Study of *tert*-amino effect: the role of substituents in isomerization of 5-amino-4-vinyl-3(2*H*)-pyridazinones

Beáta Dajka-Halász,[a] Ágota A. Földi,[a] Krisztina Ludányi,[b, c] and Péter Mátyus[a]*

[a]Department of Organic Chemistry, [b]Department of Pharmaceutics, Semmelweis University, Budapest, Hőgyes u. 7, 1092-Hungary
[c]Chemical Research Center, Hungarian Academy of Sciences, Budapest, Hungary
E-mail: peter.matyus@szerves.sote.hu

This paper is kindly dedicated to Prof. Csaba Szántay on the occasion of his 80th birthday

Abstract

The thermal isomerization reaction of *ortho*-vinyl *tert*-anilines and their heterocyclic analogues via *tert*-amino effect affords tetrahydropyrido-fused heterocyclic ring systems with a new C-C bond formation between the vinyl and *tert*-amino groups. A novel series of 5-amino-4-vinyl-3(2*H*)-pyridazinone derivatives were prepared to study the role of substituents of the pyridazinone ring and the vinyl group in their isomerization reaction to tetrahydropyrido[2,3-*d*]pyridazines. In particular, 6-phenyl and 5-trioxopyrimidinediylmethylene substituents were found to significantly increase the rate of isomerization. Compounds possessing benzyl and methyl groups as amino substituents isomerized with the involvement of the benzyl group. On the basis of experiments with deuterated compounds, an intramolecular pathway was confirmed for the isomerization.

Keywords: *tert*-amino effect, pyridazine, steric buttressing, rearrangement, regioselective isomerization

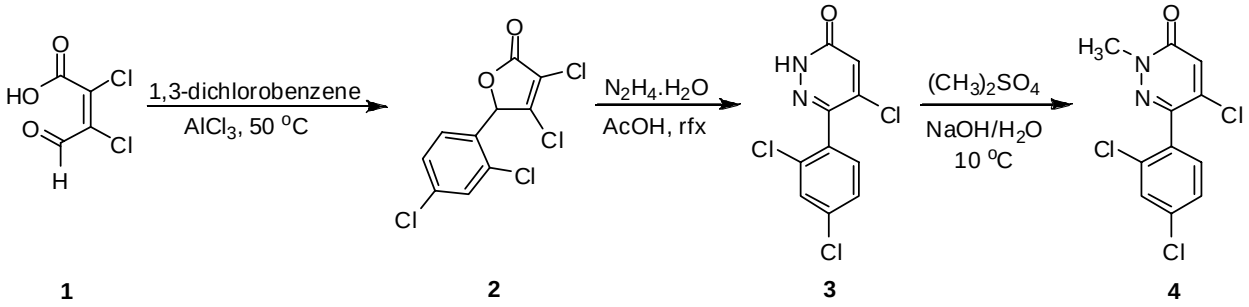
Introduction

Type 2 *tert*-amino effect, originally the thermal isomerization of *ortho*-vinyl-*tert*-anilines with ring closure to quinolines,[1] has been employed for the syntheses of angularly annelated tetrahydropyrido-fused polycyclic ring systems, including derivatives of quinolines and their aza- and diaza-analogues, with biological interest.[2] For instance, oxazinoquinolines have recently been claimed to possess remarkable antibacterial properties due to their gyrase inhibitory activity.[3] We described the synthesis of annelated analogues of CNS-active pyridazinooxazepines and -thiazepines[4] via type 2 *tert*-amino effect.[2] Several angularly-fused

pyrido[2,3-*d*]pyridazine ring systems were obtained from 5-azacycloalkyl-4-vinylpyridazinones prepared from 5-iodo-2-methyl-3(2*H*)-pyridazinone[5] in several steps. No examples have however been reported for isomerization of 5-amino-4-vinylpyridazines substituted in the 6-position or possessing a dialkylamino group. In this paper, syntheses of such new pyridazinones, and their thermal isomerization to otherwise hardly accessible polycyclic compounds will be reported.

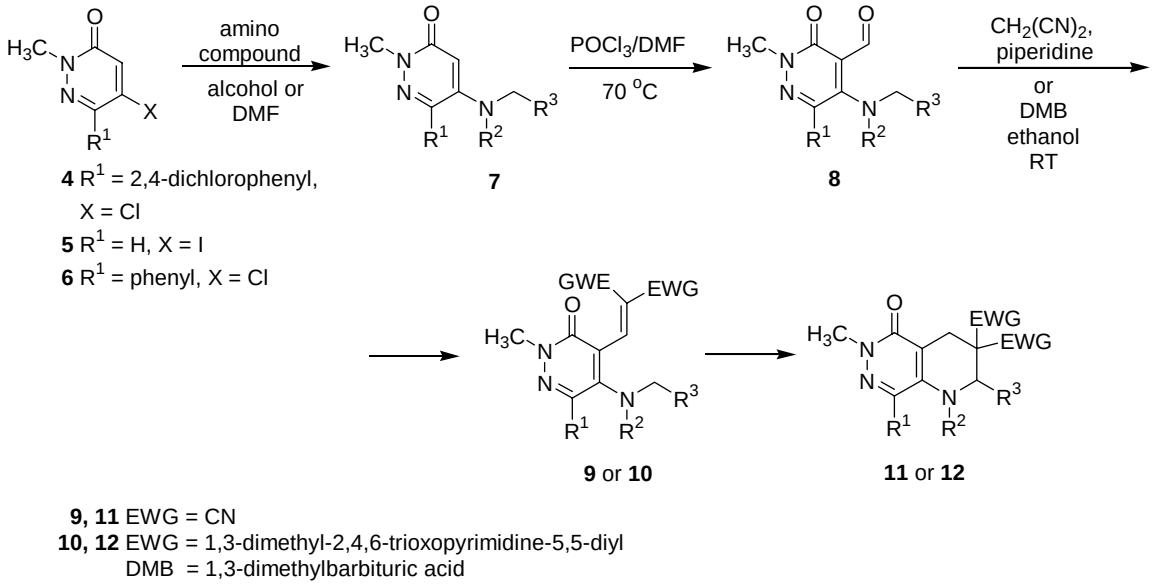
Results and Discussion

Following our synthetic strategy applied earlier for 5-morpholino- and 5-pyrrolidono-4-dicyanovinyl-3(2*H*)-pyridazinones, 6-aryl-5-chloro-2-methyl-3(2*H*)-pyridazinones **4**, **5** and 5-iodo-2-methyl-3(2*H*)-pyridazinone (**6**) as starting compounds were needed for preparation of the corresponding 5-amino-4-vinylpyridazinones in order to study their cyclization tendency. As 6-aryl substituent phenyl and, as an *ortho*-substituted analogue, 2,4-dichlorophenyl were selected. Compounds **5**[6] and **6**[5] were prepared according to reported procedures, whereas 5-chloro-6-(2,4-dichlorophenyl)-2-methylpyridazin-3(2*H*)-one (**4**) was obtained in an analogous way described for compound **5**. As illustrated on Scheme 1, mucochloric acid (**1**) was converted to **2** by a Friedel-Crafts reaction. Then compound **2** was treated with hydrazine hydrate to obtain *N*-unsubstituted pyridazinone **3**, in this transformation too, hydrogen chloride elimination also occurred, similarly to the reaction of dichlorophenylfuranone with hydrazine hydrate[5]. Subsequent alkylation of **3** led to *N*-methylated pyridazinone **4**.



Scheme 1

Each 5-halopyridazinone compound (**4-6)** underwent smoothly nucleophilic substitution with secondary amines to give 5-aminopyridazinone derivatives **7.** Vilsmeier-Haack formylation and subsequent Knoevenagel condensation with malononitrile (in the presence of piperidine catalyst) or 1,3-dimethylbarbituric acid (DMB) were applied to introduce the formyl group into **8**, and form the vinyl substituent in compounds **9**, **10**, respectively (Scheme 2, Table 1).



Scheme 2

Table 1. 5-Pyridazinylamines **7**, their 4-aldehyde **8**, 4-vinyl- and 4-pyrimidinediylmethylene derivatives **9**, **10** and tetrahydropyrido[2,3-*d*]pyridazines **11**, **12**

			7	**8**	**9**	**10**	**11**		**12**	
	R^1	amino group	Yield (%)	Yield (%)	Yield (%)	Yield (%)	Yield (%)	Time (h)	Yield (%)	Time (h)
a	Ph	dimethylamino	57	80	73	84	47[c]	72	62[c] 70[f]	4 0.15
b	2,4-Cl_2Ph	dimethylamino	71	79	70	61	35[d]	6	50[c]	6
c	Ph	pyrrolidino	53	40	77	86	67[c]	9	40[c]	3
d	Ph	piperidino	63	37	78	-[b]	47[c]	3	82[g]	1
e	Ph	morpholino	65	45	65	-[b]	46[c]	9	88[g]	1
f	Ph	benzyl(methyl)-amino	63	48	-[a]	-[b]	-[a]		57[h]	1
g	Ph	dimethylamino-d_6	68	69	63	81	41[d]	6	50[c] 40[i]	8 24
h	H	tetrahydro-isoquinolino	83	51	-[a]	-[b]	-[a]		62[h]	1
i	H	dimethylamino	69	79	48	89	-[e]		40[d]	6

[a] Not carried out. [b] Not isolated. [c]DMF/100 °C. [d]DMF/reflux. [e]not formed. [f]D_2O/100 °C/μW. [g]EtOH/RT. [h] EtOH/reflux. [i]*n*-BuOH/reflux.

The thermal isomerization reaction *via* tert-amino effect was generally carried out in dry *N*,*N*-dimethylformamide (DMF). The dicyanovinyl compounds **9a**, **c-e** and pyrimidinediylmethylene derivatives **10a-c** isomerized at 100 ^{o}C to give **11a**, **c-e** and **12a-c**, respecitvely, whereas isomerization of dicyanovinyl compound **9b** to **11b** could only be achieved at reflux temperature. Generally, and in accordance with our previous findings, thermal isomerization of pyrimidinediylmethylene derivatives **10** was significantly faster than that of the respective dicyano derivatives **9**. The presence of pyrimidinetrione ring in compounds **10** may facilitate the isomerization reaction by steric and electronic effects: i) making a favorable geometric arrangement for hydrogen migration (*cf*. reference 2), and ii) efficiently delocalizing the developing negative charge in the transition state.

The 6-aryl substituent itself exerted an accelerating effect on the isomerization too. Furthermore, two sets of experiments indicated a particularly strong rate-enhancing effect of its combination with a 4-pyrimidinediyl substituent. The first comparison was made by the reactions of aldehydes **8d** and **8e** with DMB. These reactions in ethanol at ambient temperature, representing the typical conditions applied for the Knoevenagel condensation with DMB, afforded as isolable products the spiro-substituted derivatives of pyridazino[4,5-*c*]quinolizine **12d** and pyridazino[4',5':5,6]pyrido[2,1-*c*][1,4]oxazine **12e** ring systems, indicating that their formations were too fast to allow to isolate condensation products of type **10** in pure forms. In the second set of experiments isomerizations of **10a** and **10i** were compared. The former compound, due to the combined effect of 6-phenyl and 4-pyrimidinediyl substituents, reacted to tricyclic compound **12a** much faster than **10i** did to **12i**.

The important role of 6-phenyl substituent in the isomerization was also apparent from the reactions of compounds **9a** and **9i**. While compound **9a**, possessing a 6-phenyl substituent, could be smoothly isomerized to **11a** in DMF at 100 ^{o}C, its analogue **9i** with no 6-phenyl substituent, did not isomerize even upon prolonged heating (72 h) in DMF, instead, a complex mixture was obtained. No cyclization was achieved by application of $AlCl_3$ catalyst in refluxing xylene (after a 8-h reaction time, the starting material was completely unchanged, a further boiling resulted in decomposition); and decomposition could only detected in neat at 200 ^{o}C.

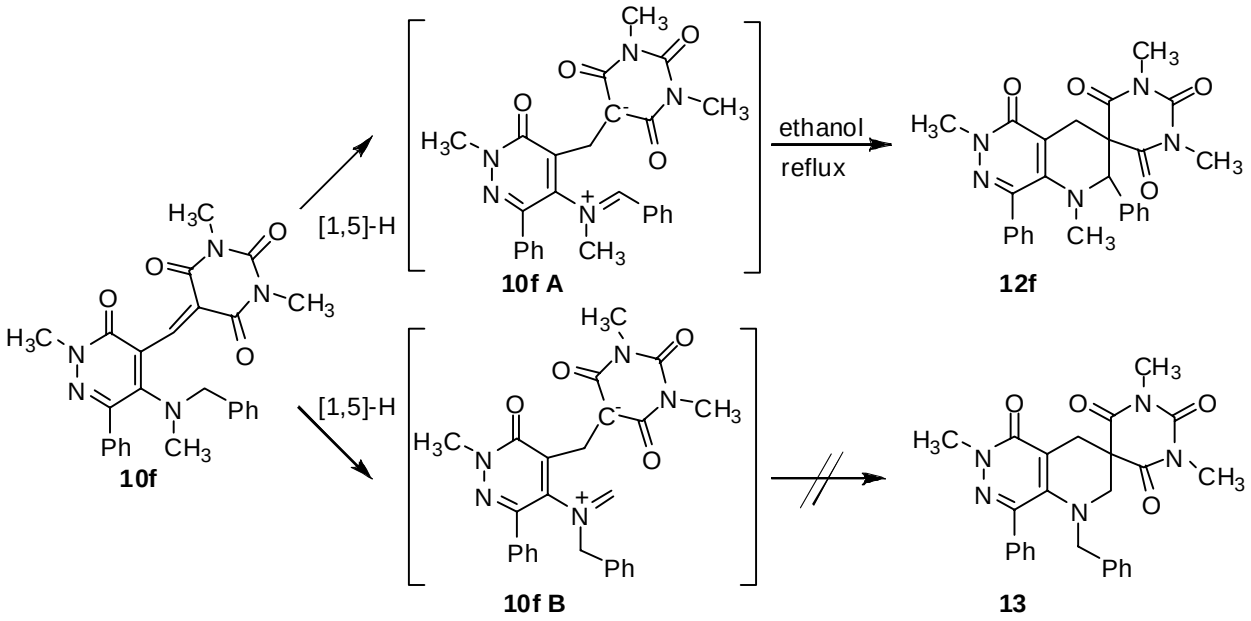
One possible explanation for the rate-accelerating role of the bulky phenyl substituent may be related to its steric buttressing effect.[7] The 6-phenyl group may reduce the conformational freedom of the neighboring *tert*-amino group, thereby favorably influencing both the hydrogen migration and ring closure.

