1-Methyl-3*H*-pyrazolo[1,2-*a*]benzo[1,2,3,4]tetrazin-3-ones. Design, Synthesis, and Biological Activity of New Antitumor Agents

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1-Methylpyrazolo[1,2-*a*]benzo[1,2,3,4]tetrazin-3-ones **4**, synthesized in good to excellent yields, were designed as novel alkylating agents because of their peculiar chemical behavior. All derivatives showed antiproliferative activity against more than 50 types of tumor cell lines with GI_{50} reaching sub-micromolar values. SAR studies revealed that the presence of a chlorine atom is well-tolerated in both positions 8 and 9, whereas in the case of the methyl group, switching from the 8 to the 9 position gives rise to the most active compound of the series, **4g**, either for the number of cell lines inhibited and for selectivity against leukaemia and renal cancer subpanels. COMPARE and 3D-MIND computations indicate, for compounds **4**, an activity profile analogous to rifamycins and cytidine analogues.

Introduction

Azolotetrazinones have been the focus of medicinal chemists in the past decades because of the outstanding antineoplastic activity exhibited by several derivatives incorporating the imidazole moiety. In particular, mitozolomide (**1**) and temozolomide (**2**) (recently marketed as Temodal, effective against malignant melanoma, mycosis fungoides, and brain tumors[1]) have attracted remarkable attention.

Compounds **1** and **2** are prodrugs that undergo, in a nucleophilic microenvironment provided by a sequence of guanine residues together with associated water molecules, in the major groove of DNA, ring opening following the nucleophilic attack at C-4 by an activated molecule of water to afford a monoalkyltriazene species, a bioactive alkylating agent. Such a reactive entity likely undergoes an S_N2 alkylation of the nucleophilic residues in the immediate vicinity such as N-7 and/or O-6 sites of guanine, eliminating nitrogen and 5-aminoimidazole-4-carboxamide.[2]

Recently our research group has reported the interesting antitumor activity of a new class of pyrrolo[2,1-*d*][1,2,3,5]tetrazinones **3** that possess the deaza skeleton of temozolomide. Most compounds of the series were found to have GI_{50} values in the low micromolar or submicromolar range and reaching, in the case of compound **3** (R = CN, R^1 = Me, R^2 = Ph, R^3 = 4-Cl-C_6H_4), nanomolar concentrations.[3] Therefore, it seems that a tetrazine ring can be an effective pharmacophore in several classes of antitumor agents.

In this context we decided to investigate if the presence of an isomeric 1,2,3,4-tetrazine moiety can also give rise to classes of biologically active compounds. Therefore, in this paper we propose 1-methylpyrazolo-[1,2-*a*]benzo[1,2,3,4]tetrazin-3-ones of type **4** as new antitumor agents and report the synthesis and the evaluation of the antiproliferative activity of a panel of derivatives belonging to this series.

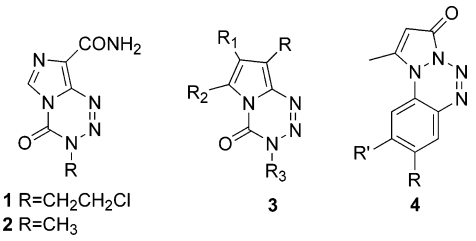

Figure 1.

Although apparently derivatives **4** do not share similarity with temozolomide and other related azolotetrazinones, since they cannot generate a monoalkyltriazene species, our interest in this class of heterocycles arises from the very peculiar behavior of the ring system (vide infra) that makes the compounds capable of generating cation intermediates that in turn might be reactive toward biologically important nucleophiles.

Chemistry

The benzo[1,2,3,4]tetrazine system has not been extensively studied and to date only few reports (26) are present in the literature dealing with its synthesis and chemical behavior. The number of known benzotetrazine condensed with other heterocycles is, if possible, even lower, and only three references can be found in Scifinder Scholar on imidazo- and pyrazolobenzotetrazinones.[4−6]

The synthetic approach to the pyrazolo[1,2-*a*]benzo-[1,2,3,4]tetrazinones was first undertaken by one of us years ago[6] and involved the use of the furan derivative **6** as starting material (Scheme 1). The reaction sequence that successfully led to the parent compound **4a** is now extended to the preparation of several derivatives of the class by using the commercially available 2-nitroanilines **5a**−**h**. The diazonium salts obtained from **5**, upon treatment with sodium nitrite in aqueous hydrochloric

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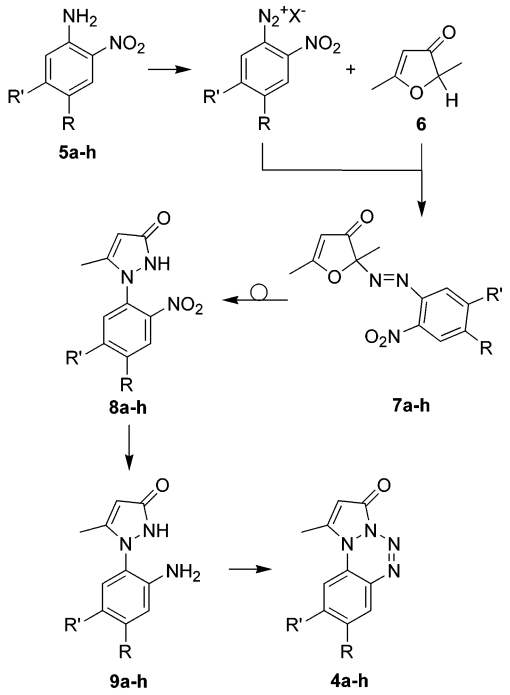
Scheme 1



	R	R'
a	H	H
b	Me	H
c	OMe	H
d	OH	H
e	Cl	H
f	F	H
g	H	Me
h	H	Cl

acid, were coupled with the furan **6** to give the 2-arylazo derivatives **7a**−**h**. Rearrangement of these upon treatment with concentrated hydrochloric acid afforded the 2-arylpyrazolones **8** through a well-established pathway[7] that can be envisaged as a ring opening−ring closure sequence. Electron-withdrawing substituents on the phenyl ring markedly favor the conversion **7**→**8**, whereas steric effects seem to be unimportant, since the presence of the nitro group in the 2 position did not preclude the rearrangement.

