethane. The combined organic layers were

dried over anhydrous sodium sulfate and evaporated to dryness. The oily residue was purified by column chromatography (eluent: dichloromethane) to yield 2.81 g (80%) of **4b** as yellow oil; ^{1}H-nmr (200 MHz, $CDCl_3$): δ 9.39 (d, $J_{2,6}$ = 1.4 Hz, 1H, pyrimidine H-2), 9.05 (d, $J_{5,6}$ = 5.1 Hz, 1H, pyrimidine H-6), 8.50-8.30 (m, 2H, Ph-H), 7.96 (dd, $J_{2,6}$ = 1.4 Hz, $J_{5,6}$ = 5.1 Hz, 1H, pyrimidine H-5), 7.90-7.60 (m, 2H, Ph-H); ir (NaCl): cm^{-1} 1680 (C=O); ms: m/z (%) 252 (M^+, 44), 224 (25), 173 (100), 145 (72), 43 (56). *Anal.* Calcd for $C_{12}H_7N_2OF_3$: C, 57.15; H, 2.80; N, 11.11. Found: C, 58.06; H, 2.64; N, 11.27.

Phenyl(5-pyrimidinyl)methanone (5a)[18]

To a cooled solution (-110°C) of 4.00 g (25 mmol) of 5-bromopyrimidine in 60 ml of a 1 : 1 mixture of dry tetrahydrofuran and dry ether were added 16 ml (25 mmol) of a 1.6 M solution of n-butyllithium in n-hexane under a nitrogen atmosphere while keeping the temperatur below -100°C. After 15 min, a solution of 2.92 g (27.5 mmol) of benzaldehyde in 10 ml of dry tetrahydrofuran was added slowly. Then the mixture was allowed to warm up to room temperature and 50 ml of saturated aqueous ammonium chloride solution were added, the organic layer was separated and the aqueous phase was exhaustively extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and evaporated to dryness. The oily residue was dissolved in 50 ml of dichloromethane and 24 g (276 mmol) of activated manganese dioxide were added slowly. The suspension was then stirred at room temperature. After 24 h, the mixture was filtered through Celite, the Celite was washed several times with dichloromethane and the combined organic layers were evaporated to dryness to give crude **5a**. Recrystallisation from water - ethanol (addition of charcoal) gave 3.68 g (80%) of **5a** as colorless needles, mp 95°C (lit.,[18] mp 92-93°C).

5-Pyrimidinyl(3-trifluoromethylphenyl)methanone (5b)

Compound (**5b**) was prepared starting from 4.79 g (27.5 mmol) of 3-trifluoromethylbenzaldehyde according to the procedure given for the synthesis of **5a**. Crude **5b** was recrystallized from water - ethanol (addition of charcoal) to give 4.00 g (64%) of **5b** as slightly yellow needles, mp 111°C; ^{1}H-nmr (200 MHz, $CDCl_3$): δ 9.38 (s, 1H, pyrimidine H-2), 9.07 (s, 2H, pyrimidine H-4/6), 8.30-7.60 (m, 4H, Ph-H); ir (KBr): cm^{-1} 1671 (C=O); ms: m/z (%) 252 (M^+, 73), 183 (73), 173 (85), 145 (89), 119 (30), 107 (52), 79 (23), 69 (100), 53 (27), 52 (22), 43 (37). *Anal.* Calcd for $C_{12}H_7N_2OF_3$: C, 57.15; H, 2.80; N, 11.11. Found: C, 57.00; H, 2.64; N, 11.02.

2-Pyrazinyl(3-trifluoromethylphenyl)methanone (**6b**)