It is noteworthy that isomerization of hexadeuterodimethylamino derivatives **9g** and **10g** in DMF gave **11g** and **12g** trideuterated in 1-*N*-methyl group, and di- and monodeuterated in 2- and 4-positions, respectively, indicating that no deuterium was lost, whereas isomerization of **10a** in D_2O by microwave heating afforded **12a** with no deuterium incorporation. These findings definitely prove the intramolecular nature of the rearrangement.[1,2]

The observation that the dimethylaminopyridazinone **9a** isomerized significantly slower than the azacycloalkyl analogues **9c-e** can be understood, supposing a two-step mechanism, by the stability difference in the respective iminium intermediates (and thereby the transition states of

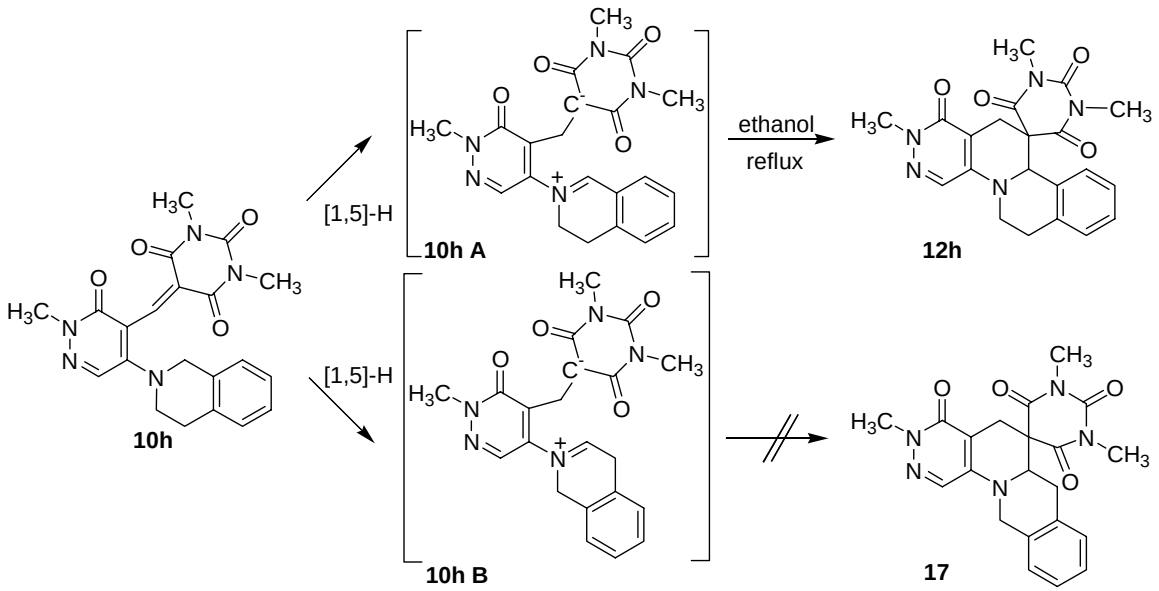
their formations) obtained via hydride (or sigmatropic hydrogen) migration from the alpha-carbon of amino group to the methylene carbon of the pyrimidinediylmethylene substituent.[2] For a similar reason, it could be expected that replacement of one of the methyl groups with a benzyl group should accelerate the isomerization with full control of the regiochemistry; in fact, the regioselective type 2 *tert*-amino effect had already been observed in a few cases.[8]

Reaction of aldehydes **8f** and **8h** with DMB gave a mixture of condensation and isomerization products **10f + 12f** and **10h + 12h**, indicating enhancement of isomerization. To make complete the ring closure reaction and to isolate the spirocyclic products **12f**, **12h** in pure forms, the reaction mixtures were shortly refluxed in ethanol (Schemes 3, 4). Interestingly, the isomerization of **10f** exclusively gave **12f**, while its regioisomer, compound **13** was not detected at all (Scheme 3).



Scheme 3

Similarly, isomerization of the isoquinolinyl derivative **10h** led to the formation triazachrysene ring system **12h** with no detectable amount of its regioisomer **14** (Scheme 4).



Scheme 4

Constitution of **12f** and **12h** could be unambiguously proven by nmr data.

The regiochemistry is determined by the migration aptitudes of hydrogens. In both cases, isomerization took place with the involvement of one of the benzylic hydrogens leading to the more stabilized iminium double bond in the dipolar intermediates **10fA** vs. **10fB**, and **10hA** vs. **10hB**, and in the respective transition states.

In summary, isomerization of novel series of 4-vinyl-5-aminopyridazinones via type 2 *tert*-amino effect led to the formation of new pyridopyridazines in moderate to high yields, indicating some new features and wide synthetic scope of the reaction. In particular, a phenyl substituent located *ortho* to the *tert*-amino group and a cyclic electron-withdrawing vinyl substituent may significantly accelerate the reaction.

While the intramolecular nature of the rearrangement reactions was confirmed by deuteration experiments, and some new information could be provided on the scope of type 2 *tert*-amino effect. Although, we feel that a step-wise mechanism may operate in the formation of tetrahydropyridine ring, a concerted mechanism for the ring formation could not be fully excluded. This question and to find new extensions of the reaction will challenge our further work.

Experimental Section

General Procedures. All melting points were determined on a Kofler apparatus, and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 1600 FTIR instrument in potassium bromide pellets. The ^{1}H NMR spectra were recorded at ambient temperature in the solvent indicated, using the ^{2}H signal of the solvent as the lock and tetramethylsilane as the internal standard. Chemical shifts (δ) are given in ppm and coupling constants (J) in Hz. Bruker AM at 200 MHz and Varian Mercury Plus spectrometer at 400 MHz were used. ^{13}C NMR spectra were recorded on the same spectrometers at 50 and 100 MHz, respectively. The assignments of ^{13}C NMR spectra were supported by DEPT-135 spectra. All new compounds gave satisfactory elementary analytical data (C, H, N); these analyses were performed on a Carlo Erba Elemental Analyzer Model 1012 apparatus. Mass spectrometric experiments were performed on a reverse geometry VG-ZAB-2SEQ instrument (in case of compounds **9a, 9c**, **9e**, **9g**, **9i**, **10a**, **10b**, **10g**, **11a**, **11g**, **12a** and **12g**). Fast atom bombardment (FAB) ionization with 30kV Cs^{+} ions was used, samples were dissolved in $CHCl_3$ and put on the probe using DHB matrix. Accelerating voltage was 8 kV. Microwave irradiation experiments were carried out a monomode CEM-Discover MW reactor in the standard configuration as delivered, including proprietary software. The experiments were executed in a MW process vial (10mL) with control of the temperature by infrared detection. After completion of the reaction, the vial was cooled to 50 ^{o}C via air jet cooling. For flash column chromatography Kieselgel 60 (Aldrich, 0.040-0.063 mm silica gel) was used; for TLC analysis Silica gel 60 F_{254} (Merck) plates were applied. Solvent mixtures used for chromatography are always given in a vol/vol ratio. The reagents were obtained from commercial sources and used as received. Solvents were dried and distilled prior to use. Compounds **5**[6] and **6**[5] were prepared according to the literature procedures cited.

3,4-Dichloro-5-(2,4-dichlorophenyl)furane-2(5*H*)-one (2). A three-neck, round-bottom flask was equipped with a reflux condenser, a thermometer and a stopper. The flask was charged with $AlCl_3$ (25.0 g, 0.19 mol) and 1,3-dichlorobenzene (100 mL, 0.87 mol). Mucochloric acid (**1**) (20.0 g, 0.12 mol) was added to the suspension and the reaction mixture was stirred and warmed at 50 °C for 10h. The orange suspension was poured onto a mixture of ice (150 g) and concentrated HCl (45 mL). After separation, the aqueous phase was extracted with toluene (2x50 mL). The toluene phases were combined with the first organic phase (1,3-dichlorobenzene), washed with water (30 mL), dried, filtered. The solvent was evaporated, and the crude product (11.0 g) thus obtained was crystallized from methanol, affording 8.9 g (25 %) white crystals: mp 136-138 °C, R_f=0.92 (chloroform: methanol 95:5). ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.80 and 7.56 (2s, 3H, H_{phenyl}), 6.67 (s, 1H, H-5). ^{13}C NMR (50 MHz, DMSO-d_6): δ 164.9 (C-2), 151.0 (C-4), 136.1 (C-1' phenyl), 134.5 and 131.7 (C-2' and C-4' phenyl), 130.0, 128.4 and 128.2 (C-3' phenyl, C-5' and C-6' phenyl), 121.0 (C-3), 79.8 (C-5). IR (potassium bromide): ν_{max} 3092, 2960, 1778, 1626, 1588, 1498, 1472, 1382, 1292, 1228, 1106, 1032, 916, 850, 820 cm^{-1}; Anal. calculated for $C_{10}H_4Cl_4O_2$ (297.95): C 40.31; H 1.35. Found: C 40.31; H 1.22.

5-Chloro-6-(2,4-dichlorophenyl)pyridazin-3(2*H*)-one (3). A three-neck, round-bottom flask was equipped with a reflux condenser, a thermometer and a dropping funnel. The flask was charged with 3,4-dichloro-5-(2,4-dichlorophenyl)furane-2(5*H*)-one (**2**) (0.027 mol), and glacial acetic acid (20 mL). The funnel was charged with 99 % hydrazine monohydrate (3.4 mL, 0.07 mol). The reaction mixture was warmed to 60 °C, and the hydrazine monohydrate was added dropwise in 15 min. Subsequently, the resulting mixture was heated under reflux for 2h. After cooling, the solid precipitate was filtered off and washed with water (5x10 mL). The crude product was crystallized from methanol, affording 2.5 g pale yellow crystals: mp 267-269 °C, R_f=0.40 (toluene: methanol 4:1). ^{1}H NMR (200 MHz, DMSO-*d*$_6$): δ 13.6 (s, 1H, N*H*), 7.81-7.58 (2s, 3H, H_{phenyl}), 7.38 (s, 1H, H-4). ^{13}C NMR (50 MHz, DMSO-d$_6$): δ 159.7 (C-3), 142.4 (C-6), 139.9 (C-5), 135.2 (C-1' phenyl), 134.0 and 132.0 (C-2' and C-4' phenyl), 132.8, 128.9, 128.4 and 127.7 (C-4, C-3' phenyl, C-5' and C-6' phenyl). IR (potassium bromide): ν_{max} 3382, 3268, 3070, 2986, 2910, 2846, 2798, 1680, 1638, 1592, 1480, 1438, 1086, 1052, 1012, 892, 870, 836, 814, 540, 490, 454 cm^{-1}. Anal. calculated for $C_{10}H_5Cl_3N_2O$ (275.52): C 43.59; H 1.83; N 10.17. Found: C 43.59; H 1.77; N 10.43.

5-Chloro-6-(2,4-dichlorophenyl)-2-methylpyridazin-3(2*H*)-one (4). A two-neck, round-bottom flask was equipped with a drying tube and a dropping funnel. The flask was charged with 5-chloro-6-(2,4-dichlorophenyl)pyridazin-3(2*H*)-one (**3**) (0.036 mol), methanol (40 mL), and sodium hydroxide solution (1.6 g, 0.04 mol, NaOH in 40 mL water). The funnel was charged with 97 % dimethyl sulphate (3.8 mL, 0.04 mol). The reaction mixture was cooled to 10 °C, and the dimethyl sulphate was added dropwise in 20 min. The resulting mixture was stirred at room temperature for 8h. The suspension was evaporated to half volume and extracted with toluene (4x100 mL). The combined organic layer was washed first with 2M sodium hydroxide (100 mL) and then with water (2x100 mL). The organic phase was dried, filtered and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography with a mixture of toluene:acetone (9:1) as the eluent, affording 6.1 g (58 %) beige crystals: mp 156-162 °C, R_f=0.42 (toluene: acetone 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (1H, d, H-3'phenyl, *J*=2.0), 7.38 (1H, dd, H-5' phenyl, J_1=8.0, J_2=2.0), 7.29 (1H, d, H-6' phenyl, *J*=8.0), 7.11 (1H, s, H-4), 3.82 (3H, s, N(2)CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2 (C-3), 142.9 (C-6), 140.3 (C-5), 136.5 (C-1' phenyl), 134.9 and 131.6 (C-2' and C-4' phenyl), 131.8 (C-4, and C-6' phenyl), 129.6 (C-3' phenyl), 127.4 (C-5' phenyl), 40.1 (N(2)CH_3). IR (potassium bromide): ν_{max} 3062, 2924, 1650, 1480, 1266, 1102, 1008, 966, 910, 834, 818, 772, 488 cm^{-1}. Anal. calculated for $C_{11}H_7Cl_3N_2O$ (289.55): C 45.63; H 2.44; N 9.67. Found: C 46.01; H 2.33; N 9.49.

