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# Dipolar Cycloaddition Reactions with Quinazolinones: A New Route for the Synthesis of Several Annelated Pyrrolo- and Pyridazinoquinazoline Derivatives

Sami S. Ghabrial  ${}^{\!\!*}$  and Hatem M. Gaber  ${}^{\!\!\dagger}$ 

National Organization for Drug Control and Research, P.O. Box 29, Cairo, A.R. Egypt.

<sup>†</sup> Current address: Department of Chemistry and Biochemistry, Florida Atlantic University, 777 Glades Road, P.O. Box 3091, Boca Raton, FL 33431-0991, U.S.A. E-mail: <u>hatemgaber@yahoo.com</u>

\* Author to whom correspondence should be addressed; e-mail: <a href="mailto:ssghabrial@hotmail.com">ssghabrial@hotmail.com</a>

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**Abstract:** The novel 2-aryl-3a,4,12,12a-tetrahydropyrrolo[3',4':4,3]-pyridazino[6,1-*b*]quinazoline-1,3,6-triones (**6a–d**), 2-aryl-10-oxopyridazino[6,1-*b*]-quinazoline-3-thiocarboxamides (**10a–d**) and 2-aryl-3-nitro-1,2,3,4-tetrahydro-pyridazino[6,1-*b*]quinazolin-10-ones (**12a–d**) were synthesized *via* a new, facile one step route involving the reactions of the zwitterion **4**, formed *in situ*, with a variety of *N*-arylmaleimides **5**, 3-aryl-2-cyanothioacrylamides **8** and  $\omega$ -nitrostyrenes **11**. Dehydrogenation of the tetrahydro derivatives **6a–d** and **12a–d** in nitrobenzene resulted in the formation of 2-arylpyrrolo[3',4':4,3]pyridazino[6,1-*b*]quinazoline-1,3,6-triones (**7a–d**) and 2-aryl-3-nitropyridazino[6,1*b*]quinazolin-10-ones (**13a–d**), respectively. The structures of the products were confirmed by elemental analysis and spectral data.

**Keywords:** Quinazolinones; pyrroloquinazolinones; pyridazinoquinazolinones; *N*-aryl-maleimides; 3-aryl-2-cyanothioacrylamides; styrenes.

### Introduction

In recent years there has been an increasing interest in the chemistry of 4(3H)-quinazolinones because of their biological significance. Many of them show antifungal, antibacterial, anticancer, antiinflammatory, anticonvulsant, immunotropic, hypolipidemic, antitumor, antiulcer analgesic and antiproliferative activities as well as inhibitory effects for thymidylate synthase and poly-(*ADP*-ribose) polymerase (*PARP*) [1-13]. On the other hand, heterocycles containing the pyridazine nucleus also exhibit various pharmacological activities; reduction of blood pressure [14], anticonvulsant activity [15] and moreover there are pyridazine derivatives that have shown an interesting affinity towards  $A_1$ receptors, and are potentially usable as cerebroprotective agents [16,17]. Because of these established biological activities, and within the framework of our systematic studies of new heterocyclic compounds with biological activity [18-21], we became interested in the synthesis of a series of novel 4(3H)-quinazolinone derivatives containing a pyridazine ring, with the aim of obtaining annelated pyridazinoquinazolines with enhanced biological significance. This contribution represents a follow-up on our previous work on the chemistry of *N*-chlorosuccinimide (NCS) [22-24].