The reduction of the nitro group was carried out by standard procedures, either with hydrogen and Pd at room temperature or with iron in acetic acid at 60 °C in the case of substrates bearing a chlorine. In all the cases the 2-(2-aminoaryl)pyrazolones **9** were isolated in yields from good to nearly quantitative. The amines **9a**−**h** were treated with sodium nitrite in concentrated sulfuric acid at 0 °C, and after keeping the reaction mixture at 60 °C for 3 h it was possible to isolate, upon neutralization, the 1-methylpyrazolo[1,2-*a*]benzo[1,2,3,4]-tetrazin-3-ones **4a**−**h** in yields from good to excellent.

The chemical behavior of this class of pyrazolotetrazinones toward selected nucleophiles was investigated under different reaction conditions. The parent compound[6] was already demonstrated to react with alcohols under reflux to give the alkoxymethylpyrazolinone **13** (R = R′=H, Nu = MeO, EtO, CD_3O) and with several other nucleophiles (Nu = β-naphthol, N_3^-) in acid conditions to originate deep-red azo compound **14** and azide **15**, respectively (Scheme 2). Similar behavior is of course evidenced now for all the other derivatives of the series without any significant difference attributable to the nature of R and R′ substituents. This means that compounds of type **4** behave as masked diazonium salts, able to generate a species of type **10** that reacts as the classical aromatic ones in coupling reactions in the presence of acid, with or without loss of nitrogen. Under thermal conditions, loss of nitrogen gives rise to the cation **11**, which intramolecularly rearranges to the methylene intermediate **12**. The same intermediate can be formed under milder conditions (i.e. room temperature), although more slowly, as testified by NMR experiments. In fact, the ^{1}H NMR spectra of compounds **4a**−**h**, measured in DMSO-d_6 in the presence of 10% H_2O, showed over a period of nearly 15 days a total conversion of pyrazolo-tetrazinones into hydroxymethylenepyrazolinones **13a**−**h** (Nu = OH), as demonstrated by the appearance of a signal at ca. 4.40 ppm, due to the presence of the methylene.

Therefore, the chemical mechanism that successfully led to alkylation under laboratory conditions can constitute the basis for creating an agent that could react with biologically important nucleophiles (Nu = DNA, enzymes) in an analogous fashion and, by the intermediacy of the exocyclic methylene species **12**, irreversibly alkylate them. With these presumptions, 1-methylpyrazolo[1,2-*a*]benzotetrazin-3-ones are designed as novel alkylating agents. Of course, the nature and position of the different substituents in the benzotetrazine moiety can affect each step of the ring-opening process outlined in Scheme 2 and therefore the alkylating ability: our choice of groups in the 8 or 9 position allows wide exploitation of the chemistry.

Biology

The pyrazolo[1,2-*a*]benzo[1,2,3,4]tetrazinone derivatives **4a**−**h** were selected by the National Cancer Institute (Bethesda, MD) for testing in the developmental therapeutics program (DTP) against a panel of approximately 60 tumor cell lines that have grouped in disease subpanels, including leukaemia, non-small-cell lung, colon, central nervous system, melanoma, ovarian, renal, prostate, and breast tumors cell lines. The in vitro test system and the information, encoded by the activity pattern over all cell lines, were obtained (see experimental) according to the previously reported methodology.[8] The antitumor activity of a test compound is given by three parameters for each cell line; pGI_{50} value (GI_{50} is the molar concentration of the compound that inhibits 50% net cell growth), pTGI value (TGI is the molar concentration of the compound leading to total inhibition of net cell growth), and pLC_{50} value (LC_{50} is the molar concentration of the compound that induces 50% net cell death). Moreover, a mean graph midpoint (MG_MID) is calculated for each of the mentioned parameters, giving an average activity parameter over all cell lines. For the calculation of the MG_MID, insensitive cell lines are included with the highest concentration tested. The discovery of compounds with new selectivity patterns is one of the targets of the screening program. Selectivity of a compound with respect to a certain cell

Scheme 2

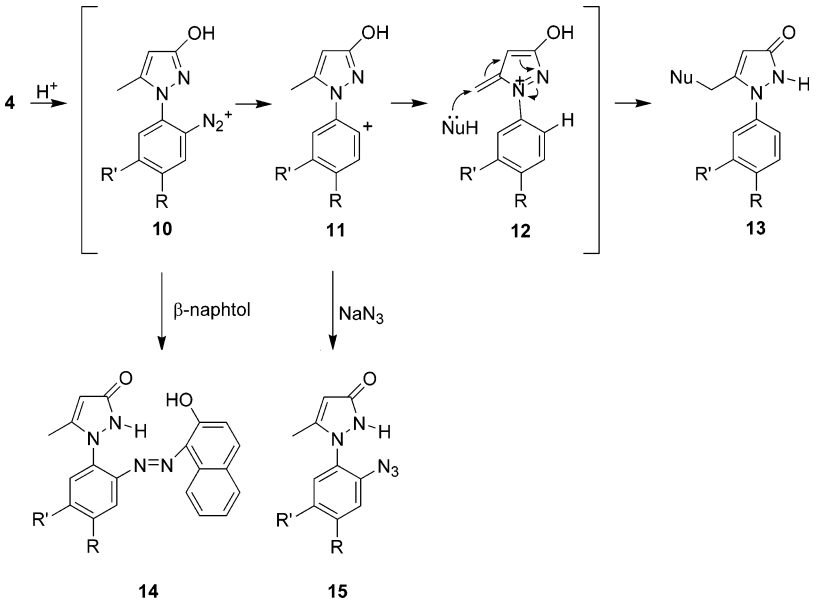


Table 1. Overview of the Results of the in Vitro Antitumor Screening for Compounds **4**[a]

		pGI_{50}[b]			pTGI[c]			pLC_{50}[d]		
compd	no. studied[e]	no. giving positive results[e]	range	MG_MID[f]	no. giving positive results[e]	range	MG_MID	no. giving positive results[e]	range	MG_MID
4a	55	53	5.68−4.53	4.75	50	5.23−4.08	4.41	40	4.26−4.06	4.14
4b	53	53	5.85−4.50	5.11	52	5.53−4.07	4.76	49	5.25−4.11	4.44
4c	55	54	5.75−4.50	4.90	50	5.45−4.00	4.59	48	5.19−4.05	4.30
4e	55	55	6.28−4.59	5.05	54	5.72−4.10	4.71	50	5.27−4.11	4.41
4f	53	51	5.75−4.67	4.96	52	5.47−4.34	4.67	50	5.21−4.01	4.34
4g	54	54	6.76−4.46	5.41	51	6.14−4.29	5.05	46	5.36−4.01	4.69
4h	54	53	6.05−4.50	4.95	52	5.53−4.02	4.61	45	5.25−4.05	4.29