2-Methyl-5-(dimethylamino)-6-phenylpyridazin-3(2*H*)-one (7a). A mixture of **c**ompound **5** (4.0 g, 0.018 mol) and 45 mL solution of dimethyl amine (25 wt. % in ethanol) was stirred at 100 ^{o}C in pressure vessel for 5h. The reaction mixture was evaporated to dryness *in vacuo*. Then water (50 mL) was added to the residue, and the mixture was extracted with chloroform (5x30 mL), and the combined organic phases were dried over anhydrous magnesium sulphate. The solvent was evaporated *in vacuo*, and the crude product was purified by short column chromatography with ethyl acetate and crystallized from cyclohexane, affording 3.1 g (74 %)

pale brown crystals: mp 105-107 °C, R_f=0.20 (ethyl acetate). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60-7.56 (2H, m, H-3' and H-5' phenyl), 7.47-7.39 (3H, m, H-2', H-4' and H-6' phenyl), 6.17 (1H, s, H-4), 3.76 (3H, s, N(2)CH_3), 2.59 (6H, s, N(5)CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.4 (C-3), 153.3 (C-5), 141.5 (C-6), 136.8 (C-1' phenyl), 128.5, 128.4, 127.6 (C-2' –6' phenyl), 106.6 (C-4), 41.7 (N(5)CH_3) 39 (N(2)CH_3). IR (potassium bromide): ν_{max} 3444, 2994, 2948, 2860, 2796, 2540, 1644, 1578, 1498, 1470, 1446, 1408, 1346, 1302, 1286, 1270, 1198, 1128, 1054, 986, 920, 836, 784, 744, 712 cm^{-1}. Anal. calculated for $C_{13}H_{15}N_3O$ (229.28): C 68.10; H 6.59; N 18.33. Found: C 68.17; H 6.59; N 18.66.

6-(2,4-Dichlorophenyl)-5-(dimethylamino)-2-methylpyridazin-3(2*H*)-one (7b). A mixture of **4** (1 g, 0.0035 mol) and 15 mL solution of dimethylamine (25 wt. % in ethanol) was stirred at 100 °C in pressure vessel for 4h. The reaction mixture was evaporated to dryness *in vacuo*. Then water (50 mL) was added to the residue, and it was extracted with chloroform (3x40 mL), and the combined organic phases were dried over anhydrous magnesium sulphate. The solvent was evaporated *in vacuo*, and the crude product was purified by column chromatography with a mixture of chloroform: ethyl acetate (9:1) as the eluent, affording 0.70 g (71 %) beige crystals: mp 175-178 °C, R_f=0.16 (chloroform: ethyl acetate 9:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.46-7.45 (1H, m, H-3' phenyl), 7.31-7.30 (2H, m, H-5' and H-6' phenyl), 6.02 (1H, s, H-4), 3.69 (3H, s, N(2)CH_3), 2.57 (6H, s, N(5)CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.4 (C-3), 152.6 (C-5), 138.1, 135.3, 134.9, 134.3 (C-6 pyridazine, C-1' phenyl, C-2' and C-4' phenyl), 131.8, 129.8, 127.5 (C-3', C-4' and C-6' phenyl), 105.0 (C-4), 41.2 ((N(5)CH_3) 39.2 (N(2)CH_3). IR (potassium bromide): ν_{max} 3444, 3048, 3014, 2942, 2870, 2798, 1636, 1578, 1548, 1492, 1474, 1446, 1412, 1382, 1350, 1300, 1248, 1196, 1158, 1138, 1100, 1078, 1060, 1044, 988, 866, 824, 774, 700, 458 cm^{-1}. Anal. calculated for $C_{13}H_{13}Cl_2N_3O$ (298.17): C 52.37; H 4.39; N 14.09, Cl 23.78. Found: C 52.00; H 4.36; N 13.92, Cl 23.89.

2-Methyl-6-phenyl-5-pyrrolidinopyridazin-3(2*H*)-one (7c). A mixture of **5** (1.0 g, 0.045 mol) and pyrrolidine (0.76 mL, 0.09 mol) was refluxed in 8 mL of ethanol for 20h. The reaction mixture was evaporated to dryness *in vacuo*. Then water (15 mL) was added to the residue, and the crystals were filtered off, washed with water (3x10 mL) and crystallized from cyclohexane, affording 0.6 g (53 %) beige crystals: mp 142-143 °C, R_f=0.64 (chloroform: methanol 95:5). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42-7.34 (5H, m, H_{phenyl}), 5.89 (1H, s, H-4), 3.71 (3H, s, N(2)CH_3), 2.91-2.85 (4H, m, N-CH_2 pyrrolidine), 1.78-1.71 (4H, m, CH_2-CH_2 pyrrolidine). ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.5 (C-3), 149.0 (C-5), 140.3 (C-6), 137.6 (C-1' phenyl), 128.3, 128.29 (C-2'-6' phenyl), 101.1 (C-4), 50.7 (C-2,5 pyrrolidine) 39 (N(2)CH_3), 25.4 (C-3,4 pyrrolidine). IR (potassium bromide): ν_{max} 3422, 2960, 2892, 2832, 1636, 1568, 1494, 1430, 1356, 1296, 1234, 1176, 1136, 1076, 988, 820, 774, 742, 706, 578 cm^{-1}. Anal. calculated for $C_{15}H_{17}N_3O$ (255.31): C 70.56; H 6.71; N 16.46. Found: C 70.40; H 6.69; N 16.60.

2-Methyl-6-phenyl-5-piperidinopyridazin-3(2*H*)-one (7d). Compound **5** (2 g, 0.009 mol) and piperidine (2.24 mL, 0.011 mol) was refluxed in 8 mL of anhydrous DMF (monitored by TLC). After completion of the reaction, it was evaporated to dryness *in vacuo*. Then water (15 mL) was added to the residue, and the crystals were filtered off, washed with water (3x10 mL). The crude

product was purified by column chromatography, using dichloromethane and ethyl acetate (1:1) as the eluent, affording 1.54 g (63 %) beige crystals: mp 123-124 °C (lit.[9] mp 121-122 °C), R_f=0.32 (ethyl acetate: dichloromethane (1:1, v/v)). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.85-7.60 (2H, m, H-3' and H-5' phenyl), 7.55-7.30 (3H, m, H-2', H-4', H-6' phenyl), 6.23 (1H, s, H-4), 3.76 (3H, s, N(2)CH_3), 2.95-2.65 (4H, m, N-CH_2 piperidine), 1.65-1.35 (6H, m, CH_2-CH_2-CH_2 piperidine). ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.7 (C-3), 154.3 (C-5), 142.7 (C-6), 136.5 (C-1' phenyl), 128.7, 128.5, 127.6 (C-2'-6' phenyl), 109.5 (C-4), 50.8 (C-2,6 piperidine) 39.4 (N(2)CH_3), 25.1 (C-3,5 piperidine), 23.6 (C-4 piperidine). IR (potassium bromide): ν_{max} 3422, 2934, 2848, 1648, 1582, 1568, 1412, 1382, 1278, 1226, 1130, 1110, 1016, 740, 700 cm^{-1}. Anal. calculated for $C_{16}H_{19}N_3O$ (269.35): C 71.35; H 7.11; N 15.60. Found: C 71.43; H 7.16; N 15.72.

2-Methyl-5-morpholino-6-phenylpyridazin-3(2*H*)-one (7e). A mixture of **5** (1.95 g, 0.0088 mol) and morpholine (3.8 mL, 0.044 mol) was refluxed in 20 mL of *n*-butanol for 23h (monitored by TLC). The reaction mixture was evaporated to dryness *in vacuo*. Then water (20 mL) was added to the residue, and the crystals were filtered off, washed with water (3x10 mL) and crystallized from methanol, affording 1.56 g (65 %) pale brown crystals: mp 142-144 °C, R_f=0.24 (ethyl acetate). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.71-7.67 (2H, m, H-3' and H-5' phenyl), 7.47-7.40 (3H, m, H-2', H-4' and H-6' phenyl), 6.25 (1H, s, H-4), 3.78 (3H, s, N(2)CH_3), 3.62 (4H, t, O-CH_2 morpholine, *J*=4.8), 2.84 (4H, t, N-CH_2 morpholine, *J*=4.8). ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.5 (C-3), 153.3 (C-5), 142.2 (C-6), 136 (C-1' phenyl), 129, 128.7, 127.8 (C-2'-6' phenyl), 110.0 (C-4), 66.0 (C-2,6 morpholine), 49.8 (C-3,5 morpholine), 39.4 (N(2)CH_3). IR (potassium bromide): ν_{max} 3446, 3060, 2974, 2950, 2904, 2860, 2826, 1652, 1582, 1496, 1446, 1412, 1372, 1338, 1320, 1304, 1274, 1226, 1212, 1112, 1030, 990, 902, 882, 742, 704, 622, 582, 534 cm^{-1}. Anal. calculated for $C_{15}H_{17}N_3O_2$ (271.31): C 66.40; H 6.32; N 15.49. Found: C 66.38; H 6.38; N 15.55.

5-[Benzyl(methyl)amino]-2-methyl-6-phenylpyridazin-3(2*H*)-one (7f). A mixture of **5** (2.0 g, 0.009 mol), *N*-benzyl-*N*-methylamine (1.42 mL, 0.01 mol) and potassium carbonate (1.5 g, 0.01 mol) was stirred in anhydrous DMF (6 mL) at 150 °C for 12h. After cooling, water (50 mL) was added to the reaction mixture, and it was extracted with chloroform (3x40 mL). The combined organic phases were dried over anhydrous magnesium sulphate. The solvent was evaporated *in vacuo*, and the oily crude product was purified by repeated column chromatography using toluene and acetone (7:3) as the eluent, affording 0.90 g (33 %) beige crystals: mp 94-96 °C, R_f=0.36 (toluene: acetone 7:3). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.70-6.95 (10H, m, $H_{aromatic}$), 6.17 (1H, s, H-4), 3.98 (2H, s, N-CH_2-Ph), 3.78 (3H, s, N(2)CH_3), 2.53 (3H, s, N(5)CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.5 (C-3), 152.9 (C-5), 142.0 (C-6), 136.8 and 135.9 (C-1' phenyl and C-1'' benzyl), 128.7, 128.5, 127.9, 127.8 and 127.6 ($C_{aromatic}$), 108.7 (C-4), 57.5 (N-$\underline{C}H_2$-Ph), 39.3 and 39.0 (N-CH_3 benzyl and N(2)CH_3). IR (potassium bromide): ν_{max} 3459, 3059, 2947, 1646, 1496, 1447, 1409, 1279, 1224, 1157, 1098, 1054, 992, 846, 739, 700, 589 cm^{-1}. Anal. calculated for $C_{19}H_{19}N_3O$ (305.38): C 74.73; H 6.27; N 13.76. Found: C 74.71; H 6.33; N 13.66.

5-(Dimethylamino-d_6)-2-methyl-6-phenylpyridazin-3(2*H*)-one (7g). A mixture of **5** (0.5 g, 0.0022 mol), dimethyl-d_6-amine hydrochloride (0.004 mol) and triethyl amine (0.007 mol) in

isopropyl alcohol (10 mL) was stirred at 100 °C in pressure vessel for 12h. The reaction mixture was then evaporated to dryness *in vacuo*. Water (10 mL) was added to the residue, and it was extracted with chloroform (3x10 mL). The combined organic phases were dried over anhydrous magnesium sulphate. The solvent was evaporated *in vacuo*, and the crude product was purified by column chromatography, using ethyl acetate as the eluent, affording 0.36 g (68 %) beige crystals: mp 104-105 °C, R_f=0.17 (ethyl acetate). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.58-7.56 (2H, m, H-3' and H-5' phenyl), 7.48-7.37 (3H, m, H-2', H-4' and H-6' phenyl), 6.13 (1H, s, H-4), 3.76 (3H, s, N(2)CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.5 (C-3), 153.4 (C-5), 141.6 (C-6), 136.9 (C-1' phenyl), 128.6, 128.5, 127.8 (C-2'-6' phenyl), 106.6 (C-4), 41.4 and 40.9 (N(5)CD_3) 39.2 (N(2)CH_3). IR (potassium bromide): ν_{max} 2946, 1640, 1574, 1422, 1290, 1260, 1000, 782, 712 cm^{-1}. Anal. calculated for $C_{13}H_9D_6N_3O$ (235.32): C 66.35; H+D 6.42; N 17.86. Found: C 66.25; H+D 6.37; N 17.90.

5-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2-methylpyridazin-3(2*H*)-one (7h). A mixture of **6** (2 g, 0.0085 mol), tetrahydroisoqinoline (1.3 mL, 0.01 mol) and potassium carbonate (1.4 g, 0.01 mol) was stirred in anhydrous DMF (6 mL) at 110 °C for 9h. After cooling, water (40 mL) was added to the mixture, and the crude product was filtered off, washed with water (3x50 mL) and recrystallized from ethanol, affording 1.7 g (83 %) beige crystals: mp 175-176 °C, R_f=0.28 (toluene: acetone (7:3, v/v)). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.73 (1H, d, H-6, *J*=2.8 Hz), 7.26-7.13 (4H, m, $H_{aromatic}$), 5.92 (1H, d, H-4, *J*=2.8), 4.44 (2H, s, H_2-1 isoquinoline), 3.70 (3H, s, N(2)CH_3), 3.59 (2H, t, H_2-3 isoquinoline, *J*=5.9), 2.98 (2H, t, H_2-4 isoquinoline, *J*=5.9). ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.8 (C-3), 149.2 (C-5), 134.3 and 132.3 (C-4a and C-8a isoquinoline), 128.1, 128.0, 127.2, 126.7, 126.4 (C-6 pyridazine, C-5, -6, -7, -8 isoquinoline), 99.7 (C-4), 47.9 (C-1 isoquinoline) 43.8 (C-3 isoquinoline), 39 (N(2)CH_3), 28.5 (C-4 isoquinoline). IR (potassium bromide): ν_{max} 3446, 3068, 3030, 2934, 2908, 2878, 2836, 1652, 1624, 1586, 1516, 1500, 1446, 1408, 1390, 1374, 1358, 1332, 1312, 1296, 1258, 1230, 1182, 1152, 1112, 1046, 1020, 986, 812, 750, 612 cm^{-1}. Anal. calculated for $C_{14}H_{15}N_3O$ (241.29): C 69.69; H 6.27; N 17.41. Found: C 69.69; H 6.29; N 17.66.

