Synthesis of pyridazines and fused pyridazines *via* [3+3] atom combination using Chitosan as a green catalyst

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Abstract

A series of arylhydrazones **1a-c** were prepared and reacted with α,β-unsaturated nitriles **2a-e** to yield 1,4-dihydropyridazines and fused pyridazinoquinazoline. The prepared pyridazines and fused pyridazines are then used as precursors for synthesis of polycondensed pyridazine ring systems.

Keywords: Azaenamine, Chitosan, 1,4-dihydropyridazine, pyridazino[1,6-*a*]quinazoline, pentaazabenzo[*a*]fluoren, pyrimido[4,5-*c*]pyridazin-5-one, pyridazino[1,6-*a*]quinazoline-4-carbonylformimidate

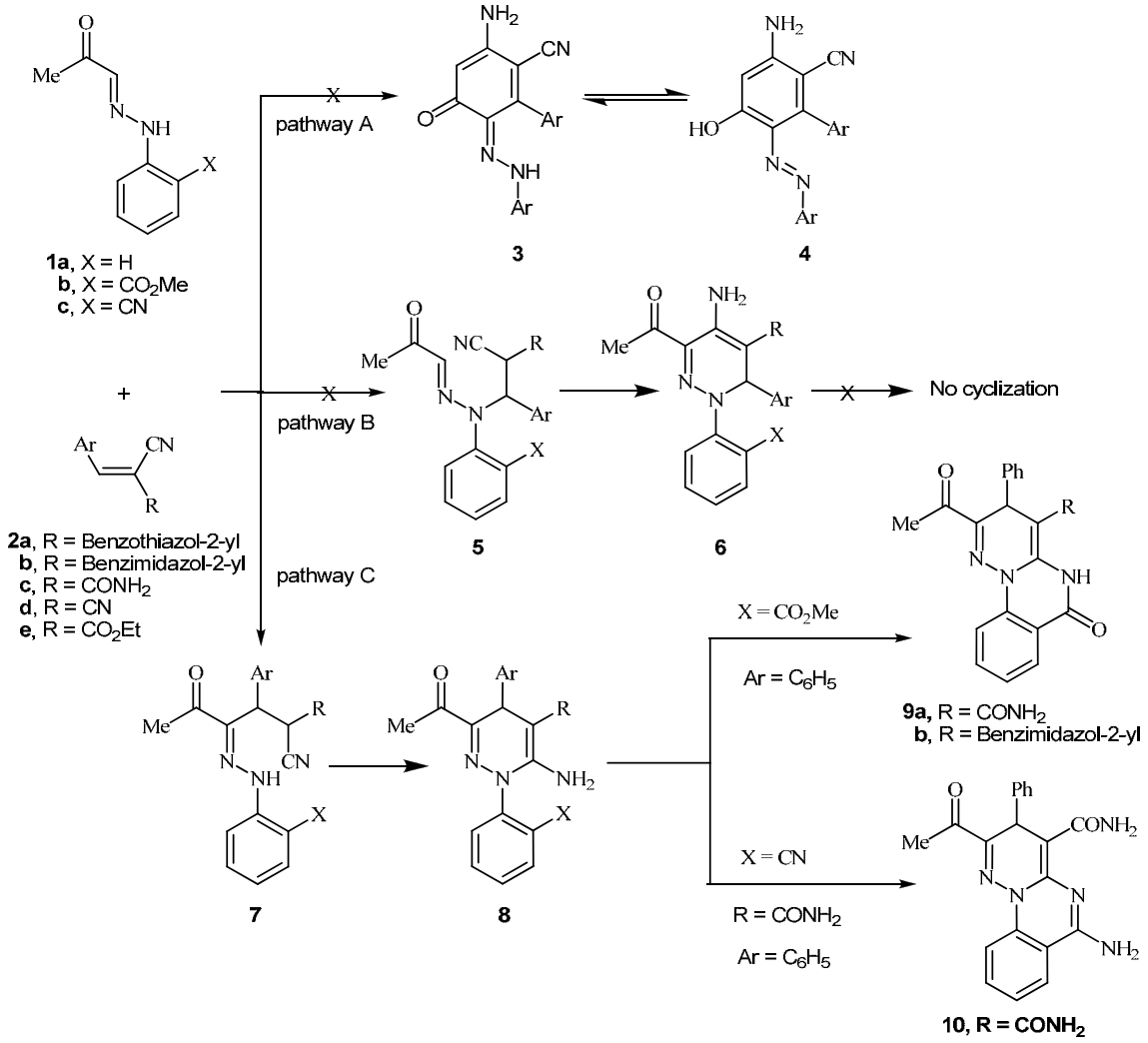
Introduction

Pyridazines and fused pyridazines are an important class of heterocycles of considerable interest, which have been the subject of extensive research, particularly in the pharmaceutical and agrochemical areas, so their synthesis and applications have been comprehensively reviewed.[1-6] 1,4-Dihydropyridazine derivatives including their carboxylic esters can be obtained in the cycloaddition reactions of 1,2,4,5-tetrazines with different dienophiles,[7] by the reaction of aminocarbonylazoalkenes with β-tricarbonyl compounds,[8] *via* the cycloaddition of diazomethane to cyclopropenes,[9] etc. In this article we tried to prepare different derivatives of pyridazines and fused pyridazines utilizing simple routes.