[a] Data obtained from the NCI's in vitro disease-oriented human tumor cells screen. [b] pGI_{50} is the −log of the molar concentration that inhibits 50% net cell growth. [c] pTGI is the −log of the molar concentration giving total growth inhibition. [d] pLC_{50} is the −log of the molar concentration leading to 50% net cell death. [e] Refers to the number of cell lines. [f] MG_MID = mean graph midpoint = arithmetical mean value for all tested cancer cell lines. If the indicated effect was not attainable within the used concentration interval, the highest tested concentration was used for the calculation.

line of the screen is characterized by a high deviation of the particular cell line parameter compared to the MG_MID value. The data from these in vitro screenings can be presented in different formats; herein we report in Table 1 the results in terms of number of cell lines investigated and activity range, together with the MG_MID values.

Results and Discussion

An evaluation of the data reported in the table revealed that, with the sole exception of compound **4d**, which was inactive in all the screening tests, all the new pyrazolo[1,2-*a*]benzo[1,2,3,4]tetrazinones showed antiproliferative activity against every type of tumor cell lines investigated. Considering the MG_MID values, the most active compound of the series was demonstrated to be derivative **4g**, at either GI_{50} and TGI level, followed by **4b** and **4e**. Compound **4f** inhibited the 51 cell lines at micromolar concentrations at the GI_{50} level (range 5.75−4.67) and only in a few cases was less active ($p \approx 4.50$) at the TGI level. The other two derivatives, **4c** and **4h**, although less potent, inhibited a large number of the investigated cell lines, the parent compound being the least active. Only at the LC_{50} level was the number of cell lines giving positive response lower (40−50).

With respect to the tumor subpanel, the pyrazolo[1,2-*a*]benzo[1,2,3,4]tetrazinones were particularly efficacious against all kind of leukemia. In fact, the calculated pGI_{50} MG_MID values of the leukemia subpanel are always higher than the overall cell line MG_MID values (ΔMG_MID 0.57−0.93). In the non-small cell lung subpanel, the most sensitive cell line was NCI H522, which was inhibited by all the pyrazolo[1,2-*a*]benzo-[1,2,3,4]tetrazinone derivatives (range 5.77−5.23), whereas in the colon cancer one, the activity against COLO-205 and SW-620 was remarkable (range 5.85−4.73 and 5.78−5.06, respectively). The SF 539 (of the CNS subpanel) and OVCAR 3 (of the ovarian subpanel) were inhibited by derivatives **4b,c** and **4f**−**h**, generally in the low micromolar range ($pGI_{50} > 4.90$ and up to 6.05).

Excellent response was obtained in the renal subpanel in which most of the derivatives had GI_{50} in the low micromolar range, the most sensitive renal cancer lines being 786-0, CAKI-1, TK-10, and UO-31.

Pyrazolo[1,2-*a*]benzo[1,2,3,4]tetrazinones were also efficacious against breast cancer lines with particular respect to MCF7 and T-47D (with pGI_{50} reaching 5.85).

The most interesting derivative of the pyrazolo[1,2-*a*]benzo[1,2,3,4]tetrazinone series **4g**, besides the activity against renal cancer, showed the best selectivity

against all the leukemia and colon cancer cell lines, being also remarkably active against melanoma and breast cancer subpanel at GI_{50} level, whereas when TGI is considered, the leukemia, colon, and melanoma anticancer activity was retained. Analogous considerations can be drawn when LC_{50} is considered.

As far as structure−activity relationships are concerned, it seems that the presence of a chlorine atom is well-tolerated in both positions 8 and 9 of the polycyclic ring, without any remarkable difference. Whereas in the case of the methyl group, switching from the 8 to 9 position gives rise to the most active compound of the series, either for the number of cell lines inhibited and for selectivity against a certain subpanel.

The pyrazolo[1,2-*a*]benzo[1,2,3,4]tetrazinone derivatives **4b,c,e**−**h** were evaluated as anticancer agents in an in vivo animal model in which polyvinylidene fluoride hollow fibers containing various human cancer cell cultures were implanted intraperitoneally (ip) and subcutaneously (sc) into mice and compounds were administrated by the ip route.[9] The effects of the compounds on reduction of viable cancer cell mass compared to those of controls were determined. All compounds were tested in the hollow fiber assay against a 6-cell line panel consisting of the hematopoietic cell lines (K-562, MOLT-4, HL-60, SR, RPMI 8226, CCRF−CEM) as described previously.[10] The compounds were solubilized in 10% DMSO in saline/Tween-80R and administrated ip once daily for a total of four doses at each of two dose levels (150 and 100 mg/kg). The day after the last compound dose, the fibers were collected and assessed for viable cell mass. Only compounds **4c** (R═OMe), despite the poor MG_MID value reported in in vitro tests, achieved a total score 18 (out of a maximum of 24) and gave rise to a net cell kill.

The data above-described suggest that the pyrazolo-[1,2-*a*]benzo[1,2,3,4]tetrazinones **4** do behave as antitumor agent. With the aim of investigating the probable mechanism of action, preliminary DNA binding assays were carried out (data not shown), but the results were controversial, since some of the derivatives seem to interact with DNA, although it was impossible to evidence any covalent binding. Moreover, to model the biological action we carried out reaction with a purine and a pyrimidine base. However, under laboratory conditions (i.e. phosphate buffer, pH ≈8) no reaction with guanine or adenine was evidenced and again compounds of type **13** (Nu = OH) were obtained. Certainly these data are not conclusive, since solubility problems can limit the reactivity of derivatives **4** toward the nucleophile present in lower concentration. On the other hand, still other biological nucleophiles could be the final target of the generated cation, or pyrazolobenzotetrazinones may need bioactivation in vivo, a feature common to many other alkylating agents (i.e. dacarbazine or mitomycin). If ring opening of the benzotetrazine ring is the rate-determining step, an electron-withdrawing group should enhance the biological activity, but still the bioactivation can occur with a different mechanism.