5-(Dimethylamino)-2-methylpyridazin-3(2*H*)-one (7i). A mixture of **6** (2 g, 0.0085 mol) and 20 mL solution of dimethyl amine (25 wt. % in ethanol) was stirred at 40 °C for 7h. The reaction mixture was evaporated to dryness *in vacuo*. Then water (50 mL) was added to the residue, and it was extracted with chloroform (3x50 mL), and the combined organic phases were dried over anhydrous magnesium sulphate. The solvent was evaporated *in vacuo*, and the crude product was crystallized from ethanol, affording 1.1 g (88 %) beige crystals: mp 120-122 °C (lit.[10] 119-120 °C), R_f=0.15 (toluene: acetone 7:3). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.57 (1H, d, H-6, *J*=2.8), 5.73 (1H, d, H-4, *J*=2.6), 3.69 (3H, s, N(2)CH_3), 3.01 (6H, s, N(5)CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.6 (C-3), 149.6 (C-5), 127.5 (C-6), 98.4 (C-4), 39.2 (N(5)CH_3), 38.9 (N(2)CH_3). IR (potassium bromide): ν_{max} 2930, 1626, 1528, 1490, 1440, 1412, 1336, 1290, 1069, 987, 826 cm^{-1}. Anal. calculated for $C_7H_{11}N_3O$ (153.18): C 54.89; H 7.24; N 27.43. Found: C 54.99; H 7.29; N 27.49.

General procedure for preparation of aldehydes (8) by Vilsmeier-Haack reaction. Typical example

A solution of **7a** (0.0044 mol) in anhydrous DMF (8 mL) was cooled by ice-water bath. A solution of $POCl_3$ (1.3 mL) in anhydrous DMF (3.1 mL) was added dropwise to the mixture 0-6 ^oC. The reaction mixture was allowed to warm to room temperature, and was heated at 60 ^oC for 6 hours (monitored by TLC). After evaporation of the solvent (under 60 ^oC *in vacuo*), ice (30 g) was added to the brown oily residue and the mixture was allowed to warm to room temperature. Then it was made alkaline with aqueous 40 % sodium hydroxide (pH=8) and the resulting solution was extracted with chloroform (5x30 mL). The combined organic phases were dried over anhydrous magnesium sulphate. The solvent was evaporated *in vacuo* to give the crude product (in this case **8a**) which was purified by column chromatography and/or (re)crystallization.

5-(Dimethylamino)-2-methyl-3-oxo-6-phenyl-2,3-dihydropyridazine-4-carbaldehyde (8a). The crude product was purified by column chromatography with a mixture of ethyl acetate and dichloromethane (1:1) as the eluent, affording yellow crystals: yield 80 %, mp 147-148 ^oC, R_f=0.49 (ethyl acetate: dichloromethane 1:1). ^1H NMR (200 MHz, $CDCl_3$) δ 10.32 (1H, s, CHO), 7.48-7.36 (5H, m, H_{phenyl}), 3.74 (3H, s, N(2)CH_3), 2.76 (6H, s, N(5)CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 188.7 (C-formyl), 162.7 (C-3), 151 (C-5), 142.7, 137.2 (C-6 pyridazine, C-1' phenyl), 128.9, 128.0 (C-2',-6' phenyl), 110.8 (C-4), 45.4 (N(5)CH_3), 39.0 (N(2)CH_3).
IR (potassium bromide): ν_{max} 3422, 3050, 3024, 2992, 2954, 2922, 2856, 2776, 1664, 1634, 1550, 1510, 1492, 1472, 1442, 1388, 1318, 1294, 1266, 1132, 1108, 1088, 1010, 786, 776, 582 cm^{-1}. Anal. calculated for $C_{14}H_{15}N_3O_2$ (257.29): C 65.35; H 5.88; N 16.33. Found: C 65.08; H 5.93; N 16.12.

6-(2,4-Dichlorophenyl)-5-(dimethylamino)-2-methyl-3-oxo-2,3-dihydropyridazine-4-carbaldehyde (8b). The product was recrystallized from isopropyl alcohol, affording yellow crystals: yield 79 %, mp 152-153 ^oC, R_f=0.4 (ethyl acetate: dichloromethane 1:1). ^1H NMR (200 MHz, $CDCl_3$) δ 10.28 (1H, s, CHO), 7.55-7.48 (1H, m, H-3' phenyl), 7.36-7.34 (2H, m, H-5' and H-6' phenyl), 3.70 (3H, s, N(2)CH_3), 2.74 (6H, s, N(5)CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 188.3 (C-formyl), 162.7 (C-3), 151 (C-5), 139.2, 135.9, 135.1, 134.4 (C-6 pyridazine, C-1', C-2' and C-4' phenyl), 131.8, 129.7, 127.9 (C-3', C-5' and C-6' phenyl), 109.9 (C-4), 44.8 (N(5)CH_3), 39.2 (N(2)CH_3). IR (potassium bromide): ν_{max} 3070, 330, 2994, 2924, 2894, 2862, 2794, 1700, 1674, 1624, 1588, 1560, 1550, 1506, 1484, 1458, 1404, 1384, 1334, 1310, 1282, 1142, 1098, 1058, 1008, 700, 608, 508, 460 cm^{-1}. Anal. calculated for $C_{14}H_{13}Cl_2N_3O_2$ (326.18): C 51.55; H 4.02; N 12.88. Found: C 51.42; H 3.95; N 12.99.

2-Methyl-3-oxo-6-phenyl-5-pyrrolidino-2,3-dihydropyridazine-4-carbaldehyde (8c). The product was crystallized from isopropyl alcohol, affording yellow crystals: yield 40 %, mp 185-186 ^oC, R_f=0.50 (ethyl acetate: dichloromethane 1:1). ^1H NMR (200 MHz, $CDCl_3$) δ 10.20 (1H, s, CHO), 7.39 (5H, m, H_{phenyl}), 3.67 (3H, s, N(2)CH_3), 3.17-3.11 (4H, m, N-CH_2 pyrrolidine), 1.82-1.76 (4H, m, CH_2-CH_2 pyrrolidine). ^{13}C NMR (50 MHz, $CDCl_3$) δ 187.6 (C-formyl), 162.6 (C-3), 148.2 (C-5), 139.7, 137.5 (C-6 pyridazine, C-1' phenyl), 128.8, 127.7 (C-2',-6' phenyl),

105.8 (C-4), 56 (C-2,5 pyrrolidine), 38.3 (N(2)CH_3), 25 (C-3,4 pyrrolidine). IR (potassium bromide): ν_{max} 3422, 3082, 3054, 3030, 2980, 2940, 2870, 2842, 1644, 1616, 1544, 1510, 1456, 1390, 1342, 1318, 1296, 1278, 1156, 1074, 1010, 772, 716, 694, 590 cm^{-1}. Anal. calculated for $C_{16}H_{17}N_3O_2$ (283.32): C 67.83; H 6.05; N 14.83. Found: C 67.72; H 6.07; N 15.01.

2-Methyl-3-oxo-6-phenyl-5-piperidino-2,3-dihydropyridazine-4-carbaldehyde (8d). The crude product was purified by column chromatography with a mixture of ethyl acetate and dichloromethane (2:8) as the eluent, affording yellow crystals: yield 37 %, mp 151-153 ^oC, R_f=0.73 (ethyl acetate: dichloromethane 1:1). ^1H NMR (200 MHz, $CDCl_3$) δ 10.32 (1H, s, CHO), 7.30-7.60 (5H, m, H_{phenyl}), 3.71 (3H, s, N(2)CH_3), 2.93 (4H, m, H_2-2, H_2-6 piperidine), 1.51 (2H, m, H_2-4 piperidine), 1.36 (4H, m, H_2-3, H_2-5 piperidine). ^{13}C NMR (50 MHz, $CDCl_3$) δ 189.9 (C-formyl), 162.6 (C-3), 152.0 (C-5), 144.6 (C-6), 136.7 (C-1' phenyl), 128.9, 128.8, 128.6 (C-2',-6' phenyl), 114.1 (C-4), 53.5 (C-2,6, piperidine), 39.1 (N(2)CH_3), 25.2 (C-3,5 piperidine), 23.2 (C-4 piperidine). IR (potassium bromide): ν_{max} 2934, 2852, 1678, 1636, 1600, 1542, 1488, 1398, 1328, 1294, 1278, 1254, 1226, 1122, 1014, 776, 714, 578 cm^{-1}. Anal. calculated for $C_{17}H_{19}N_3O_2$ (297.36): C 68.67; H 6.44; N 14.13. Found: C 68.38; H 6.44; N 14.13.

2-Methyl-5-morpholino-3-oxo-6-phenyl-2,3-dihydropyridazine-4-carbaldehyde (8e). The crude product was purified by column chromatography with a mixture of ethyl acetate and chloroform (1:1) as the eluent, affording yellow crystals: yield 45 %, mp 195-197 ^oC, R_f=0.52 (ethyl acetate: chloroform 1:1). ^1H NMR (200 MHz, $CDCl_3$) δ 10.37 (1H, s, CHO), 7.53-7.41 (5H, m, H_{phenyl}), 3.76 (3H, s, N(2)CH_3), 3.59 (4H, t, O-CH_2 morpholine, *J*=4.8), 2.99 (4H, m, N-CH_2 morpholine, *J*=4.8). ^{13}C NMR (50 MHz, $CDCl_3$) δ 189.7 (C-formyl), 162.4 (C-3), 150.6 (C-5), 143.9 (C-6), 136.6 (C-1' phenyl), 129.2, 128.9, 128.5 (C-2'-6' phenyl), 114.3 (C-4), 66.2 (C-2,6 morpholine), 52.7 (C-3,5 morpholine), 39.3 (N(2)CH_3). IR (potassium bromide): ν_{max} 3444, 3056, 3002, 2952, 2920, 2876, 2850, 1664, 1631, 1598, 1540, 1484, 1430, 1394, 1362, 1332, 1322, 1290, 1256, 1192, 1110, 1070, 1034, 1012, 956, 918, 904, 836, 772, 732, 710, 700, 686, 612, 582, 546, 500 cm^{-1}. Anal. calculated for $C_{16}H_{17}N_3O_3$ (299.32): C 64.20; H 5.72; N 14.04. Found: C 64.26; H 5.71; N 14.02.

5-[*N*-Benzyl-*N*-methylamino]-2-methyl-3-oxo-6-phenyl-2,3-dihydropyridazine-4-carbaldehyde (8f). The crude product was purified by column chromatography with a mixture of ethyl acetate and dichloromethane (1:1) as the eluent, affording yellow crystals: yield 48 %, mp 127-128 ^oC, R_f=0.67 (ethyl acetate: dichloromethane 1:1). ^1H NMR (200 MHz, $CDCl_3$) δ 10.38 (1H, s, CHO), 7.34-7.09 (10H, m, $H_{aromatic}$), 4.07 (2H, s, N(5)CH_2), 3.78 (3H, s, N(2)CH_3), 2.57 (3H, s, N(5)CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 189.8 (C-formyl), 163.3 (C-3), 151.8 (C-5), 144.2, 137.7, 136.8 (C-6, C-1' phenyl and C-1" benzyl), 129.6, 129.5, 129.3, 129.1, 128.9, 128.8 ($C_{aromatic}$), 113.4 (C-4), 62.3 (N(2)CH_3), 43.6 (N(5)CH_3), 39.9 (N-$\underline{C}H_2$-Ph). IR (potassium bromide): ν_{max} 3568, 3410, 3056, 3022, 2952, 2926, 2852, 1670, 1634, 1538, 1510, 1492, 1432, 1406, 1392, 1316, 1294, 1268, 1244, 1180, 1156, 832, 780, 762, 710, 690, 582, 544, 506, 466 cm^{-1}. Anal. calculated for $C_{20}H_{19}N_3O_2$ (333.39): C 72.05; H 5.74; N 12.60. Found: C 71.87; H 5.59; N 12.43.

5-(Dimethylamino-d_6)-2-methyl-3-oxo-6-phenyl-2,3-dihydropyridazine-4-carbaldehyde (8g). The crude product was purified by column chromatography with a mixture of ethyl acetate and dichloromethane (1:1) as the eluent, affording yellow crystals: yield 69 %, mp 146-148 ^{o}C, R_f=0.48 (ethyl acetate: dichloromethane 1:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.32 (1H, s, CHO), 7.50-7.36 (5H, m, H_{phenyl}), 3.74 (3H, s, N(2)CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 188.7 (C-formyl), 162.7 (C-3), 151.0 (C-5), 142.6, 137.2 (C-6 pyridazine, C-1' phenyl), 128.9, 128.8 and 128.0 (C-2',-6' phenyl), 110.6 (C-4), 44.6 (N(5)CD_3), 39.0 (N(2)CH_3). IR (potassium bromide): ν_{max} 3050, 2954, 2856, 2774, 2246, 2216, 2128, 2062, 1666, 1634, 1578, 1540, 1488, 1438, 1398, 1318, 1294, 1264, 1198, 1122, 1100, 1072, 1058, 1046, 1014, 994, 940, 902, 876, 834, 810, 786, 774, 732, 716, 700, 666, 636, 578, 542 cm^{-1}. Anal. calculated for $C_{14}H_9D_6N_3O_2$ (263.15): C 63.86; H+D 5.73; N 15.96. Found: C 63.39; H+D 5.68; N 15.94.

5-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2-methyl-3-oxo-2,3-dihydropyridazin-4-carbaldehyde (8h). The product was crystallized from isopropyl alcohol, affording pale yellow crystals: yield 51 %, mp 181-183 ^{o}C, R_f=0.52 (ethyl acetate: dichloromethane 1:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.33 (1H, s, CHO), 7.87 (1H, s, H-6), 7.28-7.21 (3H, m, $H_{aromatic}$), 7.07-7.03 (1H, m, $H_{aromatic}$), 4.48 (2H, s, H_2-1 isoquinoline), 3.77 (2H, t, H_2-3 isoquinoline, *J*=5.8), 3.69 (3H, s, N(2)CH_3), 3.09 (2H, t, H_2-4 isoquinoline, *J*=5.8). ^{13}C NMR (50 MHz, $CDCl_3$) δ 188.7 (C-formyl), 162.8 (C-3), 148.2 (C-5), 133.8 and 132.7 (C-4a and C-8a isoquinoline), 128.9, 128.1, 127.3, 126.9, 126.1 (C-6 pyridazine, C-5, -6, -7, -8 isoquinoline), 107.3 (C-4), 54.3 (C-1 isoquinoline) 48.3 (C-3 isoquinoline), 39 (N(2)CH_3), 28.9 (C-4 isoquinoline). IR (potassium bromide): ν_{max} 3424, 3068, 3038, 2946, 2844, 1652, 1634, 1562, 1496, 1460, 1436, 1410, 1382, 1370, 1300, 1258, 1200, 1176, 1104, 1018, 922, 890, 868, 836, 756, 690, 646, 540 cm^{-1}. Anal. calculated for $C_{15}H_{15}N_3O_2$ (269.30): C 66.90; H 5.61; N 15.60. Found: C 66.63; H 5.44; N 15.61.