To a cooled solution (-80°C) of 2.25 g (10 mmol) of 3-trifluoromethylbromobenzene in 10 ml of a 1 : 1 mixture of dry ether and dry tetrahydrofuran was added 7 ml (11 mmol) of a 1.6 M solution of n-butyllithium in n-hexane under nitrogen atmosphere during 45 min. After additional stirring for 1 h at -80°C, a solution of 1.38 g (10 mmol) of methyl 2-pyrazinecarboxylate[13] dissolved in 20 ml of a 1 : 1 mixture of dry ether and dry tetrahydrofuran was added dropwise. Then the reaction mixture was allowed to warm up slowly to room temperature. After addition of 50 ml of saturated aqueous ammonium chloride solution, the organic layer was separated and the aqueous phase was exhaustively extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and evaporated to dryness. The oily residue was purified by column chromatography (eluent: dichloromethane) to yield 2.02 g (80%) of **6b** as an orange oil; ^{1}H-nmr (300 MHz, $CDCl_3$): δ 9.30 (d, $J_{3,6}$ = 1.5 Hz, 1H, pyrazine H-3), 8.79 (d, $J_{5,6}$ = 2.4 Hz, 1H, pyrazine H-5), 8.67 (dd, $J_{3,6}$ = 1.5 Hz, $J_{5,6}$ = 2.4 Hz, 1H, pyrazine H-6), 8.50-7.70 (m, 4H, Ph-H); ir (NaCl): cm^{-1} 1672 (C=O); ms: m/z (%) 252 (M^+, 49), 173 (100), 145 (80), 52 (26). *Anal.* Calcd for $C_{12}H_7N_2OF_3$: C, 57.15; H, 2.80; N, 11.11. Found: C, 57.18; H, 2.77; N, 11.20.

Preparation of ketoximes 7a,b - 12a,b

E- and Z-Phenyl(3-pyridazinyl)methanone oxime (**E-7a** and **Z-7a**)

A suspension of 139 mg (2 mmol) of hydroxylamine hydrochloride, 328 mg (4 mmol) of sodium acetate, and 184 mg (1 mmol) of **1a** in 6 ml of ethanol was stirred at room temperature for 24 h. After removal of the solvent under reduced pressure, the residue was recrystallized from water - ethanol to give 167 mg (84%) of **7a**[28] as pink needles. Separation by mplc (eluent: ethyl acetate) afforded 76 mg (38%) of **Z-7a**[28] (faster eluted component) and 32 mg (16%) of **E-7a**[28] (slower eluted component).

Compound (**Z-7a**) was obtained as colorless crystals of mp 182°C (ethyl acetate); ^{1}H-nmr (200 MHz, DMSO-d_6) δ 11.90 (s, 1H, OH), 9.27 (dd, $J_{5,6}$ = 4.4 Hz, $J_{4,6}$ = 2.6 Hz, 1H, pyridazine H-6), 7.90-7.80 (m, 2H, pyridazine H-4, pyridazine H-5), 7.40-7.35 (m, 5H, Ph-H); ms: m/z (%) 199 (M^+, 100), 169 (20), 168 (30), 115 (35), 78 (22). *Anal.* Calcd for $C_{11}H_9N_3O$ x 0.2 H_2O: C, 65.14; H, 4.67; N, 20.72. Found: C, 65.23; H, 4.49; N, 20.50.

Compound (**E-7a**) was obtained as colorless crystals of mp 168°C (ethyl acetate); ^{1}H-nmr (200 MHz, DMSO-d_6): δ 12.03 (s, 1H, OH), 9.19 (dd, $J_{5,6}$ = 4.8 Hz, $J_{4,6}$ = 1.6 Hz, 1H, pyridazine H-6), 8.10 (dd,

$J_{4,5}$ = 8.6 Hz, $J_{4,6}$ = 1.6 Hz, 1H, pyridazine H-4), 7.74 (dd, $J_{4,5}$ = 8.6 Hz, $J_{5,6}$ = 4.8 Hz, 1H, pyridazine H-5), 7.50-7.30 (m, 5H, Ph-H); ms: m/z (%) 199 (M^+, 76), 198 (100), 182 (24), 169 (28), 168 (44), 115 (36), 78 (34), 51 (24). *Anal.* Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.35; H, 4.69; N, 20.87.

E- and Z-Phenyl(4-pyridazinyl)methanone oxime (**E-8a** and **Z-8a**)

Compound (**8a**) was prepared from 184 mg (1 mmol) of **2a** according to the procedure given in ref.[20] The residue was recrystallized from water - ethanol to give 190 mg (95%) of **8a**[29] as colorless needles. Separation by mplc (eluent: ethyl acetate) afforded 44 mg (22%) of **Z-8a** (faster eluted component) and 22 mg (11%) of **E-8a** (slower eluted component).