# **Results and Discussion**

The starting material 3-amino-2-methyl-4(3H)-quinazolinone (2) was prepared by condensation of 2-methyl-3,1-benzoxazin-4-one (1) with hydrazine hydrate as described in the literature [25]. It was then reacted with NCS to yield *in situ* the respective 3-amino-2-chloromethyl-4(3H)-quinazolinone (3), which was isolated and its structure confirmed on the basis of analytical and spectral data. This reaction constitutes a new and facile procedure for the synthesis of this reactive compound [26]. Compound 3 was then treated with triethylamine (TEA) to afford the zwitterion 4, created by the loss of HCl (Scheme 1). This zwitterionic species 4 was used as the key intermediate for the present study. Thus, the behavior of 4 towards the N-arylmaleimides 5a-d was investigated with regards to the synthesis of annelated quinazolines. It was found that compound 2 reacted with N-phenylmaleimide (5a) in the presence of NCS and TEA in dry chloroform with stirring for 1 h at room temperature to give a reaction product of molecular formula C<sub>19</sub>H<sub>14</sub>N<sub>4</sub>O<sub>3</sub> which corresponds to the addition of one molecule of 2 to one molecule of 5a, with subsequent elimination of a HCl molecule. The IR spectrum of this product showed the presence of NH (3340 cm<sup>-1</sup>), C=O (1680 cm<sup>-1</sup>), saturated CH<sub>2</sub> and CH (2980 cm<sup>-1</sup>) and C=N groups (1635 cm<sup>-1</sup>), in addition to the CO-NAr-CO group, which appears as two widely separated bands [27] at 1780 and 1710 cm<sup>-1</sup>. Its <sup>1</sup>H-NMR spectrum revealed the presence of signals for the pyridazine H-3 and H-4, pyridazine-CH<sub>2</sub>, NH and aromatic protons in their proper positions (cf. Experimental). Based on the above data, this product was formulated as 2-phenyl-3a,4,12,12a-tetrahydropyrrolo[3',4':4,3]-pyridazino[6,1-b]quinazoline-1,3,6-trione (6a). The formation of 6a is assumed to proceed via the initial reaction of 2 with NCS to yield 3-amino-2-chloromethyl-4(3H)-quinazolinone (3), which is not isolated, but rather reacts in situ with TEA to give the zwitterionic intermediate 4, which in turn reacts with 5a via a dipolar cycloaddition to yield the final isolable pyrrolopyridazinoquinazoline derivative 6a. This constitutes a simple and easy one pot

reaction leading to a fused heterocyclic derivative which otherwise is difficult to obtain. A similar reaction with maleimides has been described in our earlier communications [23, 24]. Similarly, the diionic species **4** reacted with each of the *N*-arylmaleimides **5b-d**, under the same experimental conditions, to afford the corresponding tetrahydropyrrolo[3',4':4,3]pyridazino[6,1-*b*]quinazolinetrione derivatives **6b-d**, respectively, whose structure was based also on correct elemental analyses and spectroscopic data studies (*cf.* Experimental).

# Scheme 1



Additional confirmation of the structures d,  $Ar=C_6H_4CH_3-p$  of **6a-d** came from their dehydrogenation using boiling nitrobenzene to yield the corresponding pyrrolo[3',4':4,3]-pyridazino[6,1-*b*]quinazoline-1,3,6-triones **7a-d**, respectively (Scheme 1). The structure of the latter products was also confirmed by their elemental analyses and spectral data. Thus, the IR spectra of compounds **7a-d** displayed bands assignable to NH and saturated CH<sub>2</sub> groups, while their <sup>1</sup>H-NMR spectra revealed only the presence of signals for pyridazine H-5 and aromatic protons (and for CH<sub>3</sub> or OCH<sub>3</sub> if present). No pyridazine H-3 or H-4 signals were detected in these spectra which were found

to be in accordance with the expected outcome of the proposed dehydrogenation reaction (*cf.* Experimental).

As a continuation of our studies aimed at synthesizing pyridazinoquinazoline derivatives with potential biological activity, the behavior of the zwitterionic species 4 towards a variety of 3-aryl-2-cyanothioacrylamides **8a-d** was also examined. Thus, 4 reacted in chloroform with 3-phenyl-2-cyanothioacrylamide (**8a**) to give the respective 10-oxopyridazino[6,1-*b*]quinazoline-3-thiocarboxamide structure **10a** (Scheme 2).

