Bioorganic & Medicinal Chemistry 17 (2009) 2823–2829

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

New pyridazine derivatives: Synthesis, chemistry and biological activity

Roxana M. Butnariu, Ionel I. Mangalagiu *

'Al. I. Cuza' University of Iasi, Organic and Biochemistry Department, Bd. Carol 11, 700506 Iasi, Romania

ARTICLE INFO

Article history:
Received 19 January 2009
Revised 11 February 2009
Accepted 15 February 2009
Available online 21 February 2009

Keywords:
Pyridazine
Cycloadditions
Microwaves
Biological activities

ABSTRACT

In this paper we report a feasible study concerning synthesis, structure and biological activity of some new pyridazine derivatives. Syntheses have been done both under classical conditions and microwave [in liquid phase and interphasic transfer catalysis (PTC)]. The MW induced a remarkable acceleration for the [3+2] dipolar cycloaddition reaction of pyridazinium ylides to activated alkenes and alkynes, the yields were increased in some cases, and the amount of used solvents decrees in liquid phase (while PTC do not use solvents). Consequently, these types of reactions could be considered environmentally friendly. The in vitro antibacterial and antifungal activities of the newly obtained diazine compounds were tested, some of the compounds have proved to have a remarkable activity against *Gram positive* germs, the results on *Sarcinia luteea* being spectacular.

1. Introduction

Pyridazine derivatives have been reported[1] to posses a wide range of biological activities, these include antiviral and anticancer,[2] antituberculosis,[3] antihypertensive[4] and antimicrobial[5] activity. One of the strategies adopted for the synthesis of the pyridazine derivatives involves nitrogen ylides, as reactive species in organic chemistry.[6–8] The reaction pathway involves, in the most frequent cases, a Huisgen [3+2] dipolar cycloaddition of ylides to dipolarophiles (activated alkenes and alkynes). During the last decades microwave irradiation (MW) has became an increasingly valuable tool in organic chemistry, since it offers a versatile and facile pathway in a large variety of syntheses.[9] Furthermore, PTC reactions under MW conditions have the great advantage of using small amounts of or no organic solvents ('solvent free'), thus such reactions are more environmentally friendly and generate less side products.[9,10] So far, few studies have been reported regarding dipolar cycloaddition reactions of pyridazinium ylides and most of these have been conducted by our group.[5a,10]

The aim of this work was to perform a thorough study concerning synthesis, structure and biological activity of some new pyridazine derivatives and to establish correlation MW/classical heating (both in liquid phase and PTC conditions).

2. Results and discussion

Pyridazinium ylides (**3**) [generated in situ from the corresponding cycloimmonium salts (**2**), in alkaline medium (Et_3N)], react with symmetrically substituted *Z*-alkene via a 3+2 dipolar cycloaddition leading to fused pyridazine. When dipolarophiles are *N*-phenylmaleimide (NPMI, symmetrical cyclic *Z*-alkenes) and maleic and fumaric esters (symmetrically *cis–trans* olefins), cycloadducts (**4–6**) are obtained (Scheme 1). The Huisgen 3+2 cycloaddition occurs with high stereospecificity and no formation of other isomers was observed.

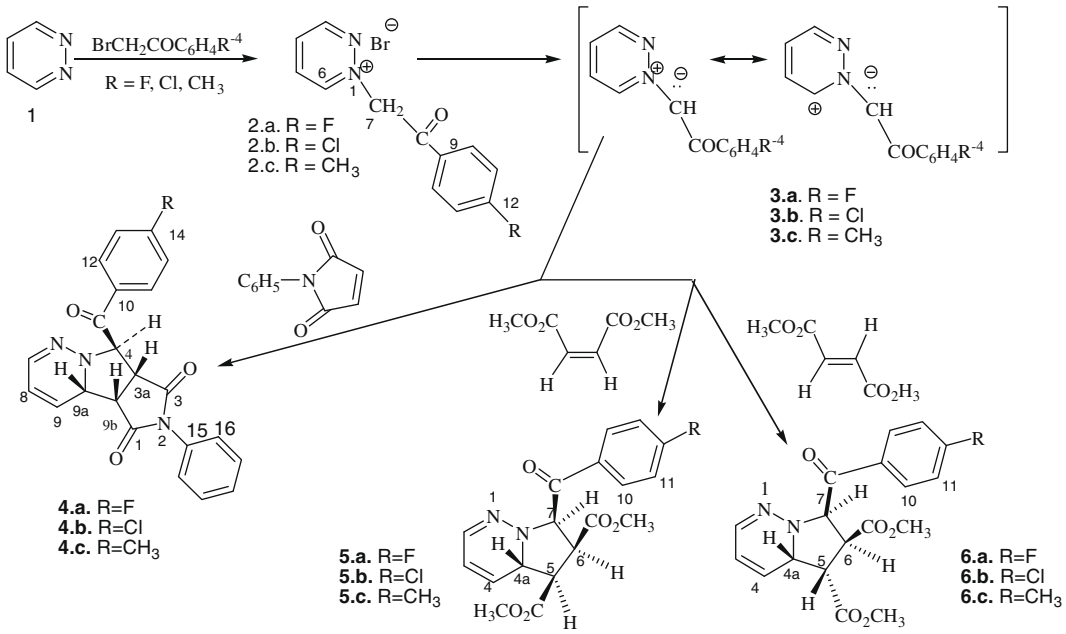
The reaction of ylides (**3**) with non-symmetrical dipolarophiles such as acrylonitrile and methyl acrylate (activated alkenes) and ethyl propiolate (activated alkynes) lead to a single isomer (regiospecific reactions), the saturated tetrahydropyrrolo pyridazine adducts (**7–8**) or the aromatized pyrrolopyridazine adducts (**9**). The reaction of ylides (**3**) with dimethyl acetylendicarboxylate (DMAD, symmetrical activated alkynes), lead to aromatized pyrrolopyridazine, (**10**). As to the mechanism, the formation of compounds (**9**) and (**10**), could be explained by oxidative dehydrogenation of saturated intermediaries (**i**) and (**ii**), which allow formation to the more stable aromatized cycloadducts (Scheme 2).

The structure of the new compounds (**4–10**) has been proved by elemental and spectral analysis (IR, MS, ^{1}H NMR, ^{13}C NMR, 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC).