To predict the probable mechanism of action, a computerized analysis COMPARE[11] was performed for the derivatives most active in vitro and in vivo, compounds **4g,b,c**, respectively. When tested as seeds against the NCI "Standard Agents" Database, the compounds showed a Pearson Correlation Coefficient (PCC) of 0.674, 0.656, and 0.734, at GI_{50} level, and a lower value, 0.617, 0.553, and 0.640, at TGI level. In all the cases the first rank was with compound S133100 (rifamycin SV), which however does not have a reported mechanism of action. We also utilized the new facility 3D-MIND[12] (drug discovery and data mining information for new directions) that allows a simultaneous examination of the information found in the DTP antitumor drug screen by using "self-organizing maps" (SOMs), which cluster these data in the high-dimensional GI_{50} space and provide a means of its visual translation into a two-dimensional anticancer map. SOM anticancer maps organize the data from tested agents into regions that share the same pattern of growth inhibition and which substantially reflect their molecular targets and modes of action. The projected cluster list gives the NSC number and the location corresponding to the projected compound. The results of this analysis on derivative **4g** indicate its location in the Q3 region map where the cytidine analogues are found and in particular derivative NSC626155. These data suggest that this class of compounds is worthy of great attention. It is our intention to undertake studies directed to elucidate the biochemical mechanism of action of this series of pyrazolo[1,2-*a*]benzo[1,2,3,4]-tetrazinones.

Conclusions

The series of pyrazolo[1,2-*a*]benzo[1,2,3,4]tetrazin-3-ones described in this paper were primarily designed to target DNA (as alkylating agents) because of their chemical reactivity. In the in vitro assays they showed inhibition of a large number of tumor cell lines at micromolar concentrations. However, their mechanism of action needs to be further elucidated, and other possible targets to be alkylated could not be excluded.

Experimental Section

Methodology of the in Vitro Cancer Screen. The human tumor cell lines of the cancer screening panel are grown in RPMI 1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine. For a typical screening experiment, cells are inoculated into 96-well microtiter plates in 100 μL at plating densities ranging from 5000 to 40 000 cells/well, depending on the doubling time of individual cell lines. After cell inoculation, the microtiter plates are incubated at 37 °C, 5% CO_2, 95% air, and 100% relative humidity for 24 h prior to addition of experimental drugs. After 24 h, two plates of each cell line are fixed in situ with TCA, to represent a measurement of the cell population for each cell line at the time of drug addition (Tz). Experimental drugs are solubilized in DMSO at 400-fold the desired final maximum test concentration and stored frozen prior to use. At the time of drug addition, an aliquot of frozen concentrate is thawed and diluted to twice the desired final maximum test concentration with complete medium containing 50 μg/mL gentamicin. Additional 4-fold, 10-fold, or $^1/_2$ log serial dilutions are made to provide a total of five drug concentrations plus control. Aliquots of 100 μL of these different drug dilutions are added to the appropriate microtiter wells already containing 100 μL of medium, resulting in the required final drug concentrations.

Following drug addition, the plates are incubated for an additional 48 h at 37 °C, 5% CO_2, 95% air, and 100% relative humidity. For adherent cells, the assay is terminated by the addition of cold TCA. Cells are fixed in situ by the gentle addition of 50 μL of cold 50% (w/v) TCA (final concentration, 10% TCA) and incubated for 60 min at 4 °C. The supernatant

is discarded, and the plates are washed five times with tap water and air-dried. Sulforhodamine B (SRB) solution (100 μL) at 0.4% (w/v) in 1% acetic acid is added to each well, and plates are incubated for 10 min at room temperature. After staining, unbound dye is removed by washing five times with 1% acetic acid, and the plates are air-dried. Bound stain is subsequently solubilized with 10 mM trizma base, and the absorbance is read on an automated plate reader at a wavelength of 515 nm. For suspension cells, the methodology is the same except that the assay is terminated by fixing settled cells at the bottom of the wells by gently adding 50 μL of 80% TCA (final concentration, 16% TCA). Using the seven absorbance measurements [time zero (Tz), control growth (*C*), and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth is calculated at each of the drug concentrations levels. Percentage growth inhibition is calculated as

$$[(\mathrm{Ti} - \mathrm{Tz})/(C - \mathrm{Tz})] \times 100$$

for concentrations for which Ti $\geq$ Tz

$$[(\mathrm{Ti} - \mathrm{Tz})/\mathrm{Tz}] \times 100$$

for concentrations for which Ti $<$ Tz

Three dose−response parameters are calculated for each experimental agent. Growth inhibition of 50% (GI_{50}) is calculated from $[(\mathrm{Ti} - \mathrm{Tz})/(C - \mathrm{Tz})] \times 100 = 50$, which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. The drug concentration resulting in total growth inhibition (TGI) is calculated from Ti = Tz. The LC_{50} (concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning), indicating a net loss of cells following treatment, is calculated from $[(\mathrm{Ti} - \mathrm{Tz})/\mathrm{Tz}] \times 100 = -50$. Values are calculated for each of these three parameters if the level of activity is reached; however, if the effect is not reached or is exceeded, the value for that parameter is expressed as greater or less than the maximum or minimum concentration tested.

Adriamycin was tested with each screening run as a quality control measure. This is done to establish the ability of the screen to generate information relevant to mechanism of growth inhibition/cell killing. It is not a reference compound that has unique importance for the compounds.

Chemistry. All melting points were taken on a Buchi-Tottoli capillary apparatus and are uncorrected; IR spectra were determined in bromoform with a Jasco FT/IR 5300 spectrophotometer; ^{1}H and ^{13}C NMR spectra were measured respectively in DMSO-d_6 solution, unless otherwise specified (TMS as internal reference), at 200 and 50.3 MHz, using a Bruker AC-E series 200 MHz spectrometer. Column chromatography was performed with Merck silica gel 230−400 mesh ASTM. Microanalyses were in agreement with theoretical values ±0.4%.

General Method for the Preparation of 2,5-Dimethyl-2-(2-nitroarylazo)-3-oxo-2,3-dihydrofurans 7a−h. To a suspension of the 2-nitroanilines **5a**−**h** (20 mmol) in water (10 mL) was added hydrochloric acid (37%, 5 mL), and the mixture was diazotized with a solution of sodium nitrite (1.48 g, 21.5 mmol) in water (8 mL) at 0 °C (only in the case of **5e** was the diazotization carried out at room temperature). The mixture was stirred for 1 h, diluted with water (50 mL), and added with concentrated hydrochloric acid (3 mL). Then, freshly distilled 2,5-dimethyl-3-oxo-2,3-dihydrofuran[13] (**6**) (2.47 g, 22 mmol) was added and the mixture was stirred for 1 h at room temperature. The solid precipitated was filtered off, washed with water, and air-dried. It was then purified by recrystallization or by column chromatography.