#### Scheme 2



Formation of **10a** is assumed to proceed *via* addition of the NH in **4** to the activated  $\alpha,\beta$ unsaturated center in **8a**, affording the cyclic adduct **9a** which spontaneously aromatizes to the final product **10a** *via* elimination of a HCN molecule and subsequent dehydrogenation. The IR spectrum of this product showed the bands of NH<sub>2</sub>, C=O and C=S groups. Moreover, its <sup>1</sup>H-NMR spectrum revealed the presence of signals corresponding to the presence of NH<sub>2</sub> function, in addition to the pyridazine CH and aromatic protons in their proper positions (*cf.* Experimental). In the same way, each of **8b-d** also reacted with **4** to yield the corresponding pyridazinoquinazolines **10b-d**, respectively, whose structures was similarly established based on elemental analysis and spectral data.

As an extension of this synthetic route, the behavior of 4 towards various  $\omega$ -nitrostyrenes **11a-d** was also studied. Thus, compound **2** and NCS in chloroform and TEA (*i.e.* 4) reacted with **11a-d** to yield the corresponding 3-nitrotetrahydropyridazino[6,1-*b*]quinazolin-10-ones **12a-d**, respectively (Scheme 2). Both elemental analyses and spectral data of the latter products were consistent with the assigned structures. Bands of NH and saturated CH<sub>2</sub> groups appeared in their IR spectra, while their <sup>1</sup>H-NMR spectra confirmed the presence of these groups, in addition to two pyridazine-CH and aromatic protons, in each case (*cf.* Experimental).

The 1,2,3,4-tetrahydro derivatives **12a-d** could also be dehydrogenated by the action of boiling nitrobenzene to afford the corresponding 2-aryl-3-nitropyridazino[6,1-*b*]quinazolin-10-ones **13a-d** (Scheme 2). No absorption bands for NH groups were detected in the IR spectra of **13a-d**. Additionally, their <sup>1</sup>H-NMR spectra revealed the complete absence of pyridazine-CH, pyridazine-CH<sub>2</sub> and NH signals while they revealed only the presence of signals for pyridazine H-5 and aromatic protons (and for OCH<sub>3</sub> if present).

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# Experimental

# General

All melting points are uncorrected. IR (KBr discs) were recorded on Perkin Elmer FT–IR type 4 spectrophotometer. <sup>1</sup>H-NMR Spectra were recorded on Gemini 200 MHz Spectrometer using TMS as an internal standard. <sup>13</sup>C-NMR spectra were recorded using a Varian Mercuy 300 NMR Spectrometer. Mass spectra were recorded on AEI MS 30 mass spectrometer operating at 70eV. Compounds **1** [28], **2** [25], **5** [29] and **11** [30] were prepared according to the reported literature procedures.

## *Synthesis of 3-amino-2-chloromethyl-4(3H)-quinazolinone* (3) [26].

A solution of **2** (0.01 mol) in dry chloroform (10 mL) containing pyridine (2 drops) was stirred with NCS (0.01 mol) for 20 min. Removal of the solvent gave a residue which was recrystallized from ethanol to give the title compound as colorless crystals, yield 98%, m.p. 156°C; Anal. Calcd. for C<sub>9</sub>H<sub>8</sub>ClN<sub>3</sub>O: C, 51.56; H, 3.84; N, 20.04; Cl, 16.91%; Found: C, 51.8; H, 3.9; N, 20.3; Cl, 17.1%; IR: v = 3400, 3350 (NH<sub>2</sub>), 2980 (sat. CH<sub>2</sub>), 1680 (C=O), 1630 (C=N) cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  = 4.51 (s, 2H, CH<sub>2</sub>), 5.90 (br s, 2H, NH<sub>2</sub>), 7.30-7.92 (m, 4H, H-arom.) ppm.

General Procedure for the Synthesis of 2-aryl-3a,4,12,12a-tetrahydropyrrolo[3',4':4,3]-pyridazino-[6,1-b]quinazoline-1,3,6-triones (**6a–d**), 2-aryl-10-oxopyridazino[6,1-b]quinazoline-3-thiocarboxamides (**10a–d**) and 2-aryl-3-nitro-1,2,3,4-tetrahydropyridazino[6,1-b]quinazolin-10-ones (**12a–d**).