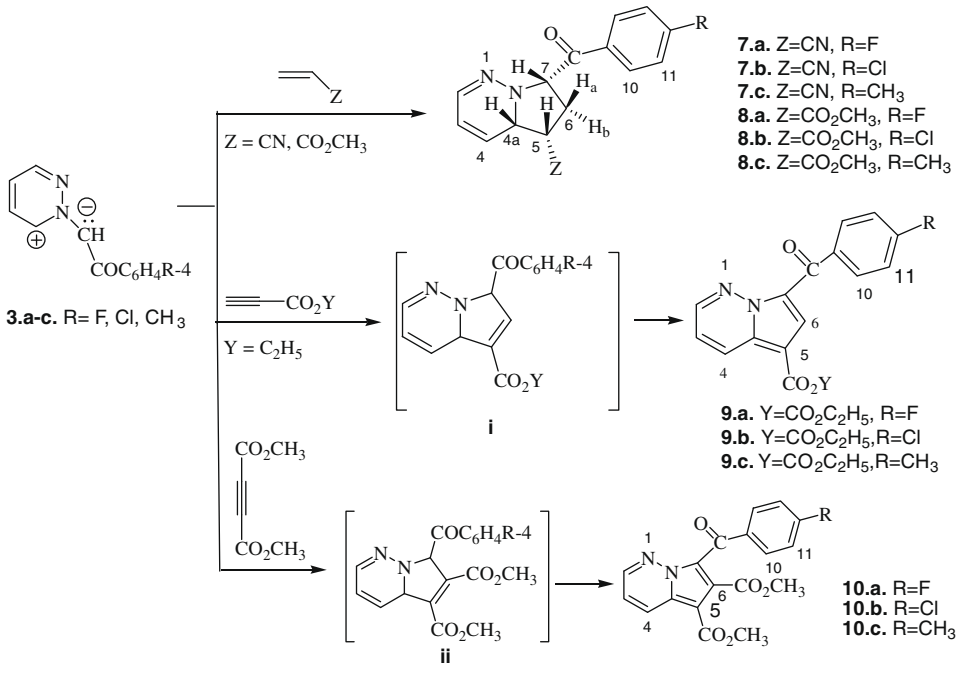
Influence of MW irradiation (both in liquid phase and PTC conditions) concerning the cycloaddition reactions was also studied. Table 1 lists the optimized conditions, under MW and classical heating (liquid phase, chloroform). Using MW irradiation, in liquid phase, the best results were obtained applying a constant irradiation power (25% from the full power of the magnetron, 800 W) and varying the temperature (the so-called 'power control'). Attention was then focused on PTC reactions. In this study, the solid phase was a mixture of potassium fluoride and *N*-(*p*-*R*-phenacyl)-pyridazinium bromides; the liquid phase was dipolarophiles dissolved in trioctyl-methyl-ammonium chloride-Aliquat 336 (tensioactive compound which acts as transfer catalyst). The resultant

* Corresponding author.
E-mail address: ionelm@uaic.ro (I.I. Mangalagiu).

0968-0896/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2009.02.028



Scheme 1. Reaction pathway of pyridazinium ylides with symmetrically substituted *Z*-alkene.



Scheme 2. Reaction pathway of pyridazinium ylides with non-symmetrically substituted dipolarophiles and DMAD.

biphasic system undergoes the action of the MW using the monomode reactor at 800 W. The best results have been obtained by applying a constant temperature (130 °C) and varying the irradiation power (the so-called 'temperature control').

As indicated in Table 1, MW induced a remarkable acceleration for reactions, the reaction times decreasing dramatically, from hours to minutes (5 min for liquid phase and 15 min for PTC). Consequently, the consumed energy decrease considerably. In the some cases, under MW irradiation the yields are higher, sometimes substantially. Moreover, the amount of used solvents is two times less (see experimental) in liquid phase, while PTC do not use solvents, these types of reactions being considered as environmentally friendly.

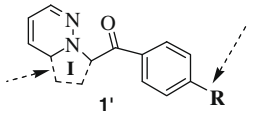
Considering the pyridazine–acetophenone skeleton (**1′**) as the pharmacophoric group for the activity,[1,5] in this work we aimed to obtain new pyridazine derivatives with antimicrobial activity, having in mind two structural modifications: introduction of a pyrrolo (**I**) ring, and a classical isosteres substituient **R** (R = Me, F, Cl) in the *para*-position of the benzoyle ring. The in vitro antibacterial and antifungal activities of the compounds were determinate by using diffusion technique on agar.[11] Six bacterial strains were included in this study: *Staphylococcus aureus* ATCC 25923, *Sarcinia luteea* ATCC 9341, *Bacillus subtillis, Pseudomonas aeruginosa, Escherichia coli* ATCC 25922, and fungus *Candida albicans ATCC 10231*. The results are listed in Table 2.

Table 1
Cycloaddition reactions for some pyridazinium ylides with activated alkenes and alkynes under MW heating and classical conditions

Compd.	Classical (chloroform, reflux)		Microwaves			
	Reaction time (min)	Yield (%)	Liquid phase (chloroform, reflux)		PTC (KF-Aliquat)	
			Reaction time (min)	Yield (%)	Reaction time (min)	Yield (%)
4.a. (R = F)	180	85	5	70	15	28
4.b. (R = Cl)	180	81		76		30
4.c. (R = CH_3)	180	45		60		21
5.a. (R = F)	180	36		23		17
5.b. (R = Cl)	180	43		27		43
5.c. (R = CH_3)	180	35		56		Trace
6.a. (R = F)	180	9		31		5
6.b. (R = Cl)	180	22		21		21
6.c. (R = CH_3)	180	14		28		7
7.a. (R = F)	180	29		23		10
7.b. (R = Cl)	180	76		84		15
7.c. (R = CH_3)	180	38		46		27
8.a. (R = F)	180	21		9		12
8.b. (R = Cl)	180	20		10		12
8.c. (R = CH_3)	180	32		13		15
9.a. (R = F)	120	25		12		12
9.b. (R = Cl)	120	83		87		62
9.c. (R = CH_3)	120	38		20		26
10.a. (R = F)	120	10		14		6
10.b. (R = Cl)	120	82		93		65
10.c. (R = CH_3)	120	12		12		6

Table 2
Inhibition zone (mean diameter of inhibition in mm) as a criterion of antibacterial and antifungal activities for some dazine derivatives described in the text

Strain→product and reference drug ↓	*S. aureus ATCC25923*	*S. luteea ATCC 9341*	*B. subtillis*	*P. aeruginosa*	*E. coli ATCC 25922*	*Candida albicans ATCC 10231*
Chloramphenicol 30 mcg/disc	30	40	26	19	25	–
Nysatin, 100 mcg/disc	–	–	–	–	–	29
2.a. (R = F)	**38**	**61**	**31**	20	**31**	19
2.b. (R = Cl)	**36**	**57**	**32**	20	**36**	29
2.c. (R = CH_3)	**47**	**81**	**40**	20	25	27
4.a. (R = F)	27	**63**	28	16	25	25
4.b. (R = Cl)	28	**54**	28	18	28	**34**
4.c. (R = CH_3)	31	**73**	**37**	18	24	29
5.a. (R = F)	29	**60**	**37**	18	**35**	24
5.b. (R = Cl)	33	**56**	**39**	18	**32**	25
5.c. (R = CH_3)	**41**	**62**	**39**	19	**37**	30
6.a. (R = F)	29	**51**	**35**	17	**35**	27
6.b. (R = Cl)	23	**54**	**36**	15	**31**	27
6.c. (R = CH_3)	**47**	**59**	**38**	17	**37**	29
7.a. (R = F)	26	**50**	27	14	20	23
7.b. (R = Cl)	30	**57**	29	14	28	**35**
7.c. (R = CH_3)	**46**	**67**	**39**	19	23	30
9.a. (R = F)	27	**48**	22	20	23	22
9.b. (R = Cl)	25	**48**	25	20	**33**	30
9.c. (R = CH_3)	**40**	**56**	**37**	18	25	28
10.a. (R = F)	27	**52**	23	15	21	21
10.b. (R = Cl)	30	**57**	26	18	**31**	24
10.c. (R = CH_3)	**46**	**65**	26	19	25	29



1'

The comparative analysis for the obtained data leads to the conclusions:

- all the pyridazine derivatives have a spectacular antimicrobial activity against *Gram positive* germ *S. luteea*;
- the pyridazine salts (**2**) have an excellent antimicrobial activity (non-selective) against *Gram positive* and *Gram negative* germs. It could be also noticed that, the pyridazine salts (**2**) are significant more active as comparative as the corresponding cycloadducts (**3–10**). A reasonable explication could be the complementary actions of the counter anion, Br^-, in salts;
- there is a certain influence of the isosters substituent **R** from the *para*- position of the benzoyle ring, compounds with R = Me being more active that those one with R = F, Cl;
- the influence of pyrrolo (**I**) moiety seems to be negligible. However, it can be noticed that the saturated tetrahydropyrrolo-pyridazine derivatives (**5**) and (**6**) are more active as compared with the others, most probably, because of the complementary action of the two carbomethoxy groups existing on the pyrrolo-moiety;
- only two pyridazine derivatives (**4b**, **7b**) have a significant activity against fungus *C. albicans*.