Compound (**Z-8a**) was obtained as colorless crystals of mp 154°C (ethyl acetate); ^{1}H-nmr (80 MHz, DMSO-d_6): δ 11.95 (s, 1H, OH), 9.32 (dd, $J_{3,6}$ = 1.2 Hz, $J_{5,6}$ = 5.3 Hz, 1H, pyridazine H-6), 9.19 (dd, $J_{3,5}$ = 2.1 Hz, $J_{3,6}$ = 1.2 Hz, 1H, pyridazine H-3), 7.66 (dd, $J_{3,5}$ = 2.1 Hz, $J_{5,6}$ = 5.3 Hz, 1H, pyridazine H-5), 7.50-7.30 (m, 5H, Ph-H); ms: m/z (%) 199 (M^+, 100), 78 (44), 51 (44). *Anal.* Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.57; H, 4.60; N, 20.83.

Compound (**E-8a**) was obtained as colorless crystals of mp 150°C (ethyl acetate); ^{1}H-nmr (80 MHz, DMSO-d_6): δ 12.24 (s, 1H, OH), 9.29 (dd, $J_{3,6}$ = 1.2 Hz, $J_{3,5}$ = 2.3 Hz, 1H, pyridazine H-3), 9.19 (dd, $J_{3,6}$ = 1.2 Hz, $J_{5,6}$ = 5.4 Hz, 1H, pyridazine H-6), 7.60-7.30 (m, 6H, pyridazine H-5, Ph-H); ms: m/z (%) 199 (M^+, 100), 182 (22), 169 (28), 78 (46), 51 (45). *Anal.* Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.62; H, 4.58; N, 21.12.

E- and Z-Phenyl(2-pyrimidinyl)methanone oxime (**E-9a** and **Z-9a**)

Compound (**9a**) was prepared from 184 mg (1 mmol) of **3a** according to the procedure given for the synthesis of **7a**. The residue was recrystallized from water - ethanol to give 107 mg (54%) of **E-9a** as pink needles of mp 242°C; ^{1}H-nmr (200 MHz, DMSO-d_6): δ 11.86 (s, 1H, OH), 8.81 (d, $J_{4/6,5}$ = 5.0 Hz, 2H, pyrimidine H-4/6), 7.47 (t, $J_{4/6,5}$ = 5.0 Hz, 1H, pyrimidine H-5), 7.40-7.25 (m, 5H, Ph-H); ms: m/z (%) 199 (M^+, 67), 198 (42), 182 (31), 169 (30), 168 (50), 115 (24), 91 (31), 77 (35), 51 (47), 43 (100). *Anal.* Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.30; H, 4.62; N, 20.96.

The mother liquid obtained from the recrystallisation of **E-9a** was evaporated *in vacuo* and the residue was subjected to preparative tlc (eluent: ethyl acetate - dichloromethane) followed by recrystallisation from

ethanol - water to afford 45 mg (23%) of **Z-9a** as slightly yellow needles of mp 203°C; ^{1}H-nmr (200 MHz, DMSO-d_6): δ 11.43 (s, 1H, OH), 8.94 (d, $J_{4/6,5}$ = 5.0 Hz, 2H, pyrimidine H-4/6), 7.56 (t, $J_{4/6,5}$ = 5.0 Hz, 1H, pyrimidine H-5), 7.45-7.25 (m, 5H, Ph-H); ms: m/z (%) 199 (M^+, 68), 198 (43), 182 (32), 169 (32), 168 (53), 115 (27), 80 (30), 77 (38), 51 (58), 43 (100). *Anal.* Calcd for $C_{11}H_9N_3O$ x 0.2 H_2O: C, 65.14; H, 4.67; N, 20.72. Found: C, 65.23; H, 4.44; N, 20.61.