5-(Dimethylamino)-2-methyl-3-oxo-2,3-dihydropyridazine-4-carbaldehyde (8i). According to the general procedure for preparation of aldehydes from **7i**. The product was crystallized from acetone, affording pale yellow crystals: yield 77 %, mp 141-143 ^{o}C (lit.[11] mp 141-142 ^{o}C), R_f=0.33 (ethyl acetate: dichloromethane 1:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.28 (1H, s, CHO), 7.74 (1H, s, H-6), 3.69 (3H, s, N(2)CH_3), 3.13 (6H, s, N(5)CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 188.7 (C-formyl), 162.7 (C-3), 149.2 (C-5), 128.9 (C-6), 106.5 (C-4), 43.7 (N(5)CH_3), 38.9 (N(2)CH_3). IR (potassium bromide): ν_{max} 3446, 2928, 2867, 1629, 1584, 1535, 1477, 1371, 1302, 1252, 1162, 1127, 1060, 852 cm^{-1}. Anal. calculated for $C_8H_{11}N_3O$ (181.21): C 53.03; H 6.12; N 23.19. Found: C 53.06; H 6.15; N 23.26.

General procedure for the synthesis of malononitriles (9a-h). **Typical example**

To a solution of aldehyde (0.005 mol) **8** in ethanol (10 ml), malononitrile (0.005) and 1-2 drops of piperidine were added. The mixture was stirred at room temperature until the starting material had been consumed (monitored by TLC). The precipitated product was then filtered off, washed with ethanol, diethyl ether and hexane. The crude product was purified by flash column chromatography with a mixture of dichloromethane and ethyl acetate (1:1) as the eluent.

{[5-(Dimethylamino)-2-methyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl]methylene} malononitrile (9a). Deep orange crystals: yield 73 %, mp 180-182 ^{o}C, R_f=0.6 (ethyl acetate: dichloromethane 1:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.3 (1H, s, CH=C), 7.48-7.44 (5H, m, H_{phenyl}), 3.72 (3H, s, N(2)CH_3), 2.93 (6H, s, N(5)CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.4 (C-3), 156.7 (=CH), 152.8 (C-5), 140.7 (C-6), 136.5 (C-1' phenyl), 129.3, 129.2, 127.8 (C-2',-6' phenyl), 114.8, 113.3 (CN), 105.7 (C-4), 78.9 (*C*$(CN)_2$), 46.1 (N(5)CH_3), 39.2 (N(2)CH_3). IR (potassium bromide): ν_{max} 3412, 3050, 2937, 2212, 1636, 1564, 1513, 1447, 1398, 1273, 1166, 1008, 943, 770 cm^{-1}. Anal. calculated for $C_{17}H_{15}N_5Ox0.2H_2O$ (308.94): C 66.09; H 5.02; N 22.64. Found: C 65.98; H 5.02; N 22.24. MS: $[M+H]^+$: 306.

{[6-(2,4-Dichlorophenyl)-5-(dimethylamino)-2-methyl-3-oxo-2,3-dihydropyridazin-4-yl] methylene}malononitrile (9b). Deep orange crystals: yield 70 %, mp 200-202 ^{o}C, R_f=0.73 (ethyl acetate: dichloromethane 1:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.1 (1H, s, CH=C), 7.60-7.30 (3H, m, $H_{aromatic}$), 3.74 (3H, s, N(2)CH_3), 2.80 (6H, s, N(5)CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.9 (C-3), 156.2 (=CH), 152.8 (C-5), 138.7, 136.3, 134.4 (C-6 pyridazine, C-1' phenyl, C-2' and C-4' phenyl), 131.9, 129.8, 128.0 (C-3' phenyl, C-5' and C-6' phenyl), 114.0, 109.2 (CN), 112.3 (C-4), 84.0 (*C*$(CN)_2$), 44.4 (N(5)CH_3), 39.7 (N(2)CH_3). IR (potassium bromide): ν_{max} 3586, 3566, 3422, 3274, 3088, 3010, 2926, 2886, 2796, 2258, 2224, 1640, 1550, 1506, 1484, 1456, 1440, 1402, 1384, 1334, 1314, 1282, 1264, 1244, 1214, 1156, 1090, 1060, 1014, 996, 938, 924, 870, 838, 796, 782, 732, 698, 570, 470 cm^{-1}. Anal. calculated for $C_{17}H_{13}Cl_2N_5O$ (374.23): C 54.56; H 3.50; N 18.71. Found: C 54.33; H 3.35; N 18.35.

[(2-Methyl-3-oxo-6-phenyl-5-pyrrolidino-2,3-dihydropyridazin-4-yl)methylene]malono-nitrile (9c). Yellow crystals: 77 %, mp 185-186 ^{o}C, R_f=0.66 ethyl acetate: dichloromethane 1:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.50 (1H, s, CH=C), 7.56-7.41 (5H, m, H_{phenyl}), 3.69 (3H, s, N(2)CH_3), 3.03 (4H, m, N-CH_2 pyrrolidine), 1.93 (4H, m, CH_2-CH_2 pyrrolidine). ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.8 (C-3), 156.5 (=CH), 148.9 (C-5), 139.7 (C-6), 136.3 (C-1' phenyl), 129.3, 129, 127.7 (C-2',-6' phenyl), 114.8, 113.3 (CN), 103.1 (C-4), 74.9 (*C*$(CN)_2$), 55.8 (C-2,5 pyrrolidine), 38.7 (N(2)CH_3), 25 (C-3,4 pyrrolidine). IR (potassium bromide): ν_{max} 3412, 2976, 2216, 1637, 1556, 1480, 1441, 1276, 1142, 1012, 927, 768, 705, 594 cm^{-1}. Anal. calculated for $C_{19}H_{17}N_5O$ (331.37): C 68.87; H 5.17; N 21.13. Found: C 68.34; H 5.17; N 20.99. HRMS calculated for $C_{19}H_{17}N_5O$: 331.1511. Found: 331.1499.

[(2-Methyl-3-oxo-6-phenyl-5-piperidino-2,3-dihydropyridazin-4-yl)methylene]malono-nitrile (9d). Deep orange crystals: 78 %, mp 170-172 ^{o}C, R_f=0.93 (ethyl acetate: dichloromethane 1:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60 (1H, s, CH=C), 7.55-7.30 (5H, m, H_{phenyl}), 3.75 (3H, s, N(2)CH_3), 3.15-2.85 (4H, m, N-CH_2 piperidine), 1.65-1.25 (6H, m, CH_2-CH_2-CH_2 piperidine). ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.7 (C-3), 153.9 (C-5), 153.5 (=CH), 143.0 (C-6), 136.3 (C-1' phenyl), 129.1, 128.9, 128.1 (C-2',-6' phenyl), 114.3, 113.5, 112.5 (C-4, CN), 86.7 (*C*$(CN)_2$), 54.1 (C-2,6 piperidine), 40.0 (N(2)CH_3), 26.6 (C-3,5 piperidine), 23.1 (C-4 piperidine). IR (potassium bromide): ν_{max} 3444, 2936, 2856, 2220, 1740, 1698, 1650, 1560, 1542, 1508, 1476, 1442, 1398, 1368, 1322, 1214, 1102, 1020, 708 cm^{-1}. Anal. calculated for $C_{20}H_{19}N_5O$ (345.40): C 69.55; H 5.54; N 20.28. Found: C 69.42; H 5.56; N 20.32.

[(2-Methyl-5-morpholino-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)methylene]malononitrile (9e). Orange crystals: 64 %, mp 184-187 °C, R_f=0.8 (ethyl acetate: dichloromethane 1:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68 (1H, s, CH=C), 7.52-7.38 (5H, m, H_{phenyl}), 3.80 (3H, s, N(2)CH_3), 3.61 (4H, t, O-CH_2 morpholine, *J*=4.6), 3.05 (4H, m, N-CH_2 morpholine, *J*=4.6). ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.7 (C-3), 153.5 (=CH), 152.8 (C-5), 142.8 (C-6), 135.8 (C-1' phenyl), 129.5, 129.2, 128.3 (C-2',-6' phenyl), 114.2, 113.8, 128.3 (C-4, CN), 88.5 (*C*$(CN)_2$), 66.8 (C-2,6 morpholine), 52.4 (C-3,5 morpholine), 40.2 (N(2)CH_3). IR (potassium bromide): ν_{max} 3412, 2963, 2906, 2852, 2220, 1646, 1567, 1545, 1481, 1436, 1322, 1256, 1204, 1111, 1031, 782, 710 cm^{-1}. Anal. calculated for $C_{19}H_{17}N_5O_2$ (347.38): C 65.69; H 4.93; N 20.16. Found: C 65.02; H 4.94; N 19.72. HRMS calculated for $C_{19}H_{17}N_5O_2$: 348.1461. Found: 348.1447.

{[5-(Dimethylamino-d_6)-2-methyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl]methylene} malononitrile (9g). Deep orange crystals: 63 %, mp 181-183 °C, R_f=0.56 ethyl acetate : dichloromethane 1:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.33 (1H, s, CH=C), 7.65-7.35 (5H, m, H_{phenyl}), 3.73 (3H, s, N(2)CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.5 (C-3), 156.8 (=CH), 152.8 (C-5), 140.6 (C-6), 136.5 (C-1' phenyl), 129.3, 129.2, 127.9 (C-2',-6' phenyl), 114.5, 113.2 (CN), 105.4 (C-4), 78.7 (C$(CN)_2$), 39.2 (N(2)CH_3). IR (potassium bromide): ν_{max} 3428, 3250, 3024, 2936, 2256, 2208, 1636, 1552, 1496, 1442, 1332, 1272, 1142, 1098, 1026, 992, 960, 768, 722, 696, 594, 542 cm^{-1}. Anal. calculated for $C_{17}H_9D_6N_5O$ (311.38): C 65.58; H+D 4.85; N 22.49. Found: C65.16; H+D 4.79; N 22.56. MS: $[M+H]^+$: 312. Based on the comparison of spectra of **9g** to those of **9a**, it was confirmed that no deuterium was lost (>98% deuterium).

{[5-(Dimethylamino)-2-methyl-3-oxo-2,3-dihydropyridazin-4-yl]methylene}malononitrile (9i). Orange crystals: 48 %, mp 180-182 °C, R_f=0.47 (ethyl acetate: dichloromethane 1:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.31 (1H, s, CH=C), 7.82 (1H, s, H-6), 3.69 (3H, s, N(2)CH_3), 3.12 (6H, s, N(5)CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.5 (C-3), 157.1 (=CH), 150.6 (C-5), 128.5 (C-6), 114, 111.9 (CN), 104.2 (C-4), 81.6 (*C*$(CN)_2$), 42.6 (N(5)CH_3), 39.3 (N(2)CH_3). IR (potassium bromide): ν_{max} 3429, 3086, 2948, 2221, 1623, 1585, 1535, 1476, 1405, 1369, 1303, 1260, 1167, 1111, 1020, 959, 757, 679 cm^{-1}. Anal. calculated for $C_{11}H_{11}N_5O$ (229.24): C 57.63; H 4.84; N 30.55. Found: C 57.31; H 4.86; N 30.00. HRMS calculated for $C_{11}H_{11}N_5O$: 230.1042. Found: 230.1033.

General procedure for the synthesis of 10a-c, 10h, 10i. Knoevenagel condensation of aldehydes with DMB. Typical example

To a s olution of formyl derivative **8** (0.001 mol) in ethanol (5 mL) 1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (1,3-dimethylbarbituric acid, DMB) (0.001 mol) was added. The mixture was stirred at ambient temperature until the starting material had been consumed (monitored by TLC). The precipitated products were then filtered off, which was then washed with ethanol, diethyl ether and hexane to give analytically pure crystals at all times.

5-{[5-(Dimethylamino)-2-methyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl]methylene}-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (10a). Yellow crystals: 84 %, mp 188-189 °C,

R_f=0.21 (toluene: acetone 7:3). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.94 (1H, s, CH=C), 7.82-7.77 (2H, m, H-3' and H-5' phenyl), 7.52-7.42 (3H, m, H-2' phenyl, H-4' and H-6' phenyl), 3.74 (3H, s, N(2)CH_3 pyridazine), 3.42 and 3.35 (3H, s, N(1)CH_3 and 3H, s, N(3)CH_3 pyrimidine), 2.78 (6H, s, N(5)CH_3 pyridazine). ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.8, 161.3, 159.5 (C-3 pyridazine, C-6 and C-4 pyrimidine), 155.7 and 151.7 (C-5 pyridazine and C-2 pyrimidine), 151.5 (=CH), 140 (C-6 pyridazine), 137.1 (C-1' phenyl), 129 and 127.6 (C-2'-6' phenyl), 112.4 and 107.6 (C-5 pyrimidine and C-4 pyridazine), 46 (N(5)CH_3), 39.1 (N(2)CH_3 pyridazine), 28.6 and 28.1 (N(1)CH_3 and N(3)CH_3 pyrimidine). IR (potassium bromide): ν_{max} 3446, 3062, 2940, 1712, 1650, 1570, 1496, 1462, 1400, 1378, 1324, 1296, 1282, 1176, 1120, 1084, 1058, 1016, 974, 960, 780, 760, 712, 576, 540, 480, 454 cm^{-1}. Anal. calculated for $C_{20}H_{21}N_5O_4$ (395.42): C 60.75; H 5.35; N 17.71. Found: C 60.59; H 5.33; N 17.65. MS: $[M+H]^+$: 396.