Results and Discussion

In conjunction to our interest in developing syntheses for biologically interesting pyridazines,[10-12] we investigated the Michael addition reaction of pyruvaldehyde-1-arylhydrazones **1a-c** towards α,β-unsaturated nitriles **2a-e**. In previous recent articles[11,12] we investigated the first reported

synthesis of pyridazines from arylhydrazones *via* 3+3 atom combination. In this article we extend our investigation utilizing different substituted cinnamonitriles to prepare pyridazines which can be used as precursors to functionally substituted fused pyridazines. Also in conjunction with our research interest in the utility of green benign approaches in organic synthesis [13-16] we used the green heterogeneous basic catalyst *chitosan* (which is amino polysaccharide) as a substituent to *piperidine* and *pyridine* catalysts and we compared the % yield in both cases. Thus it has been found that reacting pyruvaldehyde-1-arylhydrazones **1** with substituted cinnamonitriles **2a-e** affords products for which several isomeric structures seemed possible. Structure **3** or its tautomeric form **4** involving addition of acyl methyl (pathway A) was readily eliminated as ^{1}H NMR revealed methyl signal. Now the reaction product is either 4-aminopyridazine **6** that results from initial addition of NH to the activated double bond in **2** (pathway B) or 6-aminopyridazine **8** that results from initial addition of hydrazone CH to activated double bond in **2** to yield **7** that readily cyclizes into **8** (pathway C).



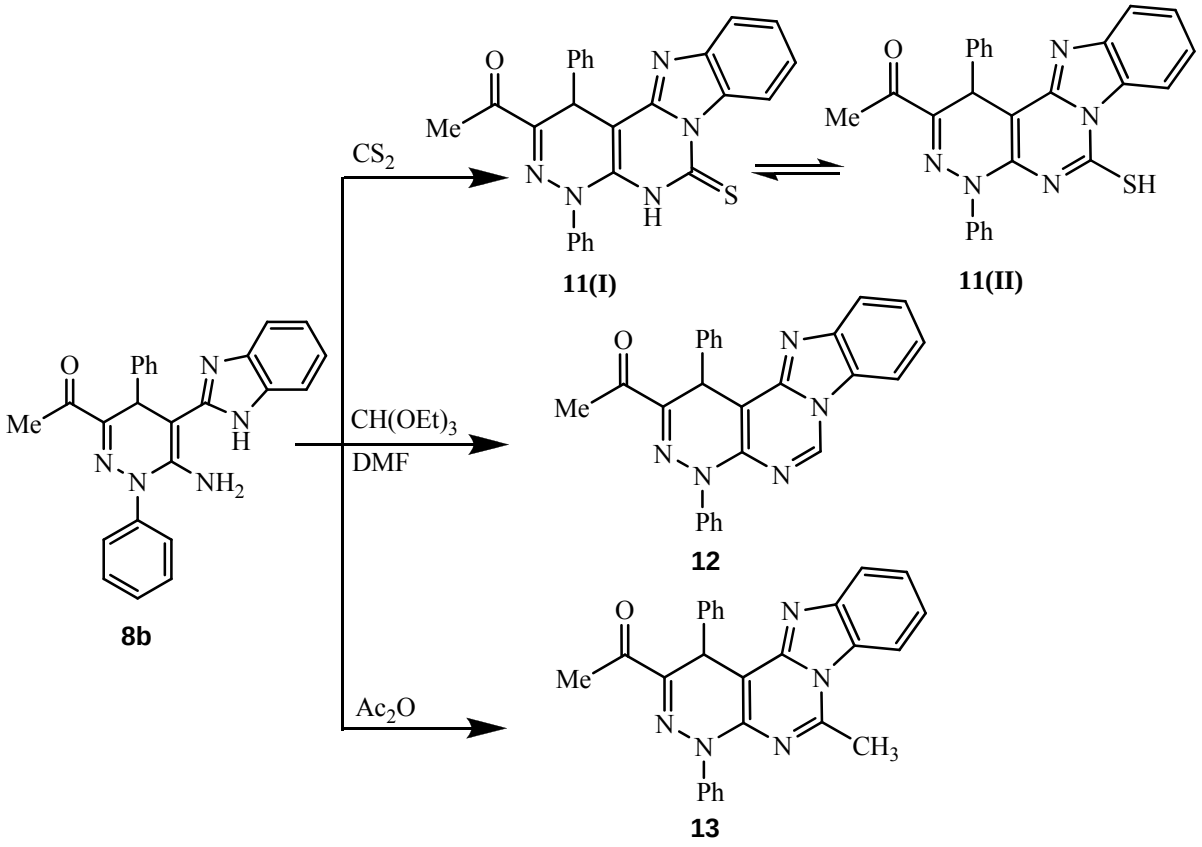
Scheme 1. Synthesis of pyridazines and fused pyridazino[1,6-a]quinazolines.