E- and Z-Phenyl(4-pyrimidinyl)methanone oxime (**E-10a** and **Z-10a**)

Compound (**10a**) was prepared from 184 mg (1 mmol) of **4a** according to the procedure given for the synthesis of **7a**. The reaction mixture was made alkaline by addition of 20 ml of saturated sodium bicarbonate solution and extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and evaporated *in vacuo*. The oily residue was recrystallized from ethyl acetate - light petroleum to give 150 mg (75%) of **10a** as violet crystals. Separation by column chromatography (eluent: ethyl acetate - dichloromethane) afforded 22 mg (11%) of **Z-10a** (faster eluted component) and 34 mg (17%) of **E-10a** (slower eluted component).

Compound (**Z-10a**) was obtained as colorless crystals of mp 135°C (ethyl acetate - dichloromethane); ^{1}H-nmr (80 MHz, DMSO-d_6): δ 11.77 (s, 1H, OH), 9.30 (d, $J_{2,5}$ = 1.4 Hz, 1H, pyrimidine H-2), 8.93 (d, $J_{5,6}$ = 5.1 Hz, 1H, pyrimidine H-6), 7.67 (dd, $J_{2,5}$ = 1.4 Hz, $J_{5,6}$ = 5.2 Hz, 1H, pyrimidine H-5), 7.40-7.30 (m, 5H, Ph-H); ms: m/z (%) 199 (M^+, 30), 149 (21), 115 (28), 77 (31), 71 (48), 70 (47), 69 (45), 57 (59), 56 (66), 43 (100). *Anal.* Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.39; H, 4.69; N, 20.86.

Compound (**E-10a**) was obtained as colorless crystals of mp 162°C (ethyl acetate - dichloromethane); ^{1}H-nmr (80 MHz, DMSO-d_6): δ 12.19 (s, 1H, OH), 9.08 (d, $J_{2,5}$ = 1.4 Hz, 1H, pyrimidine H-2), 8.82 (d, $J_{5,6}$ = 5.3 Hz, 1H, pyrimidine H-6), 7.90 (dd, $J_{2,5}$ = 1.4 Hz; $J_{5,6}$ = 5.3 Hz, 1H, pyrimidine H-5), 7.50-7.20 (m, 5H, Ph-H); ms: m/z (%) 199 (M^+, 36), 115 (32), 114 (33), 85 (26), 84 (27), 77 (31), 71 (44), 70 (42), 69 (30), 57 (59), 56 (62), 43 (100). *Anal.* Calcd for $C_{11}H_9N_3O$ x 0.2 H_2O: C, 65.14; H, 4.67; N, 20.72. Found: C, 65.47; H, 4.57; N, 20.42.

E- and Z-Phenyl(5-pyrimidinyl)methanone oxime (**E-11a** and **Z-11a**)

Compound (**11a**) was prepared from 184 mg (1 mmol) of **5a** according to the procedure given for the synthesis of **10a**, but the reaction was carried out at 50°C. Separation of the oily residue by column

chromatography (eluent: ethyl acetate - dichloromethane) afforded 81 mg (41%) of **Z-11a** (faster eluted component) and 35 mg (18%) of **E-11a** (slower eluted component).

Compound (**Z-11a**) was obtained as yellow crystals of mp 138°C (ethyl acetate - dichloromethane); ^{1}H-nmr (200 MHz, DMSO-d_6): δ 11.86 (s, 1H, OH), 9.24 (s, 1H; pyrimidine H-2), 8.79 (s, 2H, pyrimidine H-4/6), 7.50-7.30 (m, 5H, Ph-H); ms: m/z (%) 199 (M^+, 42), 182 (60), 77 (70), 52 (27), 51 (50), 43 (100). *Anal.* Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.34; H, 4.58; N, 21.03.

Compound (**E-11a**) was obtained as yellow crystals of mp 165°C (ethyl acetate - dichloromethane); ^{1}H-nmr (200 MHz, DMSO-d_6): δ 11.94 (s, 1H, OH), 9.18 (s, 1H, pyrimidine H-2), 8.73 (s, 2H, pyrimidine H-4/6), 7.50-7.30 (m, 5H, Ph-H); ms: m/z (%) 199 (M^+, 78), 182 (100), 155 (36), 51 (22), 43 (54). *Anal.* Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.38; H, 4.54; N, 20.88.