3. Conclusions

In conclusion, a thorough study concerning synthesis, structure and biological activity of some new pyridazine derivatives is reported. Syntheses have been done both under classical and

microwave (MW), in liquid phase and interphasic transfer catalysis (PTC). The MW induced a remarkable acceleration for the [3+2] dipolar cycloaddition reaction of pyridazinium ylides to activated alkenes and alkynes, the yields were increased in some cases, and the amount of used solvents decrees in liquid phase (while PTC do not use solvents). Consequently, these types of reactions could be considered environmentally friendly. The in vitro antibacterial and antifungal activities of the newly obtained diazine compounds were tested, some of the compounds have proved to have a remarkable activity against *Gram positive* germs, the results on *S. luteea* being spectacular. Against fungus *C. albicans* pyridazine derivatives have no significant activity. Correlation structure-biological activity have been done.

4. Experimental

The ^{1}H and ^{13}C NMR spectra and two-dimensional 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC) experiments were recorded on a Bruker Avance 400 DRX spectrometer operating at 400/100 MHz. Chemical shifts are given in ppm (δ-scale), coupling constants (J) in hertz. The IR spectra were recorded on a FTIR Shimadzu Prestige 8400s spectrophotometer in KBr. Melting points were determined on a MELTEMP II apparatus and are uncorrected. For the microwave irradiation we used a 800 W STAR SYSTEM-2 monomode reactor (CEM Corporation).

4.1. General procedure for syntheses of diazine salts (2a–c)

A solution of 2-bromo-4′-*R*-acetophenone (R = F, Cl, CH_3) (10 mmol, dissolved in 15 ml of anhydrous benzene) and pyridazine (10 mmol, dissolved in 10 ml of anhydrous benzene), was stirred for 3 h at room temperature to give the corresponding cycloimmonium salt (**2**). The obtained salts were filtered off and dried in vacuo. No purification required.

4.1.1. 1-[2-(4-Methylphenyl)-2-oxoethyl] pyridazinium bromide (2c)

White crystals, (94%), mp 235–237 °C. IR (cm^{-1}): 1687 (C=O keto). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45 (s, 3H, CH_3 from 12 position), 6.80 (s, 2H, CH_2 from 7), 7.49–7.47 (d, J = 8.0 Hz, 2H, H_{11}), 8.02–8.00 (d, J = 8.0 Hz, 2H, H_{10}), 8.79–8.75 (dtd, J = 12.0, 8.0, 5.2 Hz, 1H, H_4), 8.94–8.89 (dtd, J = 12.0, 4.0 Hz, 1H, H_5), 9.76–9.75 (dd, J = 4 Hz, 1H, H_3), 10.0–9.98 (d, J = 5.6 Hz, 1H, H_6). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 21.34 (CH_3 from 12 position), 70.13 (CH_2 from 7 position), 128.55 (C_{10}), 129.67 (C_{11}), 130.81 (C_9), 135.91 (C_5), 137.43 (C_4), 145.74 (C_{12}), 151.79 (C_6), 154.63 (C_3), 189.69 (C_8, keto).

4.2. General procedure for obtaining [3+2] dipolar cycloadducts

The corresponding cycloimmonium salt (**2**) (2 mmol) was suspended in 50 ml of chloroform. A solution of an activated alkene or alkyne (2 mmol) and triethylamine (2.2 mmol) in the same solvent (5 ml) was then added. The solution was refluxed for 2 h (alkynes) and for 3 h (alkenes). Under microwave heating, in liquid phase the solution was exposed to microwave irradiation for 5 min (25% magnetron power), and the amount of solvent was half (10 ml). The resulting mixture was washed thoroughly three times with water (50 ml), dried with sodium sulfate, filtered and evaporated. In interphasic transfer catalysis we exposed to microwave for 15 min a mixture of potassium fluoride (1 mmol) and cycloimmonium salt (**2**) (1 mmol), the dipolarophile (1.1 mmol) and trioctylmethylammonium chloride-Aliquat 336 (0.5 mmol); a mechanical stirrer was used to mix the resulted slurry. After cooling, 15 ml chloroform was added. The solution was filtered and the solvent evaporated. In all cases, the crude product was purified by flash chromatography (silica, CH_2Cl_2–MeOH) and than crystallized from an appropriate solvent.

4.2.1. 4-(4-Fluorobenzoyl)-2-phenyl-9a,9b,3a,4-tetrahydro-pyrrolo[3′,4′:3,4]pyrrolo[1,2-*b*]pyridazine-1,3-dione (4a)

White crystals (85%), mp 166–168 °C. IR (cm^{-1}): 1708 (C=O imide), 1681(C=O keto). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.58–3.54 (dd, J = 8.0, 8.0 Hz, 1H, H_{9b}), 4.08–4.06 (d, J = 8.0 Hz, 1H, H_{3a}), 4.24–4.20 (t, J = 8.0, 5.6 Hz, 1H, H_{9a}), 5.94 (s, 1H, H_4), 5.96–5.95 (dd, J = 8.0, 3.6 Hz, 1H, H_8), 6.29–6.25 (m, J = 5.6, 3.6 Hz, 1H, H_9), 6.87–6.85 (dd, J = 3.2 Hz, 1H, H_7), 7.21–7.16 (m, J = 8.0, 4.4 Hz, 2H, H_{16}), 7.42–7.38 (t, J = 7.2, 3.6 Hz, 1H, H_{18}), 7.49–7.45 (t, J = 7.6 Hz, 2H, H_{17}), 8.27–8.23 (dd, J = 8.4, 5.2 Hz, 2H, H_{12}). ^{13}C NMR: 44.60 (C_{3a}), 50.32 (C_{9b}), 57.40 (C_{9a}), 76.20 (C_4), 174.21 (C_3, keto imide), 176.70 (C_1, keto imide), 192.97 (C_{10}, keto). Anal. $C_{22}H_{16}N_3O_3F$: C, 67.86; H, 4.14; N, 10.79. Found: C, 67.78; H, 4.12; N, 10.74.

4.2.2. 4-(4-Chlorobenzoyl)-2-phenyl-9a,9b,3a,4-tetrahydro-pyrrolo[3′,4′:3,4] pyrrolo[1,2-*b*]pyridazine-1,3-dione (4b)

White crystals (81%), mp 193–195 °C. IR (cm^{-1}): 1713 (C=O imide), 1684 (C=O keto). ^{1}H NMR: 3.57–3.53 (dd, J = 8.0, 8.0 Hz, 1H, H_{9b}), 4.07–4.05 (d, J = 8.0 Hz, 1H, H_{3a}), 4.21–4.18 (t, J = 8.0, 5.6 Hz, 1H, H_{9a}), 5.92 (s, 1H H_4), 5.95–5.93 (m, J = 2.4 Hz,1H, H_8), 6.28–6.25 (dd, J = 9.0, 5.6 Hz, 1H, H_9), 6.86–6.85 (d, J = 3.2 Hz, 1H, H_7), 7.21–7.19 (d, J = 7.2 Hz, 2H, H_{16}), 7.41–7.38 (dd, J = 7.2, 3.6 Hz, 1H, H_{18}), 7.49–7.45 (m, 4H, $2H_{13}$, $2H_{17}$), 8.16–8.13 (d, J = 8.8 Hz, 2H, H_{12}). ^{13}C NMR: 44.76 (C_{3a}), 51.39 (C_{9b}), 56.61 (C_{9a}), 75.90 (C_4), 174.45 (C_3, keto imide), 176.64 (C_1, keto imide), 192.61 (C_{10}, keto). Anal. Calcd for $C_{22}H_{16}N_3O_3Cl$: C, 65.11; H, 3.97; N, 10.35. Found: C, 65.02; H, 3.92; N, 10.30.