2,5-Dimethyl-2-(2-nitrophenylazo)-3-oxo-2,3-dihydrofuran (**7a**) was recrystallized from ethanol (yield 90%): mp 74 °C; IR 1680 (CO), 1535 and 1340 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.76 (3H, s, CH_3), 2.40 (3H, s, CH_3), 5.50 (1H, s, H-4), 7.10−8.00 (4H, m, C_6H_4); ^{13}C NMR ($CDCl_3$) ppm 17.1 (q), 18.7 (q), 103.0 (d), 108.1 (s), 118.8 (d), 124.3 (d), 130.8 (d), 133.5 (d) 140.4 (s), 143.1 (s), 146.0 (s), 190.9 (s).

2,5-Dimethyl-2-(4-methyl-2-nitrophenylazo)-3-oxo-2,3-dihydrofuran (**7b**) was recrystallized from ethanol (yield 80%): mp 71 °C; IR 1714 (CO), 1531 and 1340 (NO_2) cm^{-1}; ^{1}H NMR δ 1.62 (3H, s, CH_3), 2.46 (6H, bs, 2 × CH_3), 5.81 (1H, s, H-4), 7.28 (1H, d, J = 8.8 Hz, H-6′), 7.59 (1H, dd, J = 8.8, 1.0 Hz, H-5′), 7.95 (1H, d, J = 1.0 Hz, H-3′); ^{13}C NMR ppm 16.65 (q), 18.2 (q), 20.56 (q), 102.7 (d), 107.5 (s), 118.1 (d), 124.2 (d), 134.2 (d), 140.9 (s), 143.4 (s), 146.7 (s), 191.7 (s), 194.9 (s).

2,5-Dimethyl-2-(4-methoxy-2-nitrophenylazo)-3-oxo-2,3-dihydrofuran (**7c**) was isolated as an oil that solidified on standing (yield 98%): mp 40 °C; IR 1712 (CO), 1535 and 1338 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.73 (3H, s, CH_3), 2.43 (3H, s, CH_3), 3.90 (3H, s, OCH_3), 5.54 (1H, s, H-4), 7.07 (1H, dd, J = 8.8, 1.5 Hz, H-5′), 7.33−7.40 (2H, m, H-3′ and H-6′); ^{13}C NMR ($CDCl_3$) ppm 16.8 (q), 18.3 (q), 56.0 (q), 102.7 (d), 107.5 (s), 108.3 (d), 118.4 (d), 119.4 (d), 137.3 (s), 148.6 (s), 161.5 (s), 190.7 (s), 196.1 (s).

2,5-Dimethyl-2-(4-hydroxy-2-nitrophenylazo)-3-oxo-2,3-dihydrofuran (**7d**) was recrystallized from ethanol (yield 93%): mp 139 °C; IR 3292 (broad OH), 1688 (CO), 1585 and 1346 (NO_2) cm^{-1}; ^{1}H NMR δ 1.57 (3H, s, CH_3), 2.43 (3H, s, CH_3), 5.76 (1H, s, H-4), 7.11 (1H, dd, J = 8.8, 2.9 Hz, H-5′), 7.37 (1H, d, J = 2.9 Hz, H-3′), 7.42 (1H, d, J = 8.8 Hz, H-6′), 11.28 (1H, s, OH); ^{13}C NMR ppm 16.7 (q), 18.1 (q), 102.6 (d), 107.0 (s), 109.9 (d), 119.5 (d), 119.8 (d), 134.6 (s), 149.8 (s), 161.4 (s), 191.5 (s), 195.6 (s).

2,5-Dimethyl-2-(4-chloro-2-nitrophenylazo)-3-oxo-2,3-dihydrofuran (**7e**) was recrystallized from ethanol (yield 99%): mp 95 °C; IR 1715 (CO), 1537 and 1342 (NO_2) cm^{-1}; ^{1}H NMR δ 1.62 (3H, s, CH_3), 2.46 (3H, s, CH_3), 5.82 (1H, s, H-4), 7.41 (1H, d, J = 8.8 Hz, H-6′), 7.87 (1H, d, J = 8.8 Hz, H-5′), 8.34 (1H, s, H-3′); ^{13}C NMR ppm 16.8 (q), 18.4 (q), 102.7 (d), 107.8 (s), 120.2 (d), 124.4 (d), 134.0 (d), 136.3 (s), 141.5 (s), 147.1 (s), 191.9 (s), 194.5 (s).

2,5-Dimethyl-2-(4-fluoro-2-nitrophenylazo)-3-oxo-2,3-dihydrofuran (**7f**) was recrystallized from ethanol (yield 96%): mp 108 °C; IR 1715 (CO), 1537 and 1341 (NO_2) cm^{-1}; ^{1}H NMR δ 1.63 (3H, s, CH_3), 2.46 (3H, s, CH_3), 5.81 (1H, s, H-4), 7.51 (1H, dd, J_{HH} = 8.8 Hz, J_{FH} = 4.9 Hz, H-6′), 7.69 (1H, ddd, J_{HH} = 8.8, 2.9 Hz, J_{FH} = 8.3 Hz, H-5′), 8.19 (1H, dd, J_{HH} = 2.9 Hz, J_{FH} = 8.3 Hz, H-3′); ^{13}C NMR ppm 16.7 (q), 18.3 (q), 102.7 (d), 107.6 (s), 112.2 (d, J_{CF} = 9.6 Hz), 120.8 (d, J_{CF} = 28.3 Hz), 121.0 (d, J_{CF} = 23.1 Hz), 139.5 (s, J_{CF} = 3.9 Hz), 147.7 (s, J_{CF} = 10.5), 165.2 (s, J_{CF} = −254.1 Hz), 191.8 (s), 194.8 (s).