The de*cis*ive difference between the alternative structures **6** and **8** in the HMBC measurement is due to the fact that in case of compound **8b** the pyridazine hydrogen-H4 at δ = 5.63 ppm shows a cross peak which indicates a ^{3}J coupling to CO at δ = 196.2 ppm. In order to provide chemical evidence for the proposed structure we investigated the Michael addition reaction on pyruvaldehyde-1-arylhydrazones **1b,c** with functional substituents on ortho position, where only further cyclization occurred in case of 6-aminopyridazines, while in case of 4-aminopyridazines no further cyclization occurred. Thus the reaction of **1b** with **2b,c** results in the formation of product of cyclization with methanol elimination to give compounds **9a,b**. In a similar manner, the reaction of compound **1c** with **2c** has resulted in formation of compound **10**. Structure **10** was readily established based on IR that revealed the absence of CN signals.

Table 1. Comparison of % yield of products obtained from piperidine, chitosan and microwave irradiation (MWI)

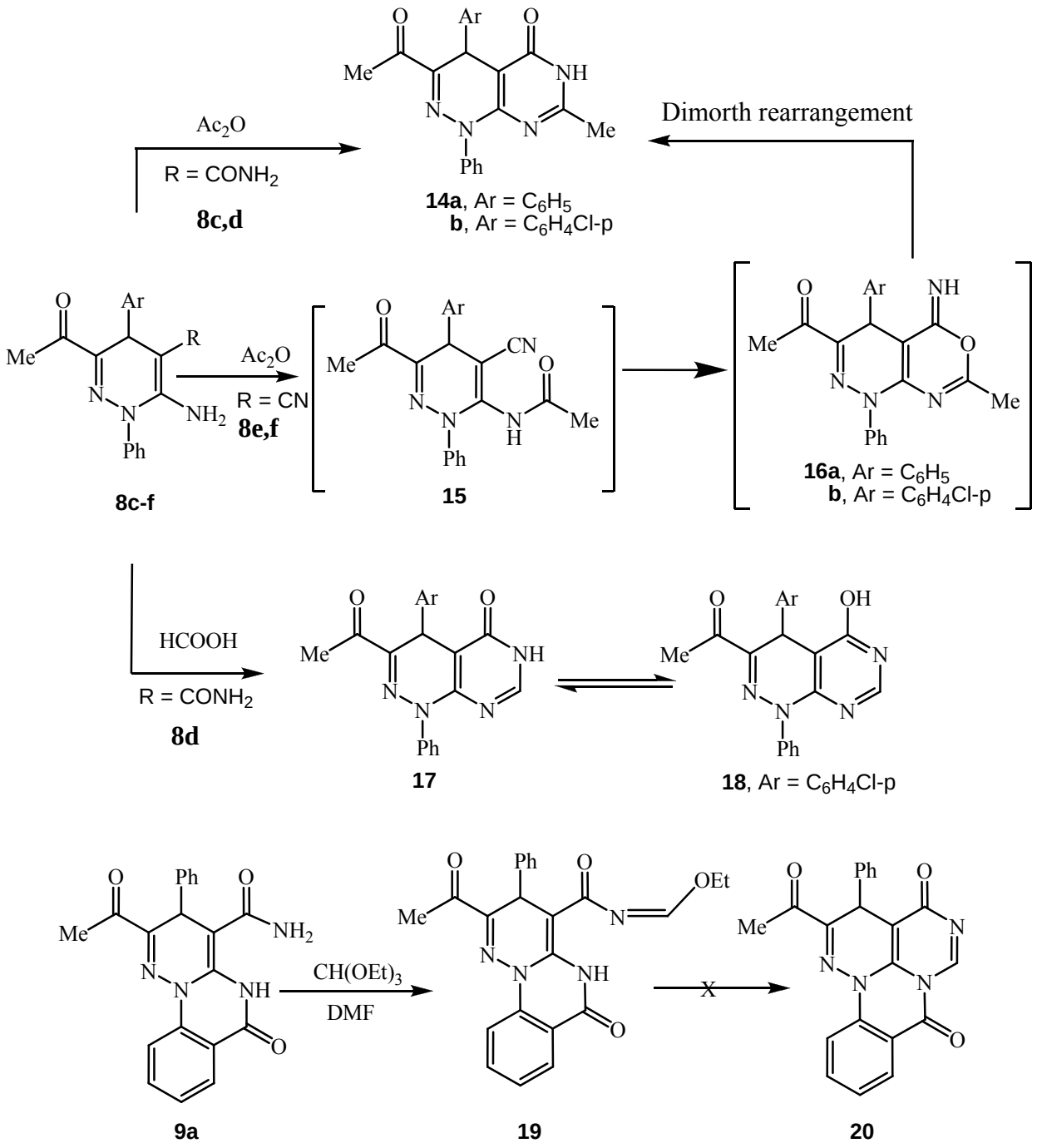
Entry	X	R	Ar	% Yield		
				Piperidine or pyridine	MWI	Chitosan
8a	H	Benzothiazol-2-yl	C_6H_5-	84	86	90
8b	H	Benzimidazol-2-yl	C_6H_5-	85	86	92
8c	H	$CONH_2$	C_6H_5-	87	89	93
8d	H	$CONH_2$	C_6H_4Cl(p)	85	86	90
8e	H	CN	C_6H_5-	85	89	90
8f	H	CN	C_6H_4Cl(p)	75	78	80
8g	H	CO_2Et	C_6H_5-	83	85	89
9a	-	$CONH_2$	C_6H_5-	85	88	88
9b	-	Benzimidazol-2-yl	C_6H_5-	80	86	86
10	-	$CONH_2$	C_6H_5-	82	85	87