4.2.3. 4-(4-Methylbenzoyl)-2-phenyl-9a,9b,3a,4-tetrahydro-pyrrolo[3′,4′:3,4] pyrrolo[1,2-*b*]pyridazine-1,3-dione (4c)

White crystals (60%), mp 180–181 °C. IR (cm^{-1}): 1708 (C=O imide), 1677 (C=O keto). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3H, CH_3 from 14 position), 3.57–3.52 (dd, J = 8.0, 8.4 Hz, 1H, H_{9b}), 4.06–4.04 (d, J = 8.0, Hz, 1H, H_{3a}), 4.27–4.24 (t, J = 8.0, 5.6 Hz, 1H, H_{9a}), 5.94–5.91 (m, J = 8.0, 5.6 Hz, 1H, H_8), 5.98 (s, 1H, H_4), 6.28–6.23 (m, J = 5.6, 4.0 Hz, 1H, H_9), 6.85–6.84 (dd, J = 3.2 Hz, 1H, H_7), 7.24–7.21 (m, J = 6.4 Hz, 2H, H_{16}), 7.32–7.30 (d, J = 8.4 Hz, 2H, H_{13}), 7.41–7.37 (m, J = 8.0, 4.4 Hz, 1H, H_{18}), 7.49–7.45 (t, J = 16.0, 5.6 Hz, 2H, H_{17}), 8.12–8.10 (d, J = 8.4 Hz, 2H, H_{12}). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 21.78 (CH_3 from 14 position), 44.99 (C_{3a}), 51.41 (C_{9b}), 56.62 (C_{9a}), 75.79 (C_4), 174.61 (C_3, keto imide), 176.79 (C_1, keto imide), 193.35 (C_{10}, keto). MS (ES): 408 (M^++Na^+). Anal. Calcd for $C_{23}H_{19}N_3O_3$: C, 71.67; H, 4.97; N, 10.90. Found:C, 71.60; H, 4.93; N, 10.83.

4.2.4. 7-(4-Fluorobenzoyl)-4a,5,6,7-tetrahydropyrrolo[2,1-*b*]pyridazine-5,6-*cis*-dicarboxylic acid dimethyl ester (5a)

Yellow crystals (36%), mp 119–120 °C. IR (cm^{-1}): 1737 (C=O ester from **5**), 1728 (C=O ester from **6**), 1687 (C=O keto). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.45–3.42 (dd, J = 7.6, 5.2 Hz, 1H, H_5), 3.65 (s, 3H, CH_3 from 5 position), 3.70 (s, 3H, CH_3 from 6 position), 3.99–3.96 (dd, J = 7.6, 7.2 Hz, 1H, H_6), 4.42–4.39 (ddd, J = 1.6, 5.2, 5.6 Hz, 1H, H_{4a}), 5.78–5.75 (ddd, J = = 10.0, 3.2, 1.6 Hz, 1H, H_3), 5.84–5.82 (ddd, J = 4.0, 1.6 Hz, 1H, H_4), 5.87–5.85 (d, J = 7.2 Hz, 1H, H_7), 6.53–6.52 (dd, J = 1.6, 3.2 Hz, 1H, H_2), 7.19–7.14 (dd, J = 2.0 Hz, 2H, H_{11}), 8.37–8.33 (dd, J = 20.0, 2H, H_{10}). ^{13}C NMR: (400 MHz, $CDCl_3$): 42.65 (C_6), 51.95 (C_5), 52.41 (CH_3, COOMe from 5), 52.70 (CH_3, COOMe from **6**), 59.27 (C_{4a}), 70.19 (C_7), 115.59 (C_{11}), 132.71 (C_{10}). Anal. Calcd for $C_{18}H_{17}N_2O_5F$: C, 60.00; H, 4.76; N, 7.77. Found: C, 59.91; H, 4.72; N, 7.73.

4.2.5. 7-(4-Chlorobenzoyl)-4a,5,6,7-tetrahydropyrrolo[2,1-*b*]pyridazine-5,6-*cis*-dicarboxylic acid dimethyl ester (5b)

Yellow crystals (43%), mp 119–120 °C. IR (cm^{-1}): 1729 (C=O ester from **5**), 1720 (C=O ester from **6**), 1681 (C=O keto). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.45–3.41 (dd, *J* = 7.6, 5.6 Hz, 1H, H_5), 3.65 (s, 3H, CH_3 from 5 position), 3.69 (s, 3H, CH_3 from 6 position), 3.99–3.96 (t, *J* = 7.6, 7.2 Hz, 1H, H_6), 4.40–4.37 (ddd, *J* = 1.2, 5.2, 5.6 Hz, 1H, H_{4a}), 5.77–5.74 (ddd, *J* = 10.0, 3.2, 1.6 Hz, 1H, H_3), 5.84–5.82 (dd, *J* = 4.4 Hz, 1H, H_4), 5.86–5.84 (d, *J* = 7.2 Hz, 1H, H_7), 6.53–6.52 (dd, *J* = 1.6, 4.0 Hz, 1H, H_2), 7.49–7.45 (dd, *J* = 2.0 Hz, 2H, H_{11}), 8.37–8.33 (dd, *J* = 2.0 Hz, 2H, H_{10}). ^{13}C NMR: 400 MHz, $CDCl_3$): 42.20 (C_6), 52.19 (CH_3, COOMe from **6**), 52.69 (CH_3, COOMe from **5**), 52.99 (C_5), 60.02 (C_{4a}), 69.82 (C_7), 128.89 (C_{11}), 131.41 (C_{10}), 192.46 (C_8, keto). Anal. Calcd for $C_{18}H_{17}N_2O_5Cl$: C, 57.38; H, 4.55; N, 7.43. Found: C, 57.31; H, 4.52; N, 7.40.

4.2.6. 7-(4-Methylbenzoyl)-4a,5,6,7-tetrahydropyrrolo[2,1-*b*]pyridazine-5,6-*cis*-dicarboxylic acid dimethyl ester (5c)

Yellow crystals (56%), mp 136–137 °C. IR (cm^{-1}): 1730 (C=O ester from **5**), 1724 (C=O ester from **6**), 1670 (C=O keto). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3H, CH_3 from 12 position), 3.45–3.42 (dd, *J* = 7.6, 5.6 Hz, 1H, H_5), 3.64 (s, 3H, CH_3 from 5 position), 3.69 (s, 3H, CH_3 from 6 position), 3.99–3.96 dd, *J* = 7.6, 7.2 Hz, 1H, H_6), 4.43–4.41 (ddd, *J* = 1.2, 5.2, 5.6 Hz, 1H, H_{4a}), 5.76–5.72 (ddd, *J* = 10.0, 3.2, 1.6 Hz, 1H, H_3), 5.84–5.80 (ddd, *J* = 10.0, 4.4, 1.2 Hz, 1H, H_4), 5.91–5.89 (d, *J* = 7.2 Hz, 1H, H_7), 6.52–6.50 (dd, *J* = 1.6, 3.2 Hz, 1H, H_2), 7.31–7.29 (dd, *J* = 8.0 Hz, 2H, H_{11}), 8.21–8.19 (dd, *J* = 8.0 Hz, 2H, H_{10}). ^{13}C NMR: (400 MHz, $CDCl_3$): 21.75 (CH_3 from 12 position), 46.70 (C_6), 52.03 (CH_3, COOMe from **5**), 52.74 (CH_3, COOMe from **6**), 55.40 (C_5), 60.01 (C_{4a}), 73.57 (C_7), 129.35 (C_{11}), 129.55 (C_{10}), 194.26 (C_8, keto). MS (ES): 379 (M^++Na^+). Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 63.98; H, 5.64; N, 7.81.