5-{[6-(2,4-Dichlorophenyl)-5-dimethylamino-2-methyl-3-oxo-2,3-dihydropyridazin-4-yl] methylene}-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (10b). Orange crystals: 61 %, mp 134-135 °C, R_f=0.27 (petroleum ether(bp 40-70 °C): ethyl acetate 1:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.69 (0.5H, broad s, CH=C), 8.00 (0.5H, broad s, CH=C), 7.53-7.30 (3H, broad m, H-3' phenyl, H-5' and H-6' phenyl), 3.75 (3H, s, N(2)CH_3 pyridazine), 3.41 and 3.35 (3H, s, N(1)CH_3 and 3H, board s, N(3)CH_3 pyrimidine), 2.66 (6H, board s, N-CH_3). Due to the atropisomerism, at room temperature in the ^{13}C NMR spectrum broadened signals are present. On heating the sample in NMR tube, transformation to **12b** occurred. IR (potassium bromide): ν_{max} 3446, 2926, 1676, 1620, 1578, 1455, 1379, 1305, 1094, 1055, 753 cm^{-1}. Anal. calculated for: $C_{20}H_{19}Cl_2N_5O_4$ (464.30): C 51.74; H 4.12; N 15.08. Found: C 51.13; H 4.02; N 14.81. HRMS calculated for $C_{20}H_{19}Cl_2N_5O_4$: 464.0892. Found: 464.0871.

1,3-Dimethyl-5-[(2-methyl-3-oxo-6-phenyl-5-pyrrolidino-2,3-dihydropyridazin-4-yl)methyl-lene]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (10c). Orange crystals: 86 %, mp 161-163 °C, R_f=0.38 (ethyl acetate). ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.27 (1H, s, CH=C), 7.94 (2H, d, H-3' and H-5' phenyl), 7.53-7.43 (3H, m, H-2' phenyl, H-4' and H-6' phenyl), 3.73 (3H, s, N(2)CH_3 pyridazine), 3.43 and 3.33 (3H, s, N(1)CH_3 and 3H, s, N(3)CH_3 pyrimidine), 2.82 (4H, m, NCH_2, pyrrolidine), 1.83 (4H, m, CH_2-CH_2, pyrrolidine). ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.8, 161.3, 159.5 (C-3 pyridazine, C-4 and C-6 pyrimidine), 153 and 151.9 (C-5 pyridazine and C-2 pyrimidine), 151.7 (=CH), 139.4 (C-6 pyridazine), 137 (C-1' phenyl), 128.9 and 127.7 (C-2'-6' phenyl), 109.2 and 104.4 (C-5 pyrimidine and C-4 pyridazine), 55.3 (C-2, -5 pyrrolidine), 38.9 (N(2)CH_3 pyridazine), 28.6 and 28 (N(1)CH_3 and N(3)CH_3 pyridazine), 24.8 (C-3,-4 pyrrolidine). IR (potassium bromide): ν_{max} 3362, 2946, 1716, 1647, 1558, 1484,1380, 1350, 1300, 1277, 1250, 1146, 1050, 955, 703 cm^{-1}. Anal. calculated for $C_{22}H_{23}N_5O_4$ (421.45): C 62.70; H 5.50; N 16.62. Found: C 62.60; H 5.61; N 16.37.

5-{[5-(Dimethylamino-d_6)-2-methyl-3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl]methylene}-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (10g). Yellow crystals: 81 %, mp 188-190 °C, R_f=0.24 (toluene: acetone 7:3). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.97 (1H, s, CH=C), 7.83-7.70 (2H, m, H-3' and H-5' phenyl), 7.60-7.35 (3H, m, H-2' phenyl, H-4' and H-6' phenyl), 3.73 (3H, s, N(2)CH_3), 3.41 and 3.35 (3H, s, N(1)CH_3 and 3H, s, N(3)CH_3 pyrimidine). ^{13}C NMR (50

MHz, $CDCl_3$) δ 162.5, 160.4, 160.2 (C-3 pyridazine, C-6 and C-4 pyrimidine), 155.8 and 151.8 (C-5 pyridazine and C-2 pyrimidine), 151.6 (=CH), 140.0 (C-6 pyridazine), 137.2 (C-1' phenyl), 129.0 and 127.7 (C-2'-6' phenyl), 112.4 and 107.5 (C-5 pyrimidine, C-4 pyridazine), 39.2 ($N(2)CH_3$ pyridazine), 28.6 and 28.1 ($N(1)CH_3$ and $N(3)CH_3$ pyrimidine). IR (potassium bromide): ν_{max} 3442, 1712, 1652, 1558, 1522, 1478, 1414, 1378, 1324, 1294, 1234, 1154, 1090, 1054, 782, 714, 480 cm^{-1}. Anal. calculated for $C_{20}H_{15}D_6N_5O_4$ (401.45): C 59.84; H+D 5.27; N 17.44. Found: C 59.36; H+D 5.19; N 17.01. MS: $[M+H]^+$: 402. Based on the comparison of spectra of **10g** to those of **10a**, it was confirmed that no deuterium was lost (>98% deuterium).

5-{[5-(Dimethylamino)-2-methyl-3-oxo-2,3-dihydropyridazin-4-yl]methylene}-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (10i). Orange crystals: 89 %, mp 207-209 °C, R_f=0.24 (ethyl acetate: chloroform 9:1). ^1H NMR (200 MHz, $CDCl_3$) δ 8.9 (1H, s, CH=C), 7.81 (1H, s, H-6), 3.69 (3H, s, $N(2)CH_3$), 3.41 and 3.28 (3H, s, $N(1)CH_3$ and 3H, s, $N(3)CH_3$ pyrimidine), 2.92 (6H, s, $N(5)CH_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.2, 160.7, 159.5 (C-3 pyridazine, C-4 and C-6 pyrimidine), 152.3, 151.6 (C-5 pyridazine, C-2 pyrimidine and =CH), 128.3 (C-6 pyridazine), 115.5 and 106.4 (C-5 pyrimidine and C-4 pyridazine), 43.1 ($N(5)CH_3$ pyridazine), 39.4 ($N(2)CH_3$ pyridazine), 28.8 and 28.2 ($N(1)CH_3$ and $N(3)CH_3$ pyrimidine). IR (potassium bromide): ν_{max} 3440, 2954, 1716, 1655, 1589, 1506, 1410, 1275, 1257, 1167, 1084, 943, 754 cm^{-1}. Anal. calculated for $C_{14}H_{17}N_5O_4$ (319.32): C 52.66; H 5.37; N 21.93. Found: C 52.64; H 5.41; N 21.68.

General procedure for the isomerization of vinyl compounds 9: preparation of compounds 11

Compound **9** (0.005 mol) in anhydrous DMF (10 ml) was heated at 100 °C (in case of compound **9b** and **9g** at 155 °C) until the starting material had been consumed (monitored by TLC). After evaporation of the solvent *in vacuo*, water (5 mL) was added to the oily residue, and the mixture was extracted with chloroform (3x5 mL). The combined organic phases were dried over anhydrous magnesium sulphate. The solvent was evaporated in *vacuo*, and the crude product was purified by column chromatography or crystallization. In case of compounds **11a**, **11b** and **11d**, the precipitated crystals were filtered off and washed with water (3x2 mL). The crude product was purified by column chromatography or crystallization.

1,6-Dimethyl-5-oxo-8-phenyl-1,4,5,6-tetrahydropyrido[2,3-*d*]pyridazine-3,3(2*H*)-dicarbonitrile (11a). The crude product was purified by column chromatography with a mixture of petroleum ether (bp 40-70 °C) and ethyl acetate (1:1) as the eluent, affording beige crystals: yield 47 %, mp 190-192 °C, R_f=0.38 (petroleum ether (bp 40-70 °C): ethyl acetate 1:1). ^1H NMR (200 MHz, $CDCl_3$) δ 7.5-7.43 (5H, m, H_{phenyl}), 3.80 (3H, s, $N(6)CH_3$), 3.75 (2H, s, H_2-2), 3.40 (2H, s, H_2-4), 2.67 (3H, s, $N(1)CH_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.2 (C-5), 145.3 and 140.3 (C-8 and C-8a), 136.0 (C-1' phenyl), 129.2 (C-4' phenyl), 129.0, 127.9 (C-2' phenyl, C-3', C-5' and C-6' phenyl), 113.8 and 111.4 (C-4a and CN), 56.1 (C-2), 43.9 ($N(1)CH_3$), 39.8 ($N(6)CH_3$), 32.1 (C-4), 26.2 (C-3). IR (potassium bromide): ν_{max} 2966, 1626, 1441, 1401, 1278, 1075, 776,

703 cm^{-1}. Anal. calculated for $C_{17}H_{15}N_5O$ (305.33): C 66.87; H 4.95; N 22.94. Found: C 67.03; H 5.11; N 23.02. MS: $[M+H]^+$: 306.

8-(2,4-Dichlorophenyl)-1,6-dimethyl-5-oxo-1,4,5,6-tetrahydropyrido[2,3-*d*]pyridazine-3,3(2*H*)-dicarbonitrile (11b). The product was crystallized from isopropyl alcohol, affording beige crystals: yield 35 %, mp 221-222 °C, R_f=0.75 (ethyl acetate: dichloromethane 1:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.51 (1H, broad s, H-3' phenyl), 7.40 (2H, broad s, H-5' and H-6' phenyl), 3.78 (3H, s, N(6)CH_3), 3.73 (1H, d, Ha-2, *J*=16.0), 3.70 (1H, d, Hb-2, *J*=16.0), 3.50 (1H, d, Ha-4, *J*=17.0), 3.25 (1H, d, Hb-4, *J*=17.0), 2.67 (3H, s, N(1)CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.1 (C-5), 145.1, 136.9, 136.1 134.3 and 133.9 (C-1' phenyl, C-2' and C-4' phenyl, C-8 and C-8a), 131.9, 129.8, 127.9 (C-3' phenyl, C-5' and C-6' phenyl), 113.6 and 110.1 (C-4a and CN), 56.3 (C-2), 42.7 and 39.8 (N(1)CH_3 and N(6)CH_3), 31.9 (C-4), 26.9 (C-3). IR (potassium bromide): ν_{max} 3748, 3674, 3650, 3614, 3588, 3566, 3422, 2926, 1700, 1682, 1634, 1578, 1558, 1542, 1508, 1490, 1474, 1458, 1436, 1412, 1378, 1102, 1024, 460 cm^{-1}. Anal. calculated for $C_{17}H_{13}Cl_2N_5O$ (374.23): C 54.56; H 3.50; N 18.71. Found: C 54.38; H 3.41; N 18.66.

3-Methyl-4-oxo-1-phenyl-3,5,6a,7,8,9-hexahydropyridazino[4,5-*e*]indolizine-6,6(4*H*)-dicarbonitrile (11c). The crude product was purified by column chromatography with a mixture of petroleum ether (bp 40-70 °C) and ethyl acetate (1:2) as the eluent, affording yellow crystals: yield 67 %, mp 224-228 °C, R_f=0.44 (petroleum ether (bp 40-70 °C): ethyl acetate 1:2). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45 (5H, m, H_{phenyl}), 3.85 (1H, d, 5-Ha, *J*=18.0), 3.81 (3H, s, N(3)CH_3), 3.10 (1H, d, 5-Hb, *J*=18.0), 2.87 (2H, m, H_2-9), 2.60-1.60 (4H, m, H_2-7 and H_2-8). ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.2 (C-4), 143.2 and 139.5 (C-1 and C-10a), 136.4 (C-1' phenyl), 129.1, 128.7 and 128.6 (C-2'-6' phenyl), 114.4 and 113.3 (CN), 107.6 (C-4a), 63.1 (C-6a), 52.5 (C-9), 39.7 (N(3)CH_3), 31.8 (C-6), 32.8, 28.8 and 23.2 (C-5, C-7, and C-8). IR (potassium bromide): ν_{max} 3676, 3652, 3630, 3568, 3238, 3064, 3022, 2990, 2946, 2920, 2898, 2864, 2248, 1626, 1547, 1496, 1434, 1372, 1352, 1318, 1274, 1246, 1192, 1158, 1094, 1072, 1016, 996, 986, 970, 786, 708, 568 cm^{-1}. Anal. calculated for $C_{19}H_{17}N_5O$ (331.37): C 68.87; H 5.17; N 21.13. Found: C 68.85; H 5.25; N 21.38.

3-Methyl-4-oxo-1-phenyl-3,5,7,8,9,10-hexahydro-4*H*-pyridazino[4,5-*c*]quinolizine-6,6(6a*H*)-dicarbonitrile (11d). The product was crystallized from isopropyl alcohol, affording white crystals: yield 46 %, mp 188-190 °C, R_f=0.58 (ethyl acetate: dichloromethane 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.50 (2H, m, H-3' and H-5' phenyl), 7.49-7.40 (3H, m, H-2' phenyl, H-4' and H-6' phenyl), 3.77 (3H, s, N(3)CH_3), 3.71 (1H, d, Ha-5 *J*=18.0), 3.45 (1H, m, Ha-10), 3.24 (1H, m, H-6a), 3.13 (1H, d, Hb-5, *J*=18.0), 2.41 (1H, m, Hb-10), 2.32 (1H, m, Ha-7), 1.98 (1H, m, Ha-9), 1.85 (1H, m, Hb-7), 1.49 (1H, m, Hb-9), 1.22-1.33 (2H, m, H_2-8). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9 (C-4), 145.8 and 140.6 (C-1 and C-11a), 137.3 (C-1' phenyl), 129.8 (C-4' phenyl), 129.7 (C-2' and C-6 phenyl), 127.8 (C-3' and C-5' phenyl), 114.5 and 113.4 (CN), 111.4 (C-4a) 62.7 (C-6a), 52.3 (C-10), 40.2 (N(3)CH_3), 36.6 (C-6), 32.4, 29.2, 24.4 and 23.9 (C-5, C-7, C-8 and C-9). IR (potassium bromide): ν_{max} 3784, 3698, 3658, 3634, 3574, 3428, 3056, 3022, 2932, 2852, 2822, 2728, 2612, 1972, 1902, 1856, 1630, 1592, 1550, 1498, 1442, 1414,

1370, 1332, 1310, 1284, 1260, 1236, 1210, 1168, 1138, 1098, 1074, 1048, 1020, 990, 968, 918, 776, 706, 574, 546 cm^{-1}. Anal. calculated for $C_{20}H_{19}N_5O$ (345.40): C 69.55; H 5.54; N 20.28. Found: C 69.76; H 5.49; N 20.38.