In conjunction with the interest in the chemistry and biological activity of polycondensed pyridazines,[17] we reacted pyridazine **8b** with carbon disulphide, triethylorthoformate and acetic anhydride to give the polycondensed benzimidazo[1,2-*c*]pyrimido[4,5-*c*]pyridazine derivative **11**, **12** and **13**, respectively. ^{1}H NMR spectra of **11** showed two signals for NH and SH, so there may be an equilibrium between compound **11** and its tautomeric form **11(I)**.



Scheme 2. Synthesis of benzimidazo[1,2-c]pyrimido[4,5-c]pyridazine derivatives.

Pyridazines **8c-f** can be also used for synthesis of condensed pyrimido[4,5-*c*]pyridazine derivatives, thus, boiling compound **8c** or **d** in acetic anhydride for long period results in the formation of **14a** and **b**, respectively. The same products were obtained upon heating **8e** or **f** in acetic anhydride, whereas the initially formed pyridazino[3,4-*d*][1,3]oxazin-5-imine **16a** and **b** undergo Dimroth type rearrangement to give **14a** and **b**. Heating pyridazine **8d** in formic acid gives compound **17** that may tautomerise into compound **18**. On the other hand, pyridazino[1,6-*a*]quinazoline-4-carbonyl-formimidate **19** was obtained with better yields by reacting 1,4-dihydropyridazino[1,6-*a*]quinazoline **9a** with triethylorthoformate. Trials to cyclise compound **19** into **20** failed.



Scheme 3. Synthesis of pyrimido[4,5-c]pyridazines and pyridazino[1,6-a]quinazoline-4-carbonylformimidate.

Conclusions

It is now obvious that hydrazone CH in **1** is highly reactive towards electrophiles and thus can undergo Michael addition to a variety of α-substituted cinnamonitriles under mild conditions yielding 1,4-dihydropyridazine and pyridazino[1,6-*a*]quinazoline derivatives. Utility of the prepared pyridazines in further chemical transformations was also achieved.

Experimental Section

General Procedures. The melting points were determined on a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded as KBr pellets using a FTIR unit Bruker-vector 22 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 as solvent at 300 MHz and 75 MHz, respectively on Varian Gemini NMR spectrometer using TMS as internal standard. Chemical shifts are reported in δ units (ppm). Mass spectra were measured on a Shimadzu GMMS -QP-1000 EX mass spectrometer at 70 eV. The elemental analyses were performed at the Micro analytical Center, Cairo University.

General procedures for compounds 8a-g, 9a-b and 10

Method A. A mixture of azaenamine **1**(**a**, **b** or **c**) (10 mmol), and benzylidene derivatives **2a-e** was refluxed in ethanol (20 ml) in presence of *piperidine* (0.5 ml) for 3 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from ethanol or ethanol/dioxan.

Method B. A solution of each of **1**(**a**, **b** or **c**) (10 mmol) and the benzylidene derivatives **2a-e** (10 mmol) in pyridine (2 ml) was irradiated in *microwave oven* for two minutes, then poured onto water and acidified with dilute hydrochloric acid. The solid product obtained was crystallized from ethanol or ethanol/dioxan**.**

Method C. A mixture of azaenamine **1**(**a**, **b** or **c**) (10 mmol), and benzylidene derivatives **2a-e** was refluxed in ethanol or dioxan (20 ml) in presence of *chitosan* (0.2 g) for 3 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from ethanol or ethanol/dioxan. The catalyst, *chitosan* is removed by filtration prior or during the crystallization process.

1-(6-Amino-5-(benzothiazol-2-yl)-1,4-diphenyl-1,4-dihydropyridazin-3-yl)-ethanone (8a). Yield: (84% piperidine, 86% MWI, 90% chitosan), Mp:148-150 ^{o}C; IR (KBr): ν 3473 and 3390 (NH_2), 1678 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d6): δ = 2.35 (s, 3H, C*H*$_3$CO), 5.21 (s, 1H, pyridazine- *H4*), 7.17 – 7.89 (m, 16H, Ar *H* and N*H*$_2$); MS (EI): m/z (%) = 424 (M^+, 24.3), 381 (15.5). Anal. Calcd. for $C_{25}H_{20}N_4OS$ (424.53): C, 70.73; H, 4.75; N, 13.20; S, 7.55. Found: C, 70.62; H, 4.72; N, 13.11; S, 7.45.