To a solution of NCS (0.01 mol) in dry chloroform (30 mL) and pyridine (2 drops), compound 2 (0.01 mol) was added and stirred for 20 min. To this solution, each of the appropriate *N*-aryl-maleimides **5a–d**, 3-aryl-2-cyanothioacrylamides **8a–d** or  $\omega$ -nitrostyrenes **11a–d** (0.015 mol) was added and the reaction mixture was stirred for additional 10 min. at room temperature. A solution of TEA (0.12 mol) in dry chloroform (5 mL) was added dropwise over *ca*. 30 min. Stirring was continued for an extra 60 min. then the solution was washed with water (2x15 mL), dried and evaporated *in vacuo*. The residues were triturated and recrystallized from ethanol to yield **6a-d**, **10a-d** and **12a–d**, respectively.

**6a:** Brown crystals, yield 90%, m.p. 168°C; Anal. Calcd. for C<sub>19</sub>H<sub>14</sub>N<sub>4</sub>O<sub>3</sub>: C, 65.89; H, 4.07; N, 16.17%; Found: C, 66.1; H, 4.2; N, 16.4%; IR: v = 3340 (NH), 2980 (sat. CH<sub>2</sub> and CH), 1780, 1710 (CO-NAr-CO), 1680 (C=O), 1635 (C=N) cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta = 3.61$  (m, 1H, pyridazine H-4), 4.22 (d, 1H, J = 6.4 Hz, pyridazine H-3), 4.50 (d, 2H, J = 6.0 Hz, pyridazine-CH<sub>2</sub>), 7.01-7.81 (m, 9H, H-arom.), 9.92 (br s, 1H, NH) ppm; MS: m/z = 346 (M<sup>+</sup>, 18%).

**6b:** Brown crystals, yield 92%, m.p. 185°C; Anal. Calcd. for  $C_{19}H_{13}ClN_4O_3$ : C, 59.93; H, 3.44; N, 14.71%; Cl, 9.31; Found: C, 60.1; H, 3.6; N, 14.8; Cl, 9.5%; IR: v = 3350 (NH), 2985 (sat. CH<sub>2</sub> and CH), 1770, 1720 (CO-NAr-CO), 1685 (C=O), 1630 (C=N) cm<sup>-1</sup>; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>):  $\delta = 3.62$  (m, 1H, pyridazine H-4), 4.13 (d, 1H, J = 6.5 Hz, pyridazine H-3), 4.55 (d, 2H, J = 6.0 Hz, pyridazine-CH<sub>2</sub>), 7.19-7.87 (m, 8H, H-arom.), 10.14 (br s, 1H, NH) ppm.

**6c:** Brown crystals, yield 95%, m.p. 95°C; Anal. Calcd. for  $C_{20}H_{16}N_4O_4$ : C, 63.82; H, 4.28; N, 14.88%; Found: C, 63.7; H, 4.1; N, 14.7%; IR: v = 3350 (NH), 2982 (sat. CH<sub>2</sub> and CH), 1780, 1710 (CO-NAr-CO), 1670 (C=O), 1635 (C=N) cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta = 3.60$  (m, 1H, pyridazine H-4), 3.82 (s, 3H, OCH<sub>3</sub>), 4.20 (d, 1H, J = 6.5 Hz, pyridazine H-3), 4.61 (d, 2H, J = 6.1 Hz, pyridazine-CH<sub>2</sub>), 7.11-7.80 (m, 8H, H-arom.), 9.83 (br s, 1H, NH) ppm.

**6d:** Brown crystals, yield 80%, m.p. 170°C; Anal. Calcd. for  $C_{20}H_{16}N_4O_3$ : C, 66.65; H, 4.47; N, 15.54%; Found: C, 66.4; H, 4.6; N, 15.7%; IR: v = 3330 (NH), 2980 (sat. CH<sub>2</sub> and CH), 1770, 1715 (CO-NAr-CO), 1670 (C=O), 1630 (C=N) cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta = 1.60$  (s, 3H, CH<sub>3</sub>), 3.65 (m, 1H, pyridazine H-4), 4.05 (d, 1H, J = 6.3 Hz, pyridazine H-3), 4.65 (d, 2H, J = 5.9 Hz, pyridazine-CH<sub>2</sub>), 7.00-7.71 (m, 8H, H-arom.), 9.90 (br s, 1H, NH) ppm.