3-Methyl-4-oxo-1-phenyl-3,5,6a,7,9,10-hexahydropyridazino[4',5':5,6]pyrido[2,1-*c*][1,4] oxazine-6,6(4*H*)-dicarbonitrile (11e). The crude product was purified by column chromatography with a mixture of dichloromethane and ethyl acetate (1:1) as the eluent, affording white crystals: yield 46 %, mp 239-241 °C, R_f=0.54 (ethyl acetate: dichloromethane 1:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.67-7.52 (2H, m, H-3' and H-5' phenyl), 7.48-7.42 (3H, m, H-2' phenyl, H-4' and H-6' phenyl), 4.29 (1H, dd, Ha-7, J_1=11.7, J_2=3.0), 3.96 (1H, dd, Hb-7, J_1=11.6, J_2=8.2), 3.79 (3H, s, N(3)CH_3), 3.75 (1H, d, Ha-5, J=18), 3.55-3.25 (4H, m, H_2-9, Ha-8 and Hb-10), 3.18 (1H, d, Hb-5, J=18), 2.68 (1H, m, Ha-10). ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.1 (C-4), 144.6 and 139.7 (C-1 and C-11a), 135.9 (C-1' phenyl), 129.5 (C-4' phenyl), 129.2, 127.3 (C-2', C-3', C-5' and C-6' phenyl), 113, 112.6 and 112.4 (C-4a and CN), 67.2, 66.0 (C-7, C-9), 59.2 (C-6a), 48.8 (C-5), 39.7 (N(3)CH_3), 32.5 (C-10), 30.9 (C-6). IR (potassium bromide): ν_{max} 3424, 2946, 2922, 2868, 1638, 1580, 1496, 1432, 1410, 1382, 1356, 1292, 1226, 1182, 1124, 1052, 1026, 992, 778, 708 cm^{-1}. Anal. calculated for $C_{19}H_{17}N_5O_2$ (347.37): C 65.70; H 4.93; N 20.16. Found: C 65.40; H 5.00; N 19.98.

1,6-Dimethyl-1*d*$_3$-5-oxo-8-phenyl-1,4,5,6-tetrahydro-4-*d*-pyrido[2,3-*d*]pyridazine-3,3(2*H*)-2,2-*d*$_2$-dicarbonitrile (11g). The crude product was purified by column chromatography with a mixture of petroleum ether (bp 40-70 °C) and ethyl acetate (1:1) as the eluent, affording beige crystals: yield 51 %, mp 190-192 °C, R_f=0.53 (petroleum ether (bp 40-70 °C): ethyl acetate 1:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52-7.43 (5H, m, H_{phenyl}), 3.80 (3H, s, N(6)CH_3), 3.38 (1H, s, H-4). ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.2 (C-5), 145.3 and 140.3 (C-8 and C-8a), 136.0 (C-1' phenyl), 129.2 (C-4' phenyl), 129.0, 127.9 (C-2' phenyl, C-3' phenyl, C-5' and C-6' phenyl), 113.8 and 111.4 (C-4a and CN), 39.8 (N(6)CH_3), 31.7 [t (1:1:1) due to the ^1J(C,D), *C*-4], 25.9 (C-3). IR (potassium bromide): ν_{max} 2926, 1630, 1510, 1444, 1414, 1352, 1284, 1268, 1244, 1216, 1026, 754, 708, 544, 456 cm^{-1}. Anal. calculated for $C_{17}H_9D_6N_5O$ (311.38): C 65.58; H+D 4.85; N 22.49. Found: C 65.18; H+D 4.75; N 22.52. MS: $[M+H]^+$: 312. Based on the comparison of spectra of **11g** to those of **11a**, it was confirmed that no deuterium was lost (>98% deuterium).

General procedures for the preparation of compounds 12

Method A. Thermal isomerization of compounds 10. Compound **10** (0.001 mol) in anhydrous DMF (5 mL) was heated at 100 °C (in case of compound **10i** at 155 °C) until the starting material had been consumed (monitored by TLC). After evaporation of the solvent in *vacuo*, water (10 mL) was added to the residue. Then it was filtered off and washed with water (3x2 mL). The product was purified by flash column chromatography or crystallization.

Method B. One-pot procedure from aldehydes 8. To a solution of aldehyde **8** (0.001 mol) in ethanol (5 mL), DMB (0.001 mol) was added. The mixture was stirred at room temperature until the starting material had been consumed (monitored by TLC). The precipitated product was then filtered off and washed with ethanol, diethyl ether and hexane to give analytically pure crystals

in case of compound **12d**, **12e**. Starting from **8f** or **8h** aldehydes afforded a mixture of vinyl compounds and the tetrahydropyrido-fused compounds (**10f** and **12f**, or **10h** and **12h**) (detected by TLC, ^{1}H NMR). To make complete the reaction, the product was heated in ethanol (5 mL) for 1h. After cooling, crystals precipitated were filtered off and washed with ethanol to give analytically pure compound **12h**. Compound **12f** was purified by flash column chromatography, using dichloromethane-ethyl acetate (1:1) as the eluent.

1,1',3',6-Tetramethyl-8-phenyl-4,6-dihydro-2*H*,2'*H*-spiro[pyrido[2,3-*d*]pyridazine-3,5'-pyrimidine]-2',4',5,6'(1*H*,1'*H*,3'*H*)-tetrone (12a). Following the procedure of Method A, the product was crystallized from ethanol, affording beige crystals: yield 62 %.

Compound **12a** was also prepared by using microwave-heating. Compound **10a** (50 mg) and 2 mL D_2O was irradiated in a closed vessel with pressure control at 100 ^{o}C for 10 minutes (ramp time: 2 min; hold time: 10 min) at 200 W maximum power. The precipitated product was then filtered off and washed with hexane to give analytically pure 35 mg (70 %) beige crystals.

Mp 209-211 ^{o}C, R_f=0.32 (petroleum ether (bp 40-70 ^{o}C): ethyl acetate (1:2). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55-7.53 (2H, m, H-3' and H-5' phenyl), 7.45-7.39 (3H, m, H-2' phenyl, H-4' and H-6' phenyl), 3.81 (3H, s, N(6)CH_3), 3.48 (2H, s, H_2-2), 3.31 (6H, s, N(3')CH_3 and N(1')CH_3 pyrimidine) 3.22 (2H, s, H_2-4), 2.40 (3H, s, N(1)CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 169 (C-4'and C-6' pyrimidine), 160.1 (C-5), 151 (C-2' pyrimidine), 145 and 140.5 (C-8 and C-8a), 136.8 (C-1' phenyl), 128.7 (C-4' phenyl), 128.8, 128 (C-2', C-3', C-5' and C-6' phenyl), 116.3 (C-4a), 58.1 (C-2), 46.2 (C-3), 43.6 (N(1)CH_3), 39.8 (N(6)CH_3), 29 (N(1')CH_3 and N(3')CH_3 pyrimidine), 28.3 (C-4). IR (potassium bromide): ν_{max} 3462, 2936, 1746, 1678, 1614, 1544, 1510, 1446, 1420, 1404, 1382, 1340, 1280, 1200, 1160, 1126, 1064, 778, 756, 708, 544, 474 cm^{-1}. Anal. calculated for $C_{20}H_{21}N_5O_4$ (395.42): C 60.75; H 5.35; N 17.71. Found: C 61.15; H 5.51; N 17.79. MS: $[M+H]^+$: 396.

8-(2,4-Dichlorophenyl)-1,1',3',6-tetramethyl-4,6-dihydro-2*H*,2'*H*-spiro[pyrido[2,3-*d*]pyridazine-3,5'-pyrimidine]-2',4',5,6'(1*H*,1'*H*,3'*H*)-tetrone (12b). Following the procedure of Method A, then the product was crystallized from ethanol, affording beige crystals: yield 50 %, mp 251-252 ^{o}C, R_f=0.37 (toluene: acetone 7:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.27 (3H, m, H-3', H-5', H-6' phenyl), 3.79 (3H, s, N(6)CH_3), 3.48 (1H, d, Ha-2, *J*=13.2), 3.39 (1H, d, Hb-2, *J*=13.2), 3.34 and 3.28 (6H, s, N(3')CH_3 and N(1')CH_3 pyrimidine) 3.22 (1H, d, Ha-4, *J*=18.4), 3.25 (1H, d, Hb-4, *J*=18.4), 2.41 (3H, s, N(1)CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169 (C-4'and C-6' pyrimidine), 160.1 (C-5), 151 (C-2' pyrimidine), 145 (C-8a), 137.2, 135.5, 134.7, 134.4 (C-8, and C-1' phenyl, C-2' and C-4' phenyl), 132.1, 129.7 and 127.6 (C-3'phenyl, C-5' and C-6' phenyl), 115.5 (C-4a), 58.1 (C-2), 46.4 (C-3), 42.6 (N(1)CH_3), 39.7 (N(6)CH_3), 29.2 and 28.8 (N(1')CH_3 and N(3')CH_3 pyrimidine), 28.3 (C-4). IR (potassium bromide): ν_{max} 3568, 3526, 3420, 3058, 2990, 2956, 2920, 1744, 1670, 1632, 1592, 1546, 1508, 1454, 1406, 1372, 1342, 1324, 1284, 1204, 1138, 1088, 1058, 1034, 826, 800, 750, 480, 452 cm^{-1}. Anal. calculated for $C_{20}H_{19}Cl_2N_5O_4$ (464.30): C 51.74; H 4.12; N 15.08. Found: C 51.77; H 4.06; N 15.03.

1',3,3'-Trimethyl-1-phenyl-3,5,6a,7,8,9-hexahydro-2'*H*,4*H*-spiro[pyridazino[4,5-*e*]indolizine-6,5'-pyrimidine]-2',4,4',6'(1'*H*,3'*H*)-tetrone (12c). Following the procedure of

Method A, then the product was purified by flash column chromatography, using ethyl acetate as the eluent, affording white crystals: yield 40 %, mp 207-209 ^{o}C, R_f=0.59 (ethyl acetate). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.48-7.38 (5H, m, H_{phenyl}), 3.88 (1H, m, Ha-6), 3.76 (3H, s, N(3)CH_3), 3.37 and 3.20 (3H, s, N(3')CH_3 and 3H, s, N(1')CH_3 pyrimidine), 3.26 (1H, d, Ha-5, *J*=18.4), 3.13 (1H, d, Hb-5, *J*=18.4), 2.82-2.74 (2H, m, H_2-9), 2.19-1.42 (4H, m, H_2-7 and H_2-8). ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.4, 168 (C-4' and C-6' pyrimidine), 160 (C-4), 151 (C-2' pyrimidine), 143.4 (C-10a), 139.8 (C-1), 137.4 (C-1' phenyl), 128.7, 128.6 (C-2'-6' phenyl), 112.2 (C-4a), 64.2 (C-6a), 52.5 (C-9), 46.9 (C-6), 39.6 (N(3)CH_3), 31.6, 27.6 and 23.7 (C-5, C-7 and C-8), 29.1 and 28.5 (N(1')CH_3 and N(3')CH_3 pyrimidine). IR (potassium bromide): ν_{max} 3408, 3084, 6054, 2964, 2888, 1742, 1686, 1616, 1514, 1448, 1418, 1382, 1356, 1280, 1210, 1180, 1156, 1128, 1086, 1062, 1022, 780, 756, 704, 538, 472 cm^{-1}. Anal. calculated for $C_{22}H_{23}N_5O_4$ (421.45): C 62.70; H 5.50; N 16.62. Found: C 62.75; H 5.48; N 16.51.

1',3,3'-Trimethyl-1-phenyl-3,5,7,8,9,10-hexahydro-2'*H*,4*H*,6a*H*-spiro[pyridazino[4,5-*c*]quinolizine-6,5'-pyrimidine]-2',4,4',6'(1'*H*,3'*H*)-tetrone (12d). Following the procedure of Method B, the product was obtained as beige crystals: 82 %, mp 253-254 ^{o}C, R_f=0.52 (ethyl acetate : dichloromethane 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73-7.69 (2H, m, H-3' and H-5' phenyl), 7.50-7.30 (3H, m, H-2' phenyl, H-4' and H-6' phenyl), 3.74 (3H, s, N(3)CH_3), 3.65-3.50 (1H, m, Ha-10), 3.50-3.39 (1H, m, H-6a), 3.39 and 3.29 (3H, s, N(1')CH_3 and 3H, s, N(3')CH_3 pyrimidine), 3.28 (1H, d, Ha-5 *J*=17.6), 3.02 (1H, d, Hb-5, *J*=17.6), 2.52-2.45 (1H, m, Hb-10), 1.80-1.70 (1H, m, Ha-7), 1.60-1.50 (1H, m, Hb-7), 1.50-1.35 (2H, m, H_2-9), 1.25-1.05 (2H, m, H_2-9), 1.40-1.20 (2H, m, H_2-8). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 and 167.2 (C-4' and C-6' pyrimidine) 160.3 (C-4), 150.9 (C-2' pyrimidine), 146.2 and 140.4 (C-1 and C-11a), 137.9 (C-1' phenyl), 128.9 (C-2' and C-6' phenyl), 128.8 (C-4' phenyl), 127.5 (C-3' and C-5' phenyl), 112.3 (C-4a), 62.0 (C-6a), 52.2 (C-6), 51.6 (C-10), 39.6 (N(3)CH_3), 32.3 (C-7), 29.5 and 28.9 (N(1')CH_3 and N(3')CH_3 pyrimidine), 26.8, 24.0 and 23.9 (C-5, C-8 and C-9). IR (potassium bromide): ν_{max} 3408, 2940, 2850, 1746, 1678, 1628, 1600, 1428, 1366, 1314, 1282, 1264, 1238, 1210, 1166, 1132, 1066, 968, 754, 702, 476 cm^{-1}. Anal. calculated for $C_{23}H_{25}N_5O_4$ (435.48): C 63.44; H 5.79; N 16.08. Found: C 63.23; H 5.79; N 15.92.