1-[6-Amino-5-(*1H*-benzoimidazol-2-yl)-1,4-diphenyl-1,4-dihydropyridazin-3-yl]-ethanone (8b). Yield: (85% piperidine, 86% MWI, 92% chitosan), Mp:238-240 ^{o}C; IR (KBr): ν 3386,

3279 , 3155 (NH and NH_2), 1674 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): δ = 2.40 (s, 3H, C*H*$_3$CO), 5.63 (s, 1H, pyridazine-*H4*), 7.03 – 7.63 (m, 16H, Ar *H* and N*H*$_2$), 12.04 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d6): δ = 24.6, 33.6, 66.3, 75.3, 110.1, 116.2, 120.6, 120.9, 125.0, 126.73, 127.1, 127.2, 128.5, 129.3, 133.3 140.5, 143.2, 143.9, 145.1, 153.3, 196.2; MS (EI): m/z (%) = 407 (M^+, 60), 364 (15.3). Anal. Calcd. for $C_{25}H_{21}N_5O$ (407.48): C, 73.69; H, 5.19; N, 17.19. Found: C, 73.6; H, 5.08; N, 17.11.

3-Acetyl-6-amino-1,4-diphenyl-1,4-dihydropyridazine-5-carboxamide (8c). Yield: (87% piperidine, 89% MWI, 93% chitosan), Mp:244-246 ^oC; IR (KBr): ν 3434, 3341 and 3182 (NH and NH_2), 1659 (CH_3CO), 1584 ($CONH_2$) cm^{-1}; MS (EI): m/z (%) = 333 (M-1, 60), 291 (18.5). Anal. Calcd. for $C_{19}H_{18}N_4O_2$ (334.37): C, 68.25; H, 5.43; N, 16.76. Found: C, 68.09; H, 5.31; N, 16.98.

3-Acetyl-6-amino-4-(4-chlorophenyl)-1-phenyl-1,4-dihydropyridazine-5-carboxamide (8d). Yield: (85% piperidine, 86% MWI, 90% chitosan), Mp:242-244 ^oC; IR (KBr): ν 3468, 3437, 3356 and 3182 ($CONH_2$ and NH_2), 1659 (CO), 1581 ($CONH_2$) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): δ = 2.32 (s, 3H, C*H*$_3$CO), 5.22 (s, 1H, pyridazine-*H4*), 6.66 (s, 2H, N*H*$_2$), 7.17 (br s, 2H, N*H*$_2$) 7.29 – 7.53 (m, 9H, Ar *H*; MS (EI): m/z (%) = 368 (M^+), 325 (29.1). Anal. Calcd. for $C_{19}H_{17}ClN_4O_2$ (368.83): C, 61.87; H, 4.65; Cl, 9.61; N, 15.19. Found: C, 61.79; H, 4.59; Cl, 9.52; N, 15.11.

3-Acetyl-6-amino-1,4-diphenyl-1,4-dihydropyridazine-5-carbonitrile (8e).[11] Yield: (85% piperidine, 89% MWI, 90% chitosan), mp: 228-230 °C (lit. m.p. 228-230[11]). IR (KBr, cm^{-1}): 3409 and 3313 (NH_2), 2191 (CN), 1678 (CO); ^1H NMR (300 MHz, DMSO-d6): δ, ppm: 2.33 (s, 3H, CH_3-CO), 4.79 (s, 1H, CH pyridazine), 6.01 (s, 2H, NH_2), 7.21 – 7.52 (m, 10H, Ph-H); ^{13}C NMR (75 MHz, DMSO-d6): δ, ppm 24.68, 36.11, 57.05, 120.52, 125.73, 126.83, 127.29, 127.91, 128.99, 129.54, 140.16, 142.11, 143.99, 150.30, 195.79; MS (EI): *m/z* (%) = 316 (M^+). *Anal*. Calcd. for $C_{19}H_{16}N_4O$ (316.37): C, 72.14; H, 5.10; N, 17.71. Found: C, 72.20; H, 5.31; N, 17.65.

3-Acetyl-6-amino-4-(4-chlorophenyl)-1-phenyl-1,4-dihydro-pyridazine-5-carbonitrile (8f). Yield: (75% piperidine, 78% MWI, 80% chitosan), mp: 198-200 °C. MS (EI): *m/z* (%) = 350 (M^+). *Anal*. Calcd. for $C_{19}H_{15}ClN_4O$ (350.80): C, 65.05; H, 4.31; Cl, 10.11; N, 15.97. Found: C, 65.21; H, 4.18; Cl, 10.15; N, 15.63.