2,5-Dimethyl-2-(5-methyl-2-nitrophenylazo)-3-oxo-2,3-dihydrofuran (**7g**) was recrystallized from ethanol (yield 82%): mp 89 °C; IR 1713 (CO), 1522 and 1342 (NO_2) cm^{-1}; ^{1}H NMR δ 1.64 (3H, s, CH_3), 2.43 (3H, s, CH_3), 2.46 (3H, s, CH_3), 5.82 (1H, s, H-4), 7.08 (1H, s, H-6′), 7.57 (1H, d, J = 8.8 Hz, H-4′), 8.05 (1H, d, J = 8.8 Hz, H-3′); ^{13}C NMR ppm 16.7 (q), 18.3 (q), 20.8 (q), 102.7 (d), 107.6 (s), 118.5 (d), 124.6 (d), 132.1 (d), 143.6 (s), 143.9 (s), 145.6 (s), 191.7 (s), 194.7 (s).

2,5-Dimethyl-2-(5-chloro-2-nitrophenylazo)-3-oxo-2,3-dihydrofuran (**7h**) was purified by column chromatography using light petroleum ether (bp 40−60 °C):ethyl acetate 8:2 as eluant (yield 70%): mp 87 °C; IR 1716 (CO), 1537 and 1342 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.79 (3H, s, CH_3), 2.46 (3H, s, CH_3), 5.58 (1H, s, H-4), 7.18 (1H, d, J = 2.0 Hz, H-6′), 7.54 (1H, dd, J = 8.8, 2.0 Hz, H-4′), 7.98 (1H, d, J = 8.8 Hz, H-3′); ^{13}C NMR ($CDCl_3$) ppm 17.1 (q), 18.7 (q), 103.1 (d), 108.4 (s), 118.9 (d), 125.8 (d), 130.4 (d), 134.0 (2s), 145.9 (s), 191.1 (s), 196.2 (s).

General Method for the Preparation of 5-Methyl-1-(2-nitroaryl)pyrazol-3-ones 8a−h. 2,5-Dimethyl-2-(arylazo)-3-oxo-2,3-dihydrofuran **7a**−**h** (10 mmol) was added in small portions, with stirring, to concentrated hydrochloric acid (37%, 7 mL), taking care that the temperature of the mixture does not exceed 30 °C. After the addition was complete, the stirred mixture is kept at 20−30 °C, usually for 1 h. The cooled mixture was then poured onto ice water and basified with 30% aqueous sodium hydroxide. It was then diluted with water to complete dissolution of the sodium salt of the pyrazolone. The resultant solution is extracted with diethyl ether (3 × 100 mL).

The aqueous phase was acidified with diluted hydrochloric acid, with stirring and cooling, to precipitate the product. The solid was filtered off, washed with water, and air-dried.

5-Methyl-1-(2-nitrophenyl)pyrazol-3-one (**8a**) was recrystallized from ethanol (yield 94%): mp 219 °C; IR 3200 (OH), 1535 and 1345 (NO_2) cm^{-1}; ^1H NMR δ 2.24 (3H, s, CH_3), 5.66 (1H, s, H-4), 7.60−8.10 (4H, m, C_6H_4), 9.90 (1H, s, NH); ^{13}C NMR ppm 11.4 (q), 93.6 (d), 124.8 (d), 128.4 (d), 128.6 (d), 131.8 (s), 133.2 (d), 140.8 (s), 145.9 (s), 162.0 (s).

1-(4-Methyl-2-nitrophenyl)-5-methylpyrazol-3-one (**8b**) was recrystallized from ethanol (yield 88%): mp 235 °C; IR 3200 (OH), 1537 and 1345 (NO_2) cm^{-1}; ^1H NMR δ 2.15 (3H, s, CH_3), 2.45 (3H, s, CH_3), 5.61 (1H, s, H-4), 7.55−7.64 (2H, m, H-6′ and H-5′), 7.86 (1H, s, H-3′), 9.97 (1H, s, NH); ^{13}C NMR ppm 11.6 (q), 20.4 (q), 93.6 (d), 125.0 (d), 128.5 (d), 129.6 (s), 133.8 (d), 139.4 (s), 141.0 (s), 145.9 (s), 162.1 (s).

1-(4-Methoxy-2-nitrophenyl)-5-methylpyrazol-3-one (**8c**) was recrystallized from ethanol (yield 75%): mp 194 °C; IR 3200 (OH), 1535 and 1345 (NO_2) cm^{-1}; ^1H NMR δ 2.11 (3H, s, CH_3), 3.90 (3H, s, OCH_3), 5.58 (1H, s, H-4), 7.33−7.63 (3H, m, C_6H_3), 9.90 (1H, s, NH); ^{13}C NMR ppm 11.5 (q), 56.2 (q), 92.9 (d), 110.0 (d), 118.7 (d), 124.8 (s), 130.2 (d), 141.2 (s), 147.1 (s), 158.8 (s), 161.9 (s).

1-(4-Hydroxy-2-nitrophenyl)-5-methylpyrazol-3-one (**8d**) was recrystallized from ethanol (yield 92%): mp 201 °C; IR 3200 (broad OH), 1535 and 1345 (NO_2) cm^{-1}; ^1H NMR δ 2.09 (3H, s, CH_3), 5.55 (1H, s, H-4), 7.16 (1H, dd, J = 8.8, 2.9 Hz, H-5′), 7.35 (1H, d, J = 2.9 Hz, H-3′), 7.48 (1H, d, J = 8.8 Hz, H-6′), 10.29 (2H, broad, NH and OH); ^{13}C NMR ppm 11.5 (q), 92.7 (d), 11.2 (d), 119.9 (d), 123.5 (s), 130.5 (d), 141.3 (s), 147.1 (s), 157.7 (s), 161.7 (s).

1-(4-Chloro-2-nitrophenyl)-5-methylpyrazol-3-one (**8e**) was recrystallized from ethanol (yield 76%): mp 220 °C; IR 3150 (OH), 1535 and 1344 (NO_2) cm^{-1}; ^1H NMR δ 2.11 (3H, s, CH_3), 5.66 (1H, s, H-4), 7.77 (1H, d, J = 7.3 Hz, H-6′), 7.90 (1H, d, J = 7.3 Hz, H-5′), 8.21 (1H, s, H-3′), 10.10 (1H, s, NH); ^{13}C NMR ppm 11.6 (q), 94.2 (d), 125.0 (d), 129.8 (d), 130.9 (s), 132.5 (d), 133.2 (s), 141.4 (s), 146.4 (s), 162.5 (s).