**10a:** Brown crystals, yield 80%, m.p. 184°C; Anal. Calcd. for  $C_{18}H_{12}N_4OS$ : C, 65.04; H, 3.63; N, 16.85; S, 9.64%; Found: C, 65.3; H, 3.8; N, 16.7; S, 9.4%; IR: v = 3400, 3380 (NH<sub>2</sub>), 1670 (C=O),

1630 (C=N), 1580 (C=S) cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta = 6.55$  (s, 1H, pyridazine H-5), 7.15-7.98 (m, 9H, H-arom.), 9.99 (br s, 2H, NH<sub>2</sub>) ppm; MS: m/z = 332 (M<sup>+</sup>, 15%).

**10b:** Yellow crystals, yield 75%, m.p. 137°C; Anal. Calcd. for  $C_{18}H_{11}CIN_4OS$ : C, 58.93; H, 3.02; N, 15.27; S, 8.74; Cl, 9.66%; Found: C, 59.2; H, 3.1; N, 15.6; S, 8.4; Cl, 9.5%; IR: v = 3410, 3370 (NH<sub>2</sub>), 1675 (C=O), 1630 (C=N), 1585 (C=S) cm<sup>-1</sup>; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>):  $\delta = 6.45$  (s, 1H, pyridazine H-5), 7.04-7.86 (m, 8H, H-arom.), 9.97 (br s, 2H, NH<sub>2</sub>) ppm.

**10c:** Yellow crystals, yield 95%, m.p. 200°C; Anal. Calcd. for  $C_{19}H_{14}N_4O_2S$ : C, 62.97; H, 3.89; N, 15.46; S, 8.84%; Found: C, 62.7; H, 4.0; N, 15.7; S, 8.6%; IR: v = 3390, 3350 (NH<sub>2</sub>), 1670 (C=O), 1630 (C=N), 1600 (C=S) cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta = 3.81$  (s, 3H, OCH<sub>3</sub>), 6.40 (s, 1H, pyridazine H-5), 7.02-7.80 (m, 8H, H-arom.), 9.91 (br s, 2H, NH<sub>2</sub>) ppm.

**10d:** Brown crystals, yield 90%, m.p. 145°C; Anal. Calcd. for  $C_{18}H_{11}N_5O_3S$ : C, 57.29; H, 2.92; N, 18.57; S, 8.49%; Found: C, 57.3; H, 3.1; N, 18.3; S, 8.7%; IR: v = 3380, 3360 (NH<sub>2</sub>), 1670 (C=O), 1630 (C=N), 1590 (C=S) cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta = 6.52$  (s, 1H, pyridazine H-5), 7.02-7.80 (m, 8H, H-arom.), 9.95 (br s, 2H, NH<sub>2</sub>) ppm.

**12a:** Brown crystals, yield 81%, m.p. 273°C; Anal. Calcd. for  $C_{17}H_{14}N_4O_3$ : C, 63.34; H, 4.37; N, 17.38%; Found: C, 63.6; H, 4.7; N, 17.7%; IR: v = 3350 (NH), 2980 (sat. CH<sub>2</sub> and CH), 1675 (C=O), 1630 (C=N) cm<sup>-1</sup>; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>):  $\delta = 3.62$  (m, 1H, pyridazine H-4), 4.16 (d, 1H, J = 6.3 Hz, pyridazine H-3), 4.55 (d, 2H, J = 5.9 Hz, pyridazine-CH<sub>2</sub>), 7.19-7.88 (m, 9H, H-arom.), 9.78 (br s, 1H, NH) ppm; MS: m/z = 322 (M<sup>+</sup>, 25%).