Ethyl 3-Acetyl-6-amino-1,4-diphenyl-1,4-dihydropyridazine-5-carboxylate (8g).[11] Yield: (83% piperidine, 85% MWI, 89% chitosan), m.p = 126-128 °C. IR (KBr, cm^{-1}): 3417.6 and 3301.9 (NH_2), 1658.7 (CH_3CO), 1616.2 (COOEt); ^1H NMR (300 MHz, DMSO-d6): δ, ppm: 1.17 (t, 3H, CH_3-CH_2, *J* = 7.2 Hz), 2.33 (s, 3H, CH_3-CO), 4.08 (q, 2H, CH_2, *J* = 7.2 Hz), 5.2 (s, 1H, pyridazine-H), 6.88 (s, 2H, NH_2), 7.17-7.56 (m, 10H, Ph-H); ^{13}C NMR (75 MHz, DMSO-d6): δ, ppm 14.47, 24.66, 33.91, 58.89, 75.92, 125.69, 126.67, 127.09, 127.87, 128.59, 129.64, 140.06, 143.22, 147, 151.04, 168.11, 196.03; MS (EI): *m/z* (%) = 364 (M^+). *Anal*. Calcd. for $C_{21}H_{21}N_3O_3$ (363.42): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.22; H, 5.91; N, 11.35.

2-Acetyl-6-oxo-3-phenyl-5,6-dihydro-*3H*-pyridazino[1,6-*a*]quinazoline-4-carboxamide (9a). Yield: (85% piperidine, 88% MWI, 88% chitosan), Mp: 262-264 ^oC; IR (KBr): ν 3466, 3337 and 3185 (NH and NH_2), 1696 (CH_3CO), 1612 ($CONH_2$), 1574 (CONH) cm^{-1}; ^1H NMR (300 MHz,

DMSO-d6): δ = 2.33 (s, 3H, C*H*$_3$CO), 5.4 (s, 1H, pyridazine- *H*)), 7.16 – 8.01 (m, 12H, Ar *H*, NH_2 and NH); MS (EI): m/z (%) = 360 (M^+, 3.7), 318 (9.9). Anal. Calcd. for $C_{20}H_{16}N_4O_3$ (360.38): C, 66.66; H, 4.48; N, 15.55. Found: C, 66.57; H, 4.39; N, 15.52.

2-Acetyl-4-(1*H*-benzo[d]imidazol-2-yl)-3-phenyl-*3H*-pyridazino[1,6-*a*]quinazolin-6(*5H*)-one (9b). Yield: (80% piperidine, 86% MWI, 86% chitosan), Mp:206-208 ^oC; IR (KBr): ν 3337 and 3259 (NH and CONH), 1636 (CH_3CO), 1601 (CONH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): δ = 2.33 (s, 3H, C*H*$_3$CO), 5.42 (s, 1H, pyridazine- *H4*), 7.25 – 8.36 (m, 14H, Ar *H* and indole NH), 11.4 (br s, 1H, NH); MS (EI): m/z (%) = 433 (M^+, 63.9), 390 (67.8). Anal. Calcd. for $C_{26}H_{19}N_5O_2$ (433.47): C, 72.04; H, 4.42; N, 16.16. Found: C, 71.98; H, 4.39; N, 16.08.

2-Acetyl-6-amino-3-phenyl-*3H*-pyridazino[1,6-*a*]quinazoline-4-carboxamide (10). Yield: (82% piperidine, 85% MWI, 87% chitosan), Mp:280-282 ^oC; IR (KBr): ν 3441, 3350, 3301 and 3245 ($2NH_2$), 1660 (CH_3CO), 1595 ($CONH_2$) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): δ = 2.48 (s, 3H, C*H*$_3$CO), 5.57 (s, 1H, pyridazine- *H*), 6.86 (s, 2H, N*H*$_2$), 7.06 – 8.07 (m, 9H, Ar *H*), 9.03 (s, 2H, NH_2); MS (EI): m/z (%) = 316 (M^+). Anal. Calcd. for $C_{20}H_{17}N_5O_2$ (359.39): C, 66.84; H, 4.77; N, 19.49. Found: C, 66.75; H, 4.69; N, 19.42.

1-(1,4-Diphenyl-6-thioxo-1,4,5,6-tetrahydro-3,4,5,6a,11-pentaaza-benzo[*a*]fluoren-2-yl)-ethanone (11). A mixture of pyridazine **8b** (10 mmol), and carbon disulphide (10 mmol) was stirred in DMF in the presence of NaOH for 5 h and then left overnight. The reaction mixture was then poured onto water and acidified with dilute hydrochloric acid. The solid product obtained was crystallized from ethanol / Dioxan (5:1). Yield: (82%), Mp:238-240 ^oC; IR (KBr): ν 3421 (NH), 1685 (C*H*$_3$CO), 1639 (C=S) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): δ = 2.39 (s, 3H, C*H*$_3$CO), 5.84 (s, 1H, pyridazine- *H4*), 7.19 – 7.69 (m, 14H, Ar *H*), 9.8 (s, 1H, NH), 13.9 (s, 1H, SH); MS (EI): m/z (%) = 449 (M^+, 84), 406 (34.4). Anal. Calcd. for $C_{26}H_{19}N_5OS$ (449.54): C, 69.47; H, 4.26; N, 15.58; S, 7.13. Found: C, 69.41; H, 4.19; N, 15.51; S, 7.08.