1-(4-Fluoro-2-nitrophenyl)-5-methylpyrazol-3-one (**8f**) was recrystallized from ethanol (yield 95%): mp 218 °C; IR 3150 (OH), 1537 and 1364 (NO_2) cm^{-1}; ^1H NMR δ 2.17 (3H, s, CH_3), 5.64 (1H, s, H-4), 7.71 (1H, ddd, J_{HH} = 8.8, 2.9 Hz, J_{FH} = 8.8 Hz, H-5′), 7.81 (1H, dd, J_{HH} = 8.8 Hz, J_{FH} = 4.9 Hz, H-6′), 8.07 (1H, dd, J_{HH} = 2.9 Hz, J_{FH} = 8.8 Hz, H-3′), 10.06 (1H, s, NH); ^{13}C NMR ppm 11.5 (q), 93.8 (d), 118.9 (d, J_{CF} = 28.3 Hz), 120.4 (d, J_{CF} = 22.2 Hz), 128.7 (s, J_{CF} = 3.9 Hz), 130.7 (d, J_{CF} = 8.7 Hz), 141.4 (s), 146.6 (s, J_{CF} = 9.6 Hz), 162.3 (s), 162.7 (s, J_{CF} = −249.8 Hz).

1-(5-Methyl-2-nitrophenyl)-5-methylpyrazol-3-one (**8g**) was recrystallized from ethanol (yield 84%): mp 217 °C; IR 3200 (OH), 1535 and 1345 (NO_2) cm^{-1}; ^1H NMR δ 2.16 (3H, s, CH_3), 2.45 (3H, s, CH_3), 5.61 (1H, s, H-4), 7.44 (1H, dd, J = 8.8, 1.0 Hz, H-4′), 7.52 (1H, d, 1.0 Hz, H-6′), 7.92 (1H, d, J = 8.8 Hz, H-3′), 9.98 (1H, s, NH); ^{13}C NMR ppm 11.5 (q), 20.8 (q), 93.6 (d), 124.9 (d), 129.0 (d), 129.2 (d), 132.1 (s), 140.9 (s), 143.8 (s), 144.6 (s), 162.1 (s).

1-(5-Chloro-2-nitrophenyl)-5-methylpyrazol-3-one (**8h**) was recrystallized from ethanol (yield 65%): mp 228 °C; IR 3150 (OH), 1541 and 1346 (NO_2) cm^{-1}; ^1H NMR δ 2.23 (3H, s, CH_3), 5.72 (1H, s, H-4), 7.73 (1H, d, J = 8.8 Hz, H-3′), 7.95 (1H, d, J = 2.0 Hz, H-6′), 8.07 (1H, dd, J = 8.8, 2.0 Hz, H-4′), 10.12 (1H, s, NH); ^{13}C NMR ppm 11.5 (q), 94.5 (d), 126.7 (d), 128.2 (d), 128.7 (d), 133.4 (s), 137.5 (s), 141.5 (s), 144.7 (s), 162.6 (s).

Preparation of 1-(2-aminoaryl)-5-methylpyrazol-3-ones 9a−h. Method A. A solution of nitro derivatives **8a−d,f,g** (42 mmol) in ethanol was reduced overnight over 10% Pd on charcoal in a Parr apparatus at 50 psi at room temperature. Removal of the catalyst and evaporation of the solvent under reduced pressure gave a residue that was purified by recrystallization or by column chromatography.

1-(2-Aminophenyl)-5-methylpyrazol-3-one (**9a**) was recrystallized from benzene (yield 70%): mp 203 °C; IR 3480 and 3380 (NH_2), 3100 (OH) cm^{-1}; ^1H NMR δ 2.04 (3H, s, CH_3), 4.90 (2H, s, NH_2), 5.52 (1H, s, H-4), 6.40−7.32 (4H, m, C_6H_4), 9.70 (1H, s, NH); ^{13}C NMR ppm 11.5 (q), 91.1 (d), 115.2 (2d), 124.2 (s), 127.3 (d), 128.5 (d), 140.3 (s), 144.4 (s), 161.2 (s).

1-(2-Amino-4-methylphenyl)-5-methylpyrazol-3-one (**9b**) was recrystallized from ethanol (yield 72%): mp 235 °C; IR 3476 and 3381 (NH_2), 3150 (OH) cm^{-1}; ^1H NMR δ 2.00 (3H, s, CH_3), 2.20 (3H, s, CH_3), 4.85 (2H, s, NH_2), 5.49 (1H, s, H-4), 6.41 (1H, d, J = 7.4 Hz, H-5′), 6.61 (1H, s, H-3′), 6.87 (1H, d, J = 7.4 Hz, H-6′), 9.77 (1H, s, NH); ^{13}C NMR ppm 11.6 (q), 21.0 (q), 91.3 (d), 116.2 (d), 116.8 (d), 122.2 (s), 127.3 (d), 138.1 (s), 140.6 (s), 144.3 (s), 161.2 (s).

1-(2-Amino-4-methoxyphenyl)-5-methylpyrazol-3-one (**9c**) was recrystallized from ethanol (yield 88%): mp 223 °C; IR 3480 and 3382 (NH_2), 3138 (OH) cm^{-1}; ^1H NMR δ 1.99 (3H, s, CH_3), 3.70 (3H, s, OCH_3), 4.90 (2H, s, NH_2), 5.49 (1H, s, H-4), 6.20−6.37 (2H, m, H-5′ and H-3′), 6.90 (1H, d, J = 7.1 Hz, H-6′), 9.77 (1H, s, NH); ^{13}C NMR ppm 11.5 (q), 54.9 (q), 91.1 (d), 100.2 (d), 101.8 (d), 118.1 (s), 128.6 (d), 140.8 (s), 145.9 (s), 159.7 (s), 161.7 (s).

1-(2-Amino-4-hydroxyphenyl)-5-methylpyrazol-3-one (**9d**) was recrystallized from ethanol (yield 66%): mp 190 °C; IR 3476 and 3385 (NH_2), 3140 (OH), 2971 (OH) cm^{-1}; ^1H NMR δ 2.01 (3H, s, CH_3), 4.74 (2H, s, NH_2), 5.47 (1H, s, H-4), 6.03 (1H, dd, J = 8.8, 2.0 Hz, H-5′), 6.23 (1H, d, J = 2.0 Hz, H-3′), 6.78 (1H, d, J = 8.8 Hz, H-6′), 9.28 (1H, s, NH), 9.70 (1H, broad OH); ^{13}C NMR ppm 11.5 (q), 91.0 (d), 101.8 (d), 103.6 (d), 116.9 (s), 128.5 (d), 140.7 (s), 145.9 (s), 157.9 (s), 161.1 (s).