1',3,3'-Trimethyl-1-phenyl-3,5,6a,7,9,10-hexahydro-2*H*',4*H*-spiro[pyridazino[4',5':5,6] pyrido[2,1-*c*][1,4]oxazine-6,5'-pyrimidine]-2',4,4',6'(1'*H*,3'*H*)-tetrone (12e). Following the procedure of Method B, the product was obtained as orange crystals: 88 %, mp > 260 ^{o}C, R_f=0.44 (petroleum ether (bp 40-70 ^{o}C): ethyl acetate 1:2). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.7-7.68 (2H, m, H-3' and H-5' phenyl), 7.47-7.38 (3H, m, H-2' phenyl, H-4' and H-6' phenyl), 3.79 (3H, s, N(3)CH_3), 3.75 (1H, dd, Ha-7, J_1=11.2, J_2=2.6), 3.66 (1H, dd, Ha-6, J_1=6.2, J_2=2.8), 3.60 (1H, dd, Hb-7, J_1=11.2, J_2=6.3), 3.39 and 3.27 (3H, s, N(3')CH_3 and 3H, s, N(1')CH_3 pyrimidine) 3.36 (2H, m, H_2-9), 3.3 (1H, d, Ha-5, *J*=18.2), 3.25 (1H, m, Ha-10), 3.18 (1H, d, Hb-5, *J*=18.2), 2.7-2.67 (1H, m, Hb-10). ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.5, 168.1 (C-4' and C-6' pyrimidine), 160.1 (C-4), 150.5 (C-2' pyrimidine), 145.1 and 140.2 (C-1 and C-11a), 136.8 (C-1' phenyl), 129, 128.9, 127.5 (C-2'-6' phenyl), 116 (C-4a), 66.1, 65.9 (C-7, C-9), 60.6 (C-6a), 48.9 (C-6), 47.4 (C-10), 39.7 (N(3)CH_3), 32 (C-5), 29.3 and 28.9 (N(1')CH_3 and N(3')CH_3

pyrimidine). IR (potassium bromide): ν_{max} 3410, 3052, 2998, 2966, 2886, 1744, 1684, 1630, 1596, 1444, 1414, 1384, 1346, 1294, 1282, 1264, 1230, 1190, 1120, 1044, 1018, 946, 780, 758, 704, 554, 542, 486, 470 cm^{-1}. Anal. calculated for $C_{22}H_{23}N_5O_5$ (437.45): C 60.40; H 5.30; N 16.01. Found: C 60.52; H 5.32; N 16.17.

1,1',3',6-Tetramethyl-2,8-diphenyl-4,6-dihydro-2*H*,2'*H*-spiro[pyrido[2,3-*d*]pyridazine-3,5'-pyrimidine]-2',4,4',6'(1*H*,1'*H*,3'*H*)-tetrone (12f). Following the procedure of Method B, the product was obtained as yellow crystals: 57 %, mp 260-262 °C, R_f=0.34 (ethyl acetate: dichloromethane (1:1, v/v)). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.53-7.50 (2H, m, H-2" and H-6"), 7.45-7.28 (6H, m, H-3", H-4", H-5", H-3"', H-4"' and H-5"'), 4.65 (1H, s, H-2), 3.69 (3H, s, N(6)CH_3), 3.09 (2H, s, H-4), 2.99 and 2.97 (6H, s, N(3')CH_3 and N(1')CH_3 pyrimidine), 2.21 (3H, s, N(1)CH_3). ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.5 and 167.5 (C-4'and C-6' pyrimidine), 159 (C-5), 150.3 (C-2' pyrimidine), 145.8 (C-8a), 139.3 (C-8), 137.4 (C-1" phenyl), 135.9 (C-1"' phenyl), 128.7 (C-4"' phenyl), 128.6 (C-3" and C-5" phenyl), 128.4 (C-3"' and C-5"' phenyl) 127.3 (C-2" and C-6" phenyl) 127.0 (C-2"' and C-6"' phenyl), 116.0 (C-4a), 68.8 (C-2), 52.2 (C-3), 42.6 (N(1)CH_3), 38.9 (N(6)CH_3), 28.3 and 28.2 (N(1')CH_3 and N(3')CH_3 pyrimidine), 25.3 (C-4). H" and C" are 8-phenyl and H"' and C"' are 2-phenyl atoms. IR (potassium bromide): ν_{max} 3420, 3060, 3030, 2948, 1748, 1684, 1620, 1544, 1446, 1424, 1402, 1384, 1340, 1282, 1178, 1158, 1138, 1116, 1082, 1064, 1004, 790, 754, 702, 610, 554, 532, 470 cm^{-1}. Anal. calculated for $C_{26}H_{25}N_5O_4$ (471.52): C 66.23; H 5.34; N 14.85. Found: C 66.19; H 5.32; N 14.98.

1,1',3',6-Tetramethyl-1*d*$_3$-8-phenyl-4,6-dihydro-4*d*-2*H*,2'*H*-spiro[pyrido[2,3-*d*]pyridazine-3,5'-pyrimidine]-2,2-*d*$_2$-2',4',5,6'(1*H*,1'*H*,3'*H*)-tetrone (12g). Following the procedure of Method A, then the product was crystallized from ethanol, affording beige crystals: yield 50 %.

Compound **12g** was also prepared in *n*-butanol. Compound **10g** (20 mg) was refluxed in *n*-butanol for 24 h (monitored by TLC). Evaporation of the solvent in *vacuo* gave analytically pure beige crystalline product: 10 mg (50 %), mp 210-212 °C, R_f=0.41 (petroleum ether (bp 40-70 °C): ethyl acetate 1:10). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65-7.35 (5H, m, H_{phenyl}), 3.81 (3H, s, N(6)CH_3), 3.31 (6H, s, N(3')CH_3 and N(1')CH_3 pyrimidine) 3.20 (1H, s, H-4). ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.1 (C-4'and C-6' pyrimidine), 160.1 (C-5), 150.9 (C-2' pyrimidine), 145.0 and 140.5 (C-8 and C-8a), 136.9 (C-1' phenyl), 128.7 (C-4' phenyl), 128.8, 128.1 (C-2', C-3', C-5' and C-6' phenyl), 116.2 (C-4a), 45.9 (C-3), 43.1 and 42.7 (N(1)CD_3), 39.7 (N(6)CH_3), 29.0 (N(1')CH_3 and N(3')CH_3 pyrimidine), 27.9 [t(1:1:1) due to the ^1J(C,D), *C*-4]. IR (potassium bromide): ν_{max} 3650, 3616, 3588, 3566, 3546, 3526,3420, 3058, 2954, 1748, 1676, 1624, 1542, 1510, 1446, 1410, 1376, 1286, 1212, 1110, 1062, 1024, 752, 704, 538, 468 cm^{-1}. Anal. calculated for $C_{20}H_{15}D_6N_5O_4$ (401.45): C 59.84; H+D 5.27; N 17.45. Found: C 59.35; H+D 5.17; N 16.93. MS: $[M+H]^+$: 402. Based on the comparison of spectra of **12g** to those of **12a**, it was confirmed that no deuterium was lost (>98% deuterium).

1',2,3'-Trimethyl-2,7,11b,13-tetrahydro-1*H*,2'*H*,6*H*-spiro[2,3,4b-triazachrysene-12,5'-pyrimidine]-1,2',4',6'(1'*H*,3'*H*)-tetrone (12h). Following the procedure of Method B, the product was obtained as pale yellow crystals: 62 %, mp 260-262 °C, R_f=0.33 (ethyl acetate:

chloroform 9:1). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68 (1H, s, H-4), 7.35-7.16 (3H, m, H-8, H-9 and H-10), 6.96-6.93 (1H, m, H-11), 4.55 (1H, s, H-11b), 4.02-4.00 (1H, m, Ha-6), 3.78 (3H, s, N(2)CH_3), 3.57 (1H, d, Ha-13, *J*=18.9), 3.52-3.41 (1H, m, Hb-6), 3.14 and 3.01 (3H, s, N(3')CH_3 and 3H, s, N(1')CH_3), 2.98 (1H, d, Hb-13, *J*=18.9), 2.87-2.65 (2H, m, H_2-7). ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.1 and 167.7 (C-4' and C-6' pyrimidine), 160.4 (C-1), 150 (C-2' pyrimidine), 144.2 (C-4a), 135.7 and 129.1 (C-7a and C-11a), 129.3, 128.5, 127.7, 127.5 and 126.5 (C-4, C-8, C-9, C-10, C-11), 112.1 (C-13a), 64.9 (C-11b), 53.5 (C-12), 44.5 (C-6), 39.5 (N(2)CH_3), 29.0 and 28.9 (C-7 and C-13), 28.8 and 28.4 (N(3')CH_3 and N(1')CH_3). IR (potassium bromide): ν_{max} 3429, 2927, 2861, 1679, 1630, 1447, 1380, 1047, 944, 856, 751 cm^{-1}. Anal. calculated for $C_{21}H_{21}N_5O_4$x0.2H_2O (411.02): C 61.37; H 5.25; N 17.04. Found: C 61.32; H 5.14; N 17.02.

1,1',3',6-Tetramethyl-4,6-dihydro-2*H*,2'*H*-spiro[pyrido[2,3-*d*]pyridazine-3,5'-pyrimidine]-2',4',5,6'(1*H*,1'*H*,3'*H*)-tetrone (12i). Following the procedure of Method A, the product was crystallized from isopropyl alcohol, affording beige crystals: 40 %, mp 214-215 °C, R_f=0.30 (petroleum ether (bp 40-70 °C): ethyl acetate (1:10, v/v)). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.58 (1H, s, H-8), 3.66 (3H, s, N(6)CH_3), 3.51 (2H, s, H_2-2), 3.25 (6H, s, N(3')CH_3 and N(1')CH_3 pyrimidine) 3.11 (3H, s, N(1)CH_3), 2.99 (2H, s, H_2-4). ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.9 (C-4'and C-6' pyrimidine), 160 (C-5), 150.7 (C-2' pyrimidine), 143.3 (C-8a), 126.3 (C-8), 106.3 (C-4a), 53.5 (C-2), 45.7 (C-3), 39.4 and 38.6 (N(1)CH_3 and N(6)CH_3), 29.6 (C-4), 28.9 (N(1')CH_3 and N(3')CH_3 pyrimidine). IR (potassium bromide): ν_{max} 3434, 2928, 1676, 1622, 1452, 1375, 1075, 750 cm^{-1}. Anal. calculated for $C_{14}H_{17}N_5O_4$ (319.32): C 52.66; H 5.37; N 21.93. Found: C 52.30; H 5.40; N 21.56.

Acknowledgements

This work was supported by grants from the Hungarian Scientific Research Fund (OTKA; T047328) and Ministry of Health (ETT-508/2006).

References and Notes

1. (a) Meth-Cohn, O.; Suschitzky, H. *Adv. Heterocycl. Chem.* **1972**, *14*, 211. (b) Meth-Cohn, O. *Adv. Heterocycl. Chem.* **1996**, *65*, 1.
2. (a) Ojea, V.; Muinelo, I.; Figueroa, M. C.; Ruiz, M.; Quintela, J. M. *Synlett,* **1995**, 622.; for a recent review see (b) Mátyus, P.; Éliás, O.; Tapolcsányi, P.; Bálint-Polonka, Á.; Halász-Dajka, B. *Synthesis,* **2006**, 1.
3. Barbachyn, M. R.; Dobrowolski, P. J.; Hurd, A. R.; McNamara, D. J.; Palmer, J. R.; Romero, A. G.; Ruble, J. C.; Sherry, D. A.; Thomasco, L. M.; Toogood, P. L. Int. Pat. Appl. **2004** WO2004/031195; *Chem. Abstr*. **2004**, *140*, 339202.

4. (a) Mátyus, P.; Varga, I.; Zára, E.; Mezei, A.; Behr, Á.; Simay, A.; Haider, N.; Boros, S.; Bakonyi, A.; Horváth, E.; Horváth, K. *Bioorg. Med. Chem. Lett*. **1997**, *7*, 2857. (b) Andrasi, F.; Angyal, A.; Berzsenyi, P.; Boros, S.; Harsing, L.; Horvath, K.; Matyus, P.; Moravcsik, I.; Papp, A.; Simay, A.; Szabo, E.; Szabo, K.; Tarnawa, I.; Varga, I. Int. Pat. Appl. 2000 WO2000/027851 A1 20000518; *Chem. Abstr*. **2000**, *132*, 334478.
5. (a) Mátyus, P.; Fuji, K.; Tanaka, K. *Heterocycles* **1993**, *36*, 1975.; (b) Dajka-Halász, B.; Monsieurs, K.; Éliás, O.; Károlyházy, L.; Tapolcsányi, P.; Maes, B. U. W.; Riedl, Zs.; Hajós, Gy.; Dommisse, R. A.; Lemiere, G. L. F.; Kosmrlj, J.; Mátyus, P. *Tetrahedron* **2004***, 60*, 2283.
6. Estevez, I.; Ravina, E.; Sotelo, E. *J. Heterocycl. Chem*. **1998**, *35*, 1421.
7. An example for steric buttressing see: Orlek, B. S.; Sammes, P. G.; Weller, D. J. *J. Chem. Soc. Chem. Commun*. **1993**, 1412.
8. (a) Ojea, V.; Peinador, C.; Vilar, J.; Quintela, J. M. *Synthesis*, **1993**, 152. (b) Quintela, J. M. *Recent Res. Dev. Org. Chem.* **2003**, *7*, 259.
9. Sotelo, E.; Ravina, E. *Synth. Commun.* **2002**, *32*, 1675.
10. Farina, F.; Martin, M. V.; Tito, A. *An. Quim., Serie C* **1981**, *77*, 188.