E- and Z-Phenyl(2-pyrazinyl)methanone oxime (**E-12a** and **Z-12a**)

Compound (**12a**) was prepared from 184 mg (1 mmol) of **6a** according to the procedure given for the synthesis of **7a**. The residue was recrystallized from water - ethanol to give 187 mg (94%) of **12a**[30] as colorless needles. Separation by mplc (eluent: ethyl acetate - dichloromethane) afforded 76 mg (38%) of **Z-12a**[30] (faster eluted component) and 70 mg (35%) of **E-12a**[30] (slower eluted component).

Compound (**Z-12a**) was obtained as colorless crystals of mp 138°C (ethyl acetate - dichloromethane); ^{1}H-nmr (80 MHz, DMSO-d_6): δ 11.80 (s, 1H, OH), 8.83 (d, $J_{3,6}$ = 1.4 Hz, 1H, pyrazine H-3), 8.76 (dd, $J_{3,6}$ = 1.4 Hz, $J_{5,6}$ = 2.6 Hz, 1H, pyrazine H-6), 8.68 (d, $J_{5,6}$ = 2.6 Hz, 1H, pyrazine H-5), 7.40-7.30 (m, 5H, Ph-H); ms: m/z (%) 200 (24), 199 (M^+, 100), 198 (64), 182 (30), 169 (76), 168 (48), 115 (26), 78 (30). *Anal.* Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.60; H, 4.76; N, 20.87.

Compound (**E-12a**) was obtained as colorless crystals of mp 162°C (ethyl acetate - dichloromethane); ^{1}H-nmr (80 MHz, DMSO-d_6): δ 12.02 (s, 1H, OH), 9.08 (d, $J_{3,6}$ = 1.3 Hz, 1H, pyrazine H-3), 8.60 (d, $J_{5,6}$ = 2.5 Hz, 1H, pyrazine H-5), 8.54 (dd, $J_{5,6}$ = 2.5 Hz, $J_{3,6}$ = 1.3 Hz, 1H, pyrazine H-6), 7.50-7.30 (m, 5H, Ph-H); ms: m/z (%) 199 (M^+, 100), 169 (30), 78 (23). *Anal.* Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.03; H, 4.44; N, 20.81.

E- and Z-3-Pyridazinyl(3-trifluoromethylphenyl)methanone oxime (**E-7b** and **Z-7b**)

Compound (**7b**) was prepared from 252 mg (1 mmol) of **1b** according to the procedure given for the synthesis of **7a**. The residue was recrystallized from water - ethanol to give 227 mg (85%) of **7b** as pink

needles. Separation by mplc (eluent: ethyl acetate - dichloromethane) afforded 72 mg (27%) of **Z-7b** (faster eluted component) and 67 mg (25%) of **E-7b** (slower eluted component).

Compound (**Z-7b**) was obtained as colorless crystals of mp 176°C (ethyl acetate - dichloromethane); ^{1}H-nmr (200 MHz, DMSO-d_6): δ 12.13 (s, 1H, OH), 9.30 (dd, $J_{5,6}$ = 5.0 Hz, $J_{4,6}$ = 2.1 Hz, 1H, pyridazine H-6), 7.96 (dd, $J_{4,5}$= 8.5 Hz, $J_{4,6}$ = 2.1 Hz, 1H, pyridazine H-4), 7.85 (dd, $J_{4,5}$ = 8.5 Hz, $J_{5,6}$ = 5.0 Hz, 1H, pyridazine H-5), 7.80-7.60 (m, 4H, Ph-H); ms: m/z (%) 267 (M^+, 100), 266 (57), 236 (21), 198 (31), 168 (37). *Anal.* Calcd for $C_{12}H_8N_3OF_3$: C, 53.94; H, 3.02; N, 15.73. Found: C, 54.16; H, 3.01; N, 15.49.