4.2.7. 7-(4-Fluorobenzoyl)-4a,5,6,7-tetrahydropyrrolo[2,1-*b*]pyridazine-5,6-*trans*-dicarboxylic acid dimethyl ester (6a)

Yellow crystals (31%), mp 147–148 °C. IR (cm^{-1}): 1728 (C=O ester from **5**), 1721 (C=O ester from **6**), 1674 (C=O keto). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.62, (s, 3H, CH_3 from 5 position), 3.70 (s, 3H, CH_3 from 6 position), 3.74–3.72 (dd, *J* = 6.8, 7.2 Hz, 1H, H_6), 3.79–3.75 (dd, *J* = 7.2, 8.4 Hz, 1H, H_5), 4.30–4.27 (dd, *J* = 5.2, 9.2 Hz, 1H, H_{4a}), 5.83–5.81 (d, *J* = 6.8 Hz, 1H, H_7), 5.86–5.85 (ddd, *J* = 1.2, Hz, 1H, H_3), 5.96–5.92 (ddd, *J* = 1.2, 5.2, 10.6 Hz, 1H, H_4), 6.80–6.78 (dd, *J* = 1.6, 3.2 Hz, 1H, H_2), 7.28–7.26 (dd, *J* = 8.8, Hz, 2H, H_{11}), 8.18–8.14 (dd, *J* = 8.8, 2H, H_{10}). ^{13}C NMR: 400 MHz, $CDCl_3$): 52.11 (C_5), 52.62 (C_6), 55.41 (C_{4a}), 115.93 (C_{11}), 118.13 (C_7), 132.27 (C_{10}), 171.12 (C_5, keto ester), 172.91 (C_6, keto ester), 193.08 (C_8, keto). Anal. Calcd for $C_{18}H_{17}N_2O_5F$: C, 60.00; H, 4.76; N, 7.77. Found: C, 59.94; H, 4.73; N, 7.74.

4.2.8. 7-(4-Chlorobenzoyl)-4a,5,6,7-tetrahydropyrrolo[2,1-*b*]pyridazine-5,6-*trans*-dicarboxylic acid dimethyl ester (6b)

Yellow crystals (22%), mp 160–161 °C. IR (cm^{-1}): 1731 (C=O ester from **5**), 1729 (C=O ester from **6**), 1683 (C=O keto). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.62, (s, 3H, CH_3 from 5 position), 3.70 (s, 3H, CH_3 from 6 position), 3.75–3.72 (dd, *J* = 7.2 Hz, 1H, H_6), 3.79–3.75 (dd, *J* = 7.6 Hz, 1H, H_5), 4.30–4.26 (dd, *J* = 5.6 Hz, 1H, H_{4a}), 5.81–5.79 (ddd, *J* = 6.8 Hz, 1H, H_7), 5.85–5.82 (dd, *J* = 7.2 Hz, 1H, H_3), 5.96–5.92 (dd, *J* = 5.2 Hz, 1H, H_4), 6.79–6.78 (dd, *J* = 3.2, 1.2 Hz, 1H, H_2), 7.46–7.44 (d, *J* = 8.8, Hz, 2H, H_{11}), 8.07–8.05 (d, *J* = 8.8, 2H, H_{10}). ^{13}C NMR: (400 MHz, $CDCl_3$): 46.70 (C_6), 52.07 (CH_3, COOMe from **6**), 52.74 (CH_3, COOMe from **5**), 55.40 (C_{4a}), 73.57 (C_7), 129.35 (C_{11}), 129.55(C_{10}), 173.05 (C_5, keto ester), 194.26 (C_8, keto). Anal. Calcd for $C_{18}H_{17}N_2O_5Cl$: C, 57.38; H, 4.55; N, 7.43. Found: C, 57.30; H, 4.51; N, 7.38.

4.2.9. 7-(4-Methylbenzoyl)-4a,5,6,7-tetrahydropyrrolo[2,1-*b*]pyridazine-5,6-*trans*-dicarboxylic acid dimethyl ester (6c)

Yellow crystals (28%), mp 170–171 °C. IR (cm^{-1}): 1739 (C=O ester from **5**), 1732 (C=O ester from **6**), 1666 (C=O keto). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3 from 12 position), 3.61 (s, 3H, CH_3 from 5 position), 3.70 (s, 3H, CH_3 from 6 position), 3.72–3.69 (dd, *J* = 9.2 Hz, 1H, H_6), 3.80–3.76 (dd, *J* = 9.2, 7.6 Hz, 1H, H_5), 4.32–4.29 (dd, *J* = 9.2, 5.2 Hz, 1H, H_{4a}), 5.83–5.80 (ddd, *J* = 6.8 Hz, 1H, H_3), 5.86–5.84 (dd, *J* = 7.2 Hz, 1H, H_7), 5.96–5.92 (ddd, *J* = 7.2, 1.6 Hz, 1H, H_4), 6.78–6.77 (dd, *J* = 1.2, 3.2 Hz, 1H, H_2), 7.28–7.26 (d, *J* = 8.0 Hz, 2H, H_{11}), 8.03–8.01 (d, *J* = 8.0, 2H, H_{10}). ^{13}C NMR: (400 MHz, $CDCl_3$): 21.78 (CH_3, from 12 position), 46.61 (C_6), 52.11 (CH_3, COOMe from **6**), 52.60 (CH_3, COOMe from **5**), 55.41 (C_{4a}), 73.49 (C_7), 128.98 (C_{11}), 130.80 (C_{10}), 171.08 (C_5, keto ester), 172.87 (C_6, keto ester), 193.55 (C_8, keto). MS (ES): 379 (M^++Na^+). Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 63.99; H, 5.64; N, 7.83.

4.2.10. 7-(4-Fluorobenzoyl)-4a,5,6,7-tetrahydro pyrrolo[2,1-b]pyridazine-5-carbonitrile (7a)

Dark white crystals (29%), mp 148–150 °C. IR (cm^{-1}): 2242 (CN), 1697 (C=O keto). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.14–2.08 (dtd, *J* = 12.8, 3.6, 2.8 Hz, 1H, H_{6b}), 2.81–2.74 (dtd, *J* = 12.8, 9.6, 6.8, Hz, 1H, H_{6a}), 3.26–3.20 (m, *J* = 7.2, 4.8 Hz, 1H, H_5), 4.00–4.97 (t, *J* = 12.0, 6.0 Hz, 1H, H_{4a}), 5.55–5.53 (dd, *J* = 8.4, 2.8 Hz, 1H, H_7), 6.04–6.01 (m, *J* = 10.0, 6.4 *Hz*, 1H, H_4), 6.15–6.11 (m, *J* = 10.0, 3.6 Hz, 1H, H_3), 6.88–6.85 (dd, *J* = 3.2 Hz, 1H, H_2), 7.18–7.14 (dd, *J* = 8.8 Hz, 2H, H_{11}), 8.20.8.16 (dd, *J* = 8.8 Hz, 2H, H_{10}). ^{13}C NMR: 400 MHz, $CDCl_3$): 27.60 (C_6), 35.37 (C_5), 55.83 (C_{4a}), 70.69 (C_7), 116.02 (C_{11}), 120.40 (CN), 131.22 (C_{10}), 164.90 (C_{12}), 194.00 (C_8, keto). Anal. Calcd for $C_{15}H_{12}N_3OF$: C, 66.91; H, 4.49; N, 15.61. Found: C, 66.88; H, 4.46; N, 15.57.