**12b:** Colorless crystals, yield 95%, m.p. 205°C; Anal. Calcd. for  $C_{17}H_{13}CIN_4O_3$ : C, 57.22; H, 3.65; N, 15.71; Cl, 9.96%; Found: C, 57.4; H, 3.8; N, 15.5; Cl, 10.1%; IR: v = 3320 (NH), 2985 (sat. CH<sub>2</sub> and CH), 1670 (C=O), 1630 (C=N) cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta = 3.65$  (m, 1H, pyridazine H-4), 4.15 (d, 1H, J = 6.3 Hz, pyridazine H-3), 4.57 (d, 2H, J = 6.0 Hz, pyridazine-CH<sub>2</sub>), 7.06-7.71 (m, 8H, H-arom.), 9.69 (br s, 1H, NH) ppm.

**12c:** Yellow crystals, yield 88%, m.p. 245°C; Anal. Calcd. for  $C_{18}H_{16}N_4O_4$ : C, 61.36; H, 4.57; N, 15.90%; Found: C, 61.6; H, 4.8; N, 15.7%; IR: v = 3350 (NH), 2980 (sat. CH<sub>2</sub> and CH), 1670 (C=O), 1630 (C=N) cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta = 3.61$  (m, 1H, pyridazine H-4), 3.82 (s, 3H, OCH<sub>3</sub>), 4.20 (d, 1H, J = 6.4 Hz, pyridazine H-3), 4.51 (d, 2H, J = 6.0 Hz, pyridazine-CH<sub>2</sub>), 7.11-7.70 (m, 8H, H-arom.), 9.92 (br s, 1H, NH) ppm.

**12d:** Yellow crystals, yield 78%, m.p. 265°C; Anal. Calcd. for  $C_{17}H_{13}N_5O_5$ : C, 55.59; H, 3.54; N, 19.07%; Found: C, 55.8; H, 3.5; N, 19.2%; IR: v = 3360 (NH), 2985 (sat. CH<sub>2</sub> and CH), 1670 (C=O), 1630 (C=N) cm<sup>-1</sup>; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>):  $\delta = 3.65$  (m, 1H, pyridazine H-4), 4.33 (d, 1H, J = 6.5 Hz, pyridazine H-3), 4.55 (d, 2H, J = 6.1 Hz, pyridazine-CH<sub>2</sub>), 7.12-7.80 (m, 8H, H-arom.), 10.10 (br s, 1H, NH) ppm.

General Procedure for the Synthesis of 2-arylpyrrolo[3',4':4,3]pyridazino[6,1-b]quinazoline-1,3,6triones **7a–d** and 2-aryl-3-nitropyridazino[6,1-b]quinazolin-10-ones **13a–d** 

A solution of each of **6a-d** and **12a-d** (1.0 g) was heated in nitrobenzene (15 mL) for 5 h. Nitrobenzene was steam distilled and the organic compound was extracted with ether. Removal of ether gave a residue which was crystallized from ethanol to give **7a-d** and **13a-d**, respectively.

**7a:** Brown crystals, yield 85%, m.p. 118°C; Anal. Calcd. for  $C_{19}H_{10}N_4O_3$ : C, 66.66; H, 2.94; N, 16.36%; Found: C, 66.8; H, 3.1; N, 16.6%; IR: v = 1780, 1720 (CO-NAr-CO), 1670 (C=O), 1630 (C=N) cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta = 6.30$  (s, 1H, pyridazine H-5), 7.10-7.91 (m, 9H, H-arom.) ppm; MS: m/z = 342 (M<sup>+</sup>, 21%).

**7b:** Brown crystals, yield 85%, m.p. 215°C; Anal. Calcd. for  $C_{19}H_9CIN_4O_3$ : C, 60.56; H, 2.39; N, 14.87%; Cl, 9.43; Found: C, 60.4; H, 2.4; N, 14.6; Cl, 9.3%; IR: v = 1785, 1715 (CO-NAr-CO), 1675 (C=O), 1640 (C=N) cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta = 6.42$  (s, 1H, pyridazine H-5), 7.00-7.81 (m, 8H, H-arom.) ppm.