1-(1,4-Diphenyl-1,4-dihydro-3,4,5,6a,11-pentaaza-benzo[*a*]fluoren-2-yl)-ethanone (12). A mixture of Pyridazine **8b** (10 mmol), and triethylorthoformate (20 mmol) was refluxed in DMF (20 ml) for 5 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from ethanol / Dioxan (5:1). Yield: (80%), Mp:262-264 ^oC; IR (KBr): ν 1678 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): δ = 2.45 (s, 3H, C*H*$_3$CO), 6.0 (s, 1H, pyridazine-*H4*), 7.18 – 8.32 (m, 14H, Ar *H*), 9.75 (s, 1H, pyrimidine-H); MS (EI): m/z (%) = 417 (M^+, 87.1), 374 (65.1). Anal. Calcd. for $C_{26}H_{19}N_5O$ (417.47): C, 74.8; H, 4.59; N, 16.78. Found: C, 74.72; H, 4.51; N, 16.73.

1-(6-Methyl-1,4-diphenyl-1,4-dihydro-3,4,5,6a,11-pentaaza-benzo[*a*]fluoren-2-yl)-ethanone (13). Pyridazine **8b** (10 mmol) was refluxed in acetic anhydride (20 ml) for 5 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from ethanol / Dioxan (5:1). Yield: (84%), Mp:244-246 ^oC; IR (KBr): ν 1674 (CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): δ = 2.45 (s, 3H, C*H*$_3$CO), 2.94 (s, 3H, CH_3) 5.94 (s, 1H, pyridazine- *H*), 7.17-8.08 (m, 14H, Ar *H*); ^{13}C NMR (75 MHz, DMSO-d6): δ = 23.5, 24.8, 36.6, 66.3, 96.4, 115.2, 118.7, 121.6, 124.9, 126.1, 126.6, 127.2, 127.6, 128.6, 128.7, 141.2, 141.5, 141.8, 142.6, 145.4, 148.0,

150.6, 195.7; MS (EI): m/z (%) = 431 (M^+, 100), 388 (68.4). Anal. Calcd. for $C_{27}H_{21}N_5O$ (431.5): C, 75.16; H, 4.91; N, 16.23. Found: C, 75.09; H, 4.85; N, 16.19.

General method for synthesis of compounds 14a,b

Method A. Pyridazine **8c** or **d** (10 mmol) was refluxed in acetic anhydride (20 ml) for 5 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from ethanol / Dioxan (5:1).

Method B. Pyridazine **8e** or **f** (10 mmol) was refluxed in acetic anhydride (20 ml) for 5 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from ethanol / Dioxan (5:1).

3-Acetyl-7-methyl-1,4-diphenyl-4,6-dihydro-*1H*-pyrimido[4,5-*c*]pyridazin-5-one (14a). Yield: (84%), Mp:270-272 ^oC; IR (KBr): ν 3429 (NH), 1685 (CH_3CO), 1647 (CONH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): δ = 2.14 (s, 3H, C*H*$_3$CO), 2.24 (s, 3H, C*H*$_3$), 5.35 (s, 1H, pyridazine- *H4*), 7.16 – 7.58 (m, 10H, Ar *H*), 12.44 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d6): δ = 21.2, 24.7, 32.8, 97.6, 120.6, 125.2, 126.5, 126.9, 127.3, 128.4, 128.6, 141.6, 143.5, 151.1, 157.7, 161.3, 195.6; MS (EI): m/z (%) = 358 (M^+, 57.1), 315 (51.8). Anal. Calcd. for $C_{21}H_{18}N_4O_2$ (358.4): C, 70.38; H, 5.06; N, 15.63. Found: C, 70.29; H, 4.98; N, 15.55.

3-Acetyl-4-(4-chlorophenyl)-7-methyl-1-phenyl-4,6-dihydro-*1H*-pyrimido[4,5-*c*]pyridazin-5-one (14b). Yield: (85%), Mp:300-302 ^oC; IR (KBr): ν 3386 (NH), 1681 (C*H*$_3$CO), 1643 (CONH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): δ = 2.14 (s, 3H, C*H*$_3$-CO), 2.36 (s, 3H, C*H*$_3$), 5.32 (s, 1H, pyridazine- *H4*), 7.21 – 7.58 (m, 9H, Ar *H*), 12.44 (br s, 1H, NH); MS (EI): m/z (%) = 392 (M^+, 50.6), 349 (35.9). Anal. Calcd. for $C_{21}H_{17}ClN_4O_2$ (392.85): C, 64.21; H, 4.36; Cl, 9.02; N, 14.26. Found: C, 64.15; H, 4.29; Cl, 8.95; N, 14.21.