4.2.11. 7-(4-Chlorobenzoyl)-4a,5,6,7-tetrahydro pyrrolo[2,1-*b*]pyridazine-5-carbonitrile (7b)

Brown crystals (84%, mp 156–158 °C. IR (cm^{-1}): 2242 (CN), 1692 (C=O keto). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.15–2.08 (dtd, *J* = 12.8, 3.2, 2.8, 1H, H_{6b}), 2.80–2.74 (dtd, *J* = 12.8, 8.4, 7.0, 1H, H_{6a}), 3.26–3.20 (m, *J* = 7.2, 6.4 Hz, 1H, H_5), 3.98–3.96 (t, *J* = 11.6, 6.0, 1H, H_{4a}), 5.47–5.51 (dd, *J* = 8.4, 2.8, 1H, H_7), 6.07–6.03 (dd, *J* = 9.6, 6.0, 1H, H_4), 6.14–6.11 (dd, *J* = 9.6, 3.2, 1H, H_3), 6.88–6.87 (d, *J* = 3.2, 1H, H_2), 7.49–7.47 (d, *J* = 8.8, 2H, H_{11}), 8.11–8.10 (d, *J* = 8.8, 2H, H_{10}). ^{13}C NMR: 27.49 (C_6), 35.25 (C_5), 55.83 (C_{4a}), 70.70 (C_7), 120.36 (CN), 129.06 (C_{11}), 130.85 (C_{10}), 133.08 (C_{12}), 194.39 (C_8, keto). Anal. Calcd for $C_{15}H_{12}N_3OCl$: C, 63.05; H, 4.23; N, 14.71. Found: C, 62.97; H, 4.19; N, 14.65.

4.2.12. 7-(4-Methylbenzoyl)-4a,5,6,7-tetrahydro pyrrolo[2,1-*b*]pyridazine-5-carbonitrile (7c)

Yellow crystals (46%), mp 170–171 °C. IR (cm^{-1}): 2235 (CN), 1685 (C=O keto). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.15–2.09 (m, *J* = 4.8, 12.8, Hz, 1H, H_{6b}), 2.41 (s, 3H, CH_3 from 12 position), 2.75–2.68 (dtd, *J* = 6.4, 9.6, 12.4 Hz, 1H, H_{6a}), 3.24–3.19 (m, *J* = 7.2 Hz, 1H, H_5), 4.06–4.03 (t, *J* = 6.8, 11.6 *Hz*, 1H, H_{4a}), 5.58–5.55 (dd, *J* = 8.4, 2.8 Hz, 1H, H_3), 6.04–6.01 (dd, *J* = 6.8 Hz, 1H, H_4), 6.12–6.09 (dd, *J* = 8.0, 3.6 Hz, 1H, H_7), 6.86–6.85 (dd, *J* = 16.0, 3.2 Hz, 1H, H_2), 7.29–7.26 (d, *J* = 8.0 Hz, 2H, H_{11}), 8.03–8.01 (d, *J* = 8.0, 2H, H_{10}). ^{13}C NMR: (400 MHz, $CDCl_3$): 21.74 (CH_3 from 12 position), 28.06 (C_6), 35.25 (C_5), 55.84 (C_{4a}), 70.44 (C_7), 120.48 (CN), 129.43 (C_{11}), 132.24 (C_{10}), 144.88 (C_{12}), 1995.31 (C_8, keto). Anal. Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.38; H, 5.67; N, 15.79.

4.2.13. 7-(4-Fluorobenzoyl)-4a,5,6,7-tetrahydro pyrrolo[2,1-*b*]pyridazine-5-carboxylic acid ethyl ester (8a)

Brown crystals (21%), mp 170–171 °C. IR (cm^{-1}): 1689 (C=O keto). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.35–2.32 (t, 2H, H_{6a} and

H_{6b}), 3.22–3.17 (m, J = 6.4, 6.8 Hz, 1H, H_5), 3.68 (s, 3H, CH_3 from 5 position), 4.26–4.23 (dd, J = 6.8, 12.0 Hz, 1H, H_{4a}), 5.59–5.56 (t, J = 6.4 Hz, 1H, H_7), 5.84–5.81 (m, J = 3.2, 7.6, 8.0, Hz, 1H, H_3), 5.96–5.92 (ddd, J = 3.2, 12.0 Hz, 1H, H_4), 6.68–6.67 (dd, J = 2.8, 12.0 Hz, 1H, H_2), 7.17–7.12 (t, J = 8.8 Hz, 2H, H_{11}), 8.20–8.17 (dd, J = 8.8, 5.6 2H, H_{10}). ^{13}C NMR: (400 MHz, $CDCl_3$): 25.73 (C_6), 50.20 (C_5), 51.32 (CH_3, COOMe from **5**), 57.40 (C_{4a}), 70.72 (C_7), 173.74 (C_5, keto ester), 195.39 (C_8, keto). MS (ES): 288 (M^++Na^+). Anal. Calcd for $C_{16}H_{15}N_2O_3F$: C, 63.57; H, 5.00; N, 9.27. Found: C, 63.52; H, 4.97; N, 9.24.

4.2.14. 7-(4-Chlorobenzoyl)-4a,5,6,7-tetrahydro pyrrolo[2,1-*b*]pyridazine-5-carboxylic acid ethyl ester (8b)

Yellow crystals (20%), mp 100–102 °C. IR (cm^{-1}): 1682 (C=O keto). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35–2.32 (t, 2H, H_{6a} and H_{6b}), 3.22–3.17 (m, J = 6.4 Hz, 1H, H_5), 3.68 (s, 3H, CH_3 from 5 position), 4.26–4.23 (dd, J = 5.2, 6.8 Hz, 1H, H_{4a}), 5.59–5.55 (t, J = 6.8 Hz, 1H, H_7), 5.84–5.81 (dd, J = 3.2, 7.6, 8.0Hz, 1H, H_3), 5.95–5.91 (ddd, J = 3.2, 12.0 Hz, 1H, H_4), 6.68–6.67 (dd, J = 2.8, 16.0 Hz, 1H, H_2), 7.30–7.28 (t, J = 8.8 Hz, 2H, H_{11}), 8.05–8.03 (dd, J = 8.8, 5.6 2H, H_{10}). ^{13}C NMR: 400 MHz, $CDCl_3$): 25.54 (C_6), 50.20 (C_5), 51.81 (CH_3, COOMe from **5**), 57.31 (C_{4a}), 70.89 (C_7), 173.79 (C_5, keto ester), 195.89 (C_8, keto). Anal. Calcd for $C_{16}H_{15}N_2O_3Cl$: C, 60.29; H, 4.74; N, 8.79. Found: C, 60.23; H, 4.70; N, 8.76.