**7c:** Brown crystals, yield 90%, m.p. 160°C; Anal. Calcd. for  $C_{20}H_{12}N_4O_4$ : C, 64.51; H, 3.25; N, 15.04%; Found: C, 64.7; H, 3.4; N, 15.3%; IR: v = 1780, 1710 (CO-NAr-CO), 1670 (C=O), 1630 (C=N) cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta = 3.80$  (s, 3H, OCH<sub>3</sub>), 6.41 (s, 1H, pyridazine H-5), 7.10-7.82 (m, 8H, H-arom.) ppm.

7d: Brown crystals, yield 92%, m.p. 209°C; Anal. Calcd. for  $C_{20}H_{12}N_4O_3$ : C, 67.41; H, 3.39; N, 15.72%; Found: C, 67.6; H, 3.7; N, 15.9%; IR: v = 1770, 1720 (CO-NAr-CO), 1670 (C=O), 1635 (C=N) cm<sup>-1</sup>; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>):  $\delta = 1.65$  (s, 3H, CH<sub>3</sub>), 6.42 (s, 1H, pyridazine H-5) 7.28-7.86 (m, 8H, H-arom.) ppm; <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>):  $\delta = 21.5$  (CH<sub>3</sub>), 117.6, 123.2, 125.1, 125.7, 126.2, 126.9, 127.8, 128.1, 129.4, 130.3, 134.5, 136.2, 144.0, 147.7 (C-arom.), 155.5 (C-6), 170.1, 171.3 (C-1, C-3) ppm.

**13a:** Brown crystals, yield 84%, m.p. > 300°C; Anal. Calcd. for  $C_{17}H_{10}N_4O_3$ : C, 64.15; H, 3.16; N, 17.60%; Found: C, 64.3; H, 3.4; N, 17.9%; IR: v = 1670 (C=O), 1630 (C=N) cm<sup>-1</sup>; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>):  $\delta = 6.66$  (s, 1H, pyridazine H-5), 7.05-7.80 (m, 9H, H-arom.) ppm; MS: m/z = 318 (M<sup>+</sup>, 32%); <sup>13</sup>C- NMR (DMSO-d<sub>6</sub>):  $\delta = 117.3$ , 123.6, 125.4, 125.8, 126.2, 126.7, 127.0, 127.3, 128.3, 129.8, 131.4, 148.5, 151.2, 153.0 (C-arom.), 155.3 (C=O) ppm.

**13b:** Brown crystals, yield 95%, m.p. 280°C; Anal. Calcd. for  $C_{17}H_9ClN_4O_3$ : C, 57.87; H, 2.55; N, 15.89; Cl, 10.07%; Found: C, 57.9; H, 2.3; N, 16.0; Cl, 10.1%; IR: v = 1675 (C=O), 1630 (C=N) cm<sup>-1</sup>; <sup>1</sup>H-NMR (DMSO-d\_6):  $\delta = 6.68$  (s, 1H, pyridazine H-5), 7.25-7.91 (m, 8H, H-arom.) ppm.

**13c:** Brown crystals, yield 77%, m.p. > 300°C; Anal. Calcd. for  $C_{18}H_{12}N_4O_4$ : C, 62.07; H, 3.47; N, 16.08%; Found: C, 62.3; H, 3.7; N, 16.2%; IR: v = 1670 (C=O), 1630 (C=N) cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta = 3.85$  (s, 3H, OCH<sub>3</sub>), 6.61 (s, 1H, pyridazine H-5), 7.11-7.80 (m, 8H, H-arom.) ppm.

**13d:** Brown crystals, yield 90%, m.p. > 300°C; Anal. Calcd. for  $C_{17}H_9N_5O_5$ : C, 56.20; H, 2.48; N, 19.28%; Found: C, 56.1; H, 2.6; N, 19.3%; IR: v = 1675 (C=O), 1635 (C=N) cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta = 6.71$  (s, 1H, pyridazine H-5), 7.02-7.75 (m, 8H, H-arom.) ppm.

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Sample availability: Not available

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