Compound (**E-7b**) was obtained as colorless crystals of mp 169°C (ethyl acetate - dichloromethane); ^{1}H-nmr (200 MHz, DMSO-d_6): δ 12.30 (s, 1H, OH), 9.21 (dd, $J_{5,6}$ = 5.2 Hz, $J_{4,6}$ = 1.7 Hz, 1H, pyridazine H-6), 8.17 (dd, $J_{4,5}$ = 8.6 Hz, $J_{4,6}$ = 1.7 Hz, 1H, pyridazine H-4), 7.76 (dd, $J_{4,5}$ = 8.6 Hz, $J_{5,6}$ = 5.2 Hz, 1H, pyridazine H-5), 7.85-7.60 (m, 4H, Ph-H); ms: m/z (%) 267 (M^+, 100), 266 (62), 250 (28), 237 (20), 236 (33), 198 (68), 183 (35), 168 (58), 160 (61), 159 (49), 145 (22), 43 (53). *Anal.* Calcd for $C_{12}H_8N_3OF_3$: C, 53.94; H, 3.02; N, 15.73. Found: C, 53.94; H, 2.93; N, 15.61.

E- and Z-4-Pyridazinyl(3-trifluoromethylphenyl)methanone oxime (**E-8b** and **Z-8b**)

Compound (**8b**) was prepared from 252 mg (1 mmol) of **2b** according to the procedure given for the synthesis of **10a**. Separation of the oily residue by mplc (eluent: ethyl acetate - dichloromethane) afforded 136 mg (51%) of **Z-8b** (faster eluted component) and 62 mg (23%) of **E-8b** (slower eluted component).

Compound (**Z-8b**) was obtained as colorless crystals of mp 156°C (ethyl acetate - dichloromethane); ^{1}H-nmr (200 MHz, DMSO-d_6): δ 12.30 (s, 1H, OH), 9.39 (dd, $J_{3,6}$ = 1.2 Hz, $J_{5,6}$ = 5.4 Hz, 1H, pyridazine H-6), 9.25 (dd, $J_{3,5}$ = 2.4 Hz, $J_{3,6}$ = 1.2 Hz, 1H, pyridazine H-3), 7.73 (dd, $J_{3,5}$ = 2.4 Hz, $J_{5,6}$ = 5.4 Hz, 1H, pyridazine H-5), 7.80-7.55 (m, 4H, Ph-H); ms: m/z (%) 267 (M^+, 100), 236 (22), 145 (20), 51 (20). *Anal.* Calcd for $C_{12}H_8N_3OF_3$: C, 53.94; H, 3.02; N, 15.73. Found: C, 53.68; H, 2.95; N, 15.51.

Compound (**E-8b**) was obtained as colorless crystals of mp 150°C (ethyl acetate - dichloromethane); ^{1}H-nmr (200 MHz, DMSO-d_6): δ 12.46 (s, 1H, OH), 9.33 (dd, $J_{3,6}$ = 1.1 Hz, $J_{3,5}$ = 2.3 Hz, 1H, pyridazine H-3), 9.20 (dd, $J_{3,6}$ = 1.1 Hz, $J_{5,6}$ = 5.4 Hz, 1H, pyridazine H-6), 7.80-7.50 (m, 4H, Ph-H), 7.40 (dd, $J_{3,5}$ = 2.3 Hz, $J_{5,6}$ = 5.4 Hz, 1H, pyridazine H-5); ms: m/z (%) 267 (M^+, 100), 236 (20), 145 (23). *Anal.* Calcd for $C_{12}H_8N_3OF_3$: C, 53.94; H, 3.02; N, 15.73. Found: C, 54.19; H, 2.78; N, 15.51.

E- and Z-2-Pyrimidinyl(3-trifluoromethylphenyl)methanone oxime (**E-9b** and **Z-9b**)

Compound (**9b**) was prepared from 252 mg (1 mmol) of **3b** according to the procedure given for the synthesis of **7a**. The residue was recrystallized from water - ethanol to give 174 mg (65%) of **E-9b** as pink needles of mp 183°C; ^{1}H-nmr (200 MHz, DMSO-d_6): δ 12.18 (s, 1H, OH), 8.82 (d, $J_{4/6,5}$ = 4.8 Hz, 2H, pyrimidine H-4/6), 7.80-7.55 (m, 4H, Ph-H), 7.48 (t, $J_{4/6,5}$ = 4.8 Hz, 1H, pyrimidine H-5); ms: m/z (%) 267 (M^+, 100), 266 (33), 250 (36), 217 (20), 168 (54). *Anal.* Calcd for $C_{12}H_8N_3OF_3$: C, 53.94; H, 3.02; N, 15.73. Found: C, 53.95; H, 2.83; N, 15.62.