4.2.15. 7-(4-Methylbenzoyl)-4a,5,6,7-tetrahydro pyrrolo[2,1-*b*]pyridazine-5-carboxylic acid ethyl ester (8c)

White crystals (32%), mp 75–76 °C. IR (cm^{-1}): 1679 (C=O keto). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32–2.27 (dtd, J = 8.4, 12.4 Hz, 1H, H_{6b}), 2.41–2.36 (dtd, J = 8.4, 12.8 Hz, 1H, H_{6a}), 2.43 (s, 3H, CH_3 from 12 position), 3.22–3.17 (m, J = 4.4, 8.0, 12.4 Hz, 1H, H_5), 3.69 (s, 3H, CH_3 from 5 position), 4.33–4.30 (dd, J = 5.6, 7.2 Hz, 1H, H_{4a}), 5.63–5.60 (dd, J = 3.6, 8.4 *Hz*, 1H, H_7), 5.85–5.81 (m, J = 4.4, 5.6, 12.0 Hz, 1H, H_3), 5.95–5.91 (m, J = 3.6, 4.4, 12.0 Hz, 1H, H_4), 6.68–6.67 (dd, J = 3.2, 16.0 Hz, 1H, H_2), 7.30–7.28 (d, J = 8.0 Hz, 2H, H_{11}), 8.05–8.03 (d, J = 8.0, 2H, H_{10}). ^{13}C NMR: (400 MHz, $CDCl_3$): 21.69 (C_6), 26.21 (CH_3, COOMe from 12), 50.06 (C_5), 51.77 (C_{4a}), 57.40 (C_7), 173.82 (C_5, keto ester), 196.77 (C_8, keto). Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.40; H, 6.05; N, 9.34.

4.2.16. 7-(4-Fluorobenzoyl)pyrrolo[2,1-*b*]pyridazine-5-carboxylic acid ethyl ester (9a)

Brown crystals (34%), mp 116–118 °C. IR (cm^{-1}): 1708 (C=O ester), 1647 (C=O keto). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43–1.39 (t, J = 7.2 Hz, 3H, CH_3 from 5 position), 4.42–4.37 (q, J = 7.2 Hz, 2H, CH_2 from 5 position), 7.17–7.14 (dd, J = 4.4, 9.2 Hz, 1H, H_3), 7.22–7.20 (dd, J = 8.4 Hz, 2H, H_{11}), 7.73 (s, 1H, H_6), 7.96–7.93 (dd, J = 8.4, 5.6 Hz, 2H, H_{10}), 8.54–8.52 (dd, J = 1.6, 4.4 Hz, 1H, H_2), 8.69–8.66 (dd, J = 1.6, 9.2 Hz, 1H, H_4). ^{13}C NMR: (400 MHz, $CDCl_3$): 14.72 (CH_3 from 5 position), 60.67 (CH_2 from 5 position), 115.48 (C_5), 124.61 (C_6), 128.03 (C_{11}), 132.09 (C_{10}), 133.53 (C_{4a}), 144.35 (C_{12}), 164.23 (C_5, keto ester), 182.35 (C_8, keto). Anal. Calcd for $C_{17}H_{13}N_2O_3F$: C, 65.38; H, 4.20; N, 8.97. Found: C, 65.35; H, 4.18; N, 8.95.

4.2.17. 7-(4-Chlorobenzoyl)pyrrolo[2,1-*b*]pyridazine-5-carboxylic acid ethyl ester (9b)

Light blue crystals (88%), mp 109–110 °C. IR (cm^{-1}): 1705 (C=O ester), 1640 (C=O keto). ^{1}H NMR: 1.43–1.39 (t, J = 7.2 Hz, 3H, CH_3 from 5 position), 4.42–4.37 (q, J = 7.2 Hz, 2H, CH_2 from 5 position), 7.19–7.15 (dd, J = 9.2, 4.0 Hz, 1H, H_3), 7.50–7.48 (d, J = 8.4 Hz, 2H, H_{11}), 7.73 (s, 1H, H_6), 7.86–7.84 (d, J = 8.4 Hz, 2H, H_{10}), 8.55–8.53 (d, J = 4.0 Hz, 1H, H_2), 8.69–8.66 (dd, J = 9.2 Hz, 1H, H_4). ^{13}C NMR: 14.49 (CH_3 from 5 position), 60.53 (CH_2 from 5 position), 105.53 (C_5), 124.81 (C_6), 126.30 (C_7), 128.77 (C_{11}), 130.92 (C_{10}), 133.62 (C_{4a}), 137.31 (C_{12}), 163.44 (C_5, keto ester), 183.00 (C_8, keto). Anal. Calcd for $C_{17}H_{13}N_2O_3Cl$: C, 62.11; H, 3.99; N, 8.52. Found: C, 62.06; H, 3.97; N, 8.50.

4.2.18. 7-(4-Methylbenzoyl)pyrrolo[2,1-*b*]pyridazine-5-carboxylic acid ethyl ester (9c)

Dark white crystals (14%), mp 105–107 °C. IR (cm^{-1}): 1706 (C=O ester), 1631 (C=O keto). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42–1.39 (t, J = 7.2 Hz, 3H, CH_3 from 5 position), 2.46 (s, 3H, CH_3 from 12 position), 4.41–4.36 (q, J = 7.2 Hz, 2H, CH_2 from 5 position), 7.15–7.12 (dd, J = 9.2, 4.4 Hz, 1H, H_3), 7.32–7.30 (d, J = 8.0 Hz, 2H, H_{11}), 7.74 (s, 1H, H_6), 7.84–7.82 (d, J = 8.0 Hz, 2H, H_{10}), 8.53–8.51 (dd, J = 16.0, 4.4 Hz, 1H, H_2), 8.67–8.65 (dd, J = 16.0, 9.2 Hz, 1H, H_4). ^{13}C NMR: (400 MHz, $CDCl_3$): 14.48 (CH_3 from 5 position), 21.66 (CH_3 from 12 position), 60.40 (CH_2 from 5 position), 105.20 (C_5), 124.56 (C_6), 129.11 (C_{11}), 129.77 (C_{10}), 133.29 (C_{4a}), 136.30 (C_{12}), 163.62 (C_5, keto ester), 184.15 (C_8, keto). Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.08; H, 5.20; N, 9.03.

4.2.19. 7-(4-Fluorobenzoyl)pyrrolo[1,2-*b*]pyridazine-5,6-dicarboxylic acid dimethyl ester (10a)

White crystals (14%), mp 156–158 °C. IR (cm^{-1}): 1739 (C=O ester from **5**), 1708 (C=O ester from **6**), 1652 (C=O keto). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.65 (s, 3H, CH_3 from 6 position), 3.92 (s, 3H, CH_3 from 5 position), 7.10–7.06 (dd, J = 9.2, 4.4 Hz, 1H, H_3), 7.15–7.10 (t, J = 8.8, 8.4 Hz, 2H, H_{11}), 7.72–7.70 (dd, J = 8.8, 5.2 Hz, 2H, H_{10}), 8.32–8.31 (dd, J = 16.0, 4.8 Hz 1H, H_2), 8.63–8.60 (dd, J = 16.0, 9.2 Hz 1H, H_4). ^{13}C NMR: 400 MHz, $CDCl_3$): 51.92 (CH_3 from 5 position), 52.63 (CH_3 from 6 position), 115.51 (C_5), 117.33 (C_6), 128.79 (C_7), 130.91 (C_{11}), 132.41 (C_{10}), 130.41 (C_{4a}), 162.90 (C_5, keto ester), 164.51 (C_6, keto ester), 184.01 (C_8, keto). MS (ES): 375 (M^++Na^+). Anal. Calcd for $C_{18}H_{13}N_2O_5F$: C, 60.68; H, 3.68; N, 7.86. Found: C, 60.62; H, 3.65; N, 7.82.