1-(4-(4-Chlorophenyl)-5-hydroxy-1-phenyl-1,4-dihydropyrimido[4,5-*c*]pyridazin-3-yl) ethanone (18). Pyridazine **8d** (10 mmol) was refluxed in formic acid (20 ml) for 5 h. The solvent was evaporated under vacuum. The reaction mixture was then poured onto water and neutralized with a solution of sodium bicarbonate, the solid product obtained was crystallized from ethanol. Yield: (83%), Mp:198-200 ^oC; IR (KBr): ν 3383 (OH), 1664 (CH_3CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): δ = 2.41 (s, 3H, C*H*$_3$CO), 3.75 (s, 1H, O*H*), 4.82 (s, 1H, pyridazine- *H4*), 7.26 – 7.51 (m, 9H, Ar *H*), 7.84 (s, 1H, pyrimidine-*H*); MS (EI): m/z (%) = 378 (M^+). Anal. Calcd. for $C_{20}H_{15}ClN_4O_2$ (378.81): C, 63.41; H, 3.99; N, 14.79; Cl, 9.36. Found: C, 63.37; H, 3.89; N, 14.71; Cl, 9.28.

Ethyl *N*-2-acetyl-3-(4-chlorophenyl)-6-oxo-5,6-dihydro-*3H*-pyridazino[1,6-*a*]quinazoline-4-carbonylformimidate (19). A mixture of pyridazino[1,6-*a*]quinazoline **9a** (10 mmol), and triethylorthoformate (20 mmol) was refluxed in DMF (20 ml) for 5 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from Dioxan. Yield: (78%), Mp:152-154 ^oC; IR (KBr): ν 3343 (NH), 1683, 1638, 1589 (3CO) cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): δ = 1.42 (t, 3H, C*H*$_3$, *J*=7.2Hz), 2.49 (s, 3H, C*H*$_3$CO), 4.53 (q, 2H, C*H*$_2$, *J*=7.2Hz), 6.94 (s, 1H, pyridazine-*H4*), 7.54 – 7.88 (m, 9H, Ar *H*), 8.15 (s, 1H, N=C*H*), 11.35 (s, 1H, N*H*); MS (EI): m/z (%) = 416 (M^+), 370 (20.8). Anal. Calcd. for $C_{23}H_{20}N_4O_4$ (416.43): C, 66.34; H, 4.84; N, 13.45. Found: C, 66.27; H, 4.77; N, 13.52.

References

1. Haider, N.; Holzer, W. *Sci. Synthesis* **2004**, *16*, 125.
2. Woo, G. H. C.; Snyder, J. K.; Wan, Z.-K. *Prog. Heterocycl. Chem.* **2002**, *14*, 279.
3. Cignarella, G.; Barlocco, D. *J. Heterocycl. Chem.* **2002**, *39*, 545.
4. Kolar, P.; Tisler, M. *Adv. Heterocycl. Chem.* **1999**, *75*, 167.
5. Màtyus, P.; Maes, B. U. W.; Riedl, Z.; Hajòs, G.; Lemiēre, G. L. F.; Tapolcsànyi, P.; Monsieurs, K.; Ēliàs, O.; Dommisse, R. A.; Krajsovszky, G. *Synlett* **2004**, 1123.
6. Gelain, A. *J. Heterocycl. Chem.* **2005**, *42*, 395.
7. Balci, M.; Saracoglu, N.; Menzek, A. *J. Org. Chem.* **2003**, *68*, 7009.
8. Attanasi, O. A.; Filippone, P.; Fiorucci, C.; Foresti, E.; Mantellini, F. *J. Org. Chem.* **1998**, *63*, 9880.
9. Razin, V. V.; Yakovlev, M. E.; Shataev, K. V.; Selivanov, S. I. Russ. *J. Org. Chem.* **2004**, *40*, 1027.
10. Abdelhamid, I. A.; Ghozlan, S. A. S.; Kolshorn, H.; Meier, H.; Elnagdi, M. H. *Heterocycles* **2007**, *71*, 2627.
11. Ghozlan, S. A. S.; Abdelhamid, I. A.; Hassaneen H. M.; Elnagdi, M. H. *J. Hetrocycl. Chem.* **2007**, *44*, 105.
12. Ghozlan, S. A. S.; Abdelhamid, I. A.; Elnagdi, M. H. *Arkivoc* **2006**, (*xiii*), 147.
13. Al-Awadi, N.; Abdelhamid, I. A.; Al-Etaibi, A.; Elnagdi, M. H. *Synlett* **2007**, 2205.
14. Al-Awadi, N. A.; Abdelkhalik, M. M.; Abdelhamid, I. A.; Elnagdi, M. H. *Synlett* **2007**, 2979.
15. Al-Awadi, N. A.; Ibrahim, M. I.; Abdelhamid, I. A.; Elnagdi, M. H. *Tetrahedron* **2008**, *64*, 8202.
16. Abdelhamid, I. A. *Synlett* **2009**, 625.
17. Gulevskaya, A. V.; Serduke, O. V.; Pozharskii, A. F.; Besedin, D. V. *Tetrahedron* **2003**, *59*, 7669.