The mother liquor obtained from recrystallization of **E-9b** was evaporated to dryness and the residue was subjected to preparative tlc (eluent: ethyl acetate - dichloromethane) followed by recrystallization from ethanol - water to afford 22 mg (8%) of **Z-9b** as yellowish needles of mp 151°C; ^{1}H-nmr (200 MHz, DMSO-d_6): δ 11.81 (s, 1H, OH), 8.98 (d, $J_{4/6,5}$ = 4.8 Hz, 2H, pyrimidine H-4/6), 7.60 (t, $J_{4/6,5}$ = 4.8 Hz, 1H, pyrimidine H-5), 7.80-7.50 (m, 4H, Ph-H); ms: m/z (%) 267 (M^+, 100), 266 (44), 250 (48), 217 (25), 168 (70), 160 (26), 159 (23), 43 (29). *Anal.* Calcd for $C_{12}H_8N_3OF_3$: C, 53.94; H, 3.02; N, 15.73. Found: C, 54.18; H, 2.80; N, 15.68.

E- and Z-4-Pyrimidinyl(3-trifluoromethylphenyl)methanone oxime (**E-10b** and **Z-10b**)

Compound (**10b**) was prepared from 252 mg (1 mmol) of **4b** according to the procedure given for the synthesis of **10a**. The oily residue was recrystallized from diisopropyl ether - light petroleum to give 211 mg (79%) of **10b** as violet crystals. Separation of the oily residue by column chromatography (eluent: ethyl acetate - dichloromethane) afforded 122 mg (46%) of **Z-10b** (faster eluted component) and 113 mg (42%) of **E-10b** (slower eluted component).

Compound (**Z-10b**) was obtained as colorless crystals of mp 170°C (ethyl acetate - dichloromethane); ^{1}H-nmr (200 MHz, DMSO-d_6): δ 12.18 (s, 1H, OH), 9.33 (d, $J_{2,5}$ = 1.6 Hz, 1H, pyrimidine H-2), 8.98 (d, $J_{5,6}$ = 5.2 Hz, 1H, pyrimidine H-6), 7.79 (dd, $J_{2,5}$ = 1.6 Hz, $J_{5,6}$ = 5.2 Hz, 1H, pyrimidine H-5), 7.90-7.50 (m, 4H, Ph-H); ms: m/z (%) 267 (M^+, 100), 266 (39), 237 (34), 217 (22), 183 (56), 168 (51), 145 (22), 80 (20), 52 (61), 43 (42). *Anal.* Calcd for $C_{12}H_8N_3OF_3$: C, 53.94; H, 3.02; N, 15.73. Found: C, 54.20; H, 3.20; N, 15.45.

Compound (**E-10b**) was obtained as colorless crystals of mp 160°C (ethyl acetate - dichloromethane); ^{1}H-nmr (200 MHz, DMSO-d_6): δ 12.47 (s, 1H, OH), 9.09 (d, $J_{2,5}$ = 1.2 Hz, 1H, pyrimidine H-2), 8.84 (d, $J_{5,6}$ = 5.4 Hz, 1H, pyrimidine H-6), 7.98 (dd, $J_{2,5}$ = 1.2 Hz, $J_{5,6}$ = 5.4 Hz, 1H, pyrimidine H-5), 7.85-7.55

(m, 4H, Ph-H); ms: m/z (%) 267 (M^+, 39), 183 (20), 168 (24), 69 (100), 52 (37), 43 (47). *Anal.* Calcd for $C_{12}H_8N_3OF_3$: C, 53.94; H, 3.02; N, 15.73. Found: C, 54.09; H, 3.06; N, 15.49.

E- and Z-5-Pyrimidinyl(3-trifluoromethylphenyl)methanone oxime (**E-11b** and **Z-11b**)

Compound (**11b**) was prepared from 252 mg (1 mmol) of **5b** according to the procedure given for the synthesis of **11a**. Separation of the oily residue by column chromatography (eluent: ethyl acetate - dichloromethane) afforded 82 mg (31%) of **Z-11b** (faster eluted component) and 43 mg (16%) of **E-11b** (slower eluted component).