4.2.20. 7-(4-Chlorobenzoyl)pyrrolo[1,2-*b*]pyridazine-5,6-dicarboxylic acid dimethyl ester (10b)

White crystals (93%). mp 178–179 °C. IR (cm^{-1}): 1744 (C=O ester from **5**), 1707 (C=O ester from **6**), 1648 (C=O keto). ^{1}H NMR: 3.66 (s, 3H, CH_3 from 6 position), 3.92 (s, 3H, CH_3 from 5 position), 7.11–7.08 (dd, J = 8.8, 3.2 Hz, 1H, H_3), 7.44–7.42 (d, J = 8.0 Hz, 2H, H_{11}), 7.74–7.72 (d, J = 8.4 Hz, 2H, H_{10}), 8.33–8.32 (d, J = 3.2 Hz, 1H, H_2), 8.63–8.60 (d, J = 8.8 Hz, 1H, H_4). ^{13}C NMR: 51.95 (CH_3 from 5 position), 52.69 (CH_3 from 6 position), 103.44 (C_5), 126.18 (C_6), 126.28 (C_7), 128.74 (C_{11}), 130.78 (C_{10}), 131.00 (C_{4a}), 136.21 (C_{12}), 162.86 (C_5, keto ester), 164.52 (C_6, keto ester), 184.24 (C_8, keto). Anal. Calcd for $C_{18}H_{13}N_2O_5Cl$: C, 58.00; H, 3.52; N, 7.52. Found: C, 57.92; H, 3.48; N, 7.45.

4.2.21. 7-(4-Methylbenzoyl)pyrrolo[1,2-*b*]pyridazine-5,6-dicarboxylic acid dimethyl ester (10c)

Yellow crystals (12%), mp 176–178 °C. IR (cm^{-1}): 1720 (C=O ester from **5**), 1704 (C=O ester from **6**), 1652 (C=O keto). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3H, CH_3 from 12 position), 3.59 (s, 3H, CH_3 from 6 position), 3.92 (s, 3H, CH_3 from 5 position), 7.07–7.04 (dd, J = 9.2, 4.4 Hz, 1H, H_3), 7.26–7.24 (d, J = 6.8 Hz, 2H, H_{11}), 7.72–7.70 (d, J = 8.4 Hz, 2H, H_{10}), 8.32–8.31 (dd, J = 16.0, 4.4 Hz 1H, H_2), 8.62–8.59 (dd, J = 16.0, 7.6 Hz 1H, H_4). ^{13}C NMR: (400 MHz, $CDCl_3$): 21.98 (CH_3, COOMe from **5**), 51.37 (CH_3 from 12 position), 53.69 (CH_3 from 6 position), 101.37 (C_6), 103.21 (C_5), 129.15 (C_{10}), 129.62 (C_{11}), 143.22 (C_{12}), 163.24 (C_7), 184.26 (C_8, keto). MS (ES): 331 (M^++Na^+). Anal. Calcd for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.70; H, 4.56; N, 7.88.

4.3. Microbiology

Antibacterial and antifungal activities of the compounds were determined by using diffusion technique on agar.[11] The bacteria and fungi were maintained on nutrient Mueller Hinton agar (Oxoid). The agar media were incubated with different microor-

ganisms culture tested. After 24 h of incubation at 30 °C for bacteria and 48 h of incubation at 28 °C for fungi, the diameter of inhibition zone (mm) was measured (Table 2). Chloramphenicol and nysatin were purchased from the market and used in a concentration of 30 mcg/disc and 100 mcg/disc, respectively, as references for antibacterial and antifungal activities.

Acknowledgements

To CNCSIS Bucuresti, Grants No. 1155/2006 and Grant TD No. 457/2006, for financial support.

References and notes

1. (a) Nogrady, T. In *Medicinal Chemistry*; Oxford University Press: New York, USA, 1998; (b) Silverman, R. B. In *The Organic Chemistry of Drug Design and Drug Action*; Academic Press: San Diego, 1992.
2. (a) Rodrguez-Ciria, M.; Sanz, A. M.; Yunta, M. J. R.; Gomez-Contreras, F.; Navarro, P.; Fernandez, I.; Pardo, M.; Cano, C. *Bioorg. Med. Chem.* **2003**, *11*, 2143; (b) Bloomer, L. C.; Wotring, L. L.; Townsend, L. B. *Cancer Res.* **1982**, *25*, 813.
3. Moldoveanu, C.; Mangalagiu, G.; Drochioiu, G.; Caprosu, M.; Petrovanu, M.; Mangalagiu, I. *An. Stiint. Univ. 'Al.I.Cuza' Iasi* **2003**, *11*, 367. CAN 142:56249 AN 2004:300679 CAPLUS.
4. (a) Demirayak, S.; Karaburn, A. C.; Beis, R. *Eur. J. Med. Chem.* **2004**, *39*, 1089; (b) Gokçe, M.; Dogruer, D.; Fethi Sahin, M. *Il Farmaco* **2001**, *56*, 223.
5. (a) Butnariu, R.; Caprosu, M.; Bejan, V.; Ungureanu, M.; Poiata, A.; Tuchilus, C.; Florescu, M.; Mangalagiu, I. I. *J. Heterocycl. Chem.* **2007**, *44*, 1149; (b) Caprosu, M.; Butnariu, R.; Mangalagiu, I. I. *Heterocycles* **2005**, *65*, 1871; (c) Ungureanu, M.; Mangalagiu, I. I.; Grosu, G.; Petrovanu, M. *Ann. Pharm. Fr.* **1997**, *55*, 69.
6. Padwa, A. (Ed.). *1,3-Dipolar Cycloaddition Chemistry*, Vol. 2, Chapter 12, ed. by A. Padwa, pp 277–406 and Chapter 13, ed. by K. N. Houk, K. Yamaguchi, pp 407–450 and the references cited therein, John Wiley & Sons: New York, 1984.
7. Klamann, D.; Hagen, H.. In *Organische Stickstoff-Verbindungen mit einer CN-Doppelbindung*; Houben-Weyl, Ed.; Thieme: Stuttgart, 1991; Vol. E_{14b}, Teil 1, pp 1–160. and the references cited therein.
8. (a) Caprosu, M.; Zbancioc, Ghe.; Moldoveanu, C.; Mangalagiu, I. I. *Collect. Czech. Chem. C* **2004**, *69*, 426; (b) Mangalagiu, I. I.; Mangalagiu, G.; Deleanu, C.; Drochioiu, G.; Perovanu, M. *Tetrahedron* **2003**, *59*, 111; (c) Tsuge, O.; Kanemasa, S.; Takenaka, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3137.
9. (a) Van der Eycken, E.; Kappe, O. C. In *Microwave-Assisted Synthesis of Heterocycles*; Springer: Berlin, Heidelberg, Germany, 2006; (b) Kappe, O. C.; Stadler, A. In *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, Germany, 2005; (c) Loupy, A. In *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002.
10. (a) Zbancioc, Ghe. N.; Mangalagiu, I. I. *Synlett* **2006**, 804; (b) Zbancioc, G. N.; Caprosu, M.; Moldoveanu, C.; Mangalagiu, I. I. *Arkivoc* **2005**, *5*, 174; (c) Dima, St.; Mangalagiu, I. I.; Caprosu, M.; Georgescu, M.; Petrovanu, M. *Rev. Roum. Chim.* **2000**, *45*, 555.
11. *Medicinal Microbiology* 12th ed.; Cruickshank, R., Duguid, J. P., Marion, P. B., Swain, R. H. A., Eds.; Churchill Livingstone: London, 1975; Vol. 2, pp 196–202.