Compound (**Z-11b**) was obtained as yellow crystals of mp 145°C (ethyl acetate - dichloromethane); ^{1}H-nmr (200 MHz, DMSO-d_6): δ 12.17 (s, 1H, OH), 9.26 (s, 1H, pyrimidine H-2), 8.84 (s, 2H, pyrimidine H-4/6), 7.90-7.55 (m, 4H, Ph-H), ms: m/z (%) 267 (M^+, 100), 266 (88), 250 (29), 236 (22), 235 (26), 230 (58), 198 (62), 145 (30), 43 (21). *Anal.* Calcd for $C_{12}H_8N_3OF_3$: C, 53.94; H, 3.02; N, 15.73. Found: C, 54.07; H, 2.90; N, 15.62.

Compound (**E-11b**) was obtained as yellow crystals of mp 180°C (ethyl acetate - dichloromethane); ^{1}H-nmr (200 MHz, DMSO-d_6): δ 12.18 (s, 1H, OH), 9.19 (s, 1H, pyrimidine H-2), 8.75 (s, 2H, pyrimidine H-4/6), 7.90-7.60 (m, 4H, Ph-H); ms: m/z (%) 267 (M^+, 100), 266 (20), 250 (28), 235 (23), 230 (62), 198 (77), 145 (35), 43 (35). *Anal.* Calcd for $C_{12}H_8N_3OF_3$: C, 53.94; H, 3.02; N, 15.73. Found: C, 54.16; H, 3.16; N, 15.76.

E- and Z-2-Pyrazinyl(3-trifluoromethylphenyl)methanone oxime (**E-12b** and **Z-12b**)

Compound (**12b**) was prepared from 252 mg (1 mmol) of **6b** according to the procedure given for the synthesis of **10a**. The oily residue was recrystallized from diisopropyl ether - light petroleum to give 260 mg (97%) of **12b** as yellow crystals. Separation by mplc (eluent: ethyl acetate - dichloromethane) afforded 35 mg (13%) of **Z-12b** (faster eluted component) and 91 mg (34%) of **E-12b** (slower eluted component).

Compound (**Z-12b**) was obtained as yellow crystals of mp 138°C (ethyl acetate - dichloromethane); ^{1}H-nmr (200 MHz, DMSO-d_6): δ 12.17 (s, 1H, OH), 8.99 (d, $J_{3,6}$ = 1.4 Hz, 1H, pyrazine H-3), 8.82 (dd, $J_{3,6}$ = 1.4 Hz, $J_{5,6}$ = 2.6 Hz, 1H, pyrazine H-6), 8.74 (d, $J_{5,6}$ = 2.6 Hz, 1H, pyrazine H-5), 7.90-7.55 (m, 4H, Ph-H); ms: m/z (%) 267 (M^+, 100), 266 (40), 237 (39), 217 (25), 182 (20), 168 (65), 145 (21),

79 (27), 75 (23), 52 (76), 51 (43), 50 (21). *Anal.* Calcd for $C_{12}H_8N_3OF_3$: C, 53.94; H, 3.02; N, 15.73. Found: C, 54.04; H, 3.02; N, 15.63.

Compound (**E-12b**) was obtained as yellow crystals of mp 144°C (ethyl acetate - dichloromethane); ^{1}H-*nmr* (200 MHz, DMSO-d_6): δ 12.26 (*s*, 1H, OH), 9.16 (d, $J_{3,6}$ = 1.4 Hz, 1H, pyrazine H-3), 8.62 (d, $J_{5,6}$ = 2.6 Hz, 1H, pyrazine H-5), 8.54 (dd, $J_{5,6}$ = 2.6 Hz, $J_{3,6}$ = 1.4 Hz, 1H, pyrazine H-6), 7.90-7.60 (m, 4H, Ph-H); ms: m/z (%) 267 (M^+, 50), 266 (24), 168 (27), 69 (25), 57 (20), 52 (38), 51 (24), 43 (100). *Anal.* Calcd for $C_{12}H_8N_3OF_3$: C, 53.94; H, 3.02; N, 15.73. Found: C, 54.07; H, 2.96; N, 15.54.

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