1-(2-Amino-4-fluorophenyl)-5-methylpyrazol-3-one (**9f**) was purified by chromatography using dichloromethane: methanol 95:05 as eluant and recrystallized from ethanol (yield 90%): mp 216 °C; IR 3478 and 3383 (NH_2), 3200 (OH) cm^{-1}; ^1H NMR δ 2.01 (3H, s, CH_3), 5.25 (2H, s, NH_2), 5.53 (1H, s, H-4), 6.38 (1H, ddd, J_{HH} = 8.8, 2.9 Hz, J_{FH} = 8.4 Hz, H-5′), 6.60 (1H, dd, J_{HH} = 2.9 Hz, J_{FH} =8.4 Hz, H-3′), 7.03 (1H, dd, J_{HH} = 8.8 Hz, J_{FH} = 5.9 Hz, H-6′), 9.87 (1H, s, NH); ^{13}C NMR ppm 11.4 (q), 91.7 (d), 101.5 (d, J_{CF} = 25.0 Hz), 102.2 (d, J_{CF} = 23.2 Hz), 120.7 (s, J_{CF} = 2.2 Hz), 129.3 (d, J_{CF} = 11.3 Hz), 140.9 (s), 146.8 (s, J_{CF} = 12.5 Hz), 160.0 (s), 164.8 (s, J_{CF} = −241.4 Hz).

1-(2-Amino-5-methylphenyl)-5-methylpyrazol-3-one (**9g**) was recrystallized from ethanol (yield 88%): mp 205 °C; IR 3449 and 3364 (NH_2), 3140 (OH) cm^{-1}; ^1H NMR δ 2.02 (3H, s, CH_3), 2.17 (3H, s, CH_3), 4.74 (2H, s, NH_2), 5.52 (1H, s, H-4), 6.73 (1H, d, J = 7.8 Hz, H-3′), 6.83 (1H, d, J = 2.0 Hz, H-6′), 6.92 (1H, dd, J = 7.8, 2.0 Hz, H-4′), 9.61 (1H, s, NH); ^{13}C NMR ppm 11.6 (q), 19.9 (q), 91.5 (d), 116.1 (d), 124.4 (s), 124.8 (s), 127.7 (d), 129.4 (d), 140.5 (s), 142.0 (s), 161.3 (s).

Method B. Iron powder (670 mg, 12 mmol) was added to a solution of nitro derivative **8e**,**h** (3.4 mmol) in acetic acid (30 mL). The mixture was kept at 60 °C in a steam bath for 24 h. The reaction mixture was cooled, poured onto crushed ice, and extracted with dichloromethane. The organic layer, dried over sodium sulfate and evaporated under reduced pressure, gave a residue that was purified by by recrystallization or by column chromatography.

1-(2-Amino-4-chlorophenyl)-5-methylpyrazol-3-one (**9e**) was recrystallized from ethanol (yield 90%): mp 216 °C; IR 3478 and 3383 (NH_2), 2924 (OH) cm^{-1}; ^1H NMR δ 2.02 (3H, s, CH_3), 5.29 (2H, s, NH_2), 5.53 (1H, s, H-4), 6.60 (1H, dd, J = 8.8, 2.9 Hz, H-5′), 6.85 (1H, d, J = 2.9 Hz, H-3′), 7.00 (1H, d, J = 8.8 Hz, H-6′), 9.88 (1H, s, NH); ^{13}C NMR ppm 11.5 (q), 91.9 (d), 114.8 (d), 115.2 (d), 123.0 (s), 129.0 (d), 132.9 (s), 140.8 (s), 146.1 (s), 161.5 (s).

1-(2-Amino-5-chlorophenyl)-5-methylpyrazol-3-one (**9h**) was purified by chromatography using light petroleum ether (bp 40−60 °C):ethyl acetate 8:2 as eluant (yield 90%): mp 210 °C; IR 3418 and 3343 (NH_2), 2950 (OH) cm^{-1}; ^1H NMR δ 2.04 (3H, s, CH_3), 5.16 (2H, s, NH_2), 5.54 (1H, s, H-4), 6.82 (1H, d, J = 8.8 Hz, H-3′), 7.10 (1H, dd, J = 8.8, 2.0 Hz, H-4′), 7.16 (1H, d, J = 1.95 Hz, H-6′), 9.93 (1H, s, NH); ^{13}C NMR ppm 11.5 (q), 92.0 (d), 117.0 (d), 118.5 (s), 124.8 (s), 126.9 (d), 128.6 (d), 140.9 (s), 143.8 (s), 161.6 (s).

General Method for the Preparation of 1-Methyl-8-R-9-R′-3*H*-pyrazolo[1,2-*a*]benzo[1,2,3,4]tetrazin-3-ones 4a−

h. Concentrated sulfuric acid (0.4 mL) was added to a solution of the amine **9a**−**h** (1.9 mmol) in water (10 mL) and the mixture was diazotized with sodium nitrite (145 mg, 2.1 mmol) in water (10 mL) at 0 °C. The reactants were stirred for 2 h further at room temperature, and then were kept at 60 °C for 3 h. The mixture was cooled to room temperature and made basic with solid sodium carbonate. The solid precipitate was filtered off and air-dried.

1-Methyl-3*H*-pyrazolo[1,2-*a*]benzo[1,2,3,4]tetrazin-3-one (**4a**) (yield 91%): mp 190 °C (dec); IR 1660 (CO) cm^{-1}; ^1H NMR δ 2.50 (3H, s, CH_3), 6.08 (1H, s, H-2), 7.70−8.20 (2H, m, H-9 and H-10), 8.30−8.70 (2H, m, H-7 and H-8); ^{13}C NMR ppm 13.3 (q), 101.2 (d), 109.7 (s), 128.6 (d), 131.8 (d), 136.5 (d), 140.6 (s), 145.1 (d), 150.0 (s), 165.7 (s).

1,8-Dimethyl-3*H*-pyrazolo[1,2-*a*]benzo[1,2,3,4]tetrazin-3-one (**4b**) (yield 91%): mp 147 °C (dec); IR 1678 (CO) cm^{-1}; ^1H NMR δ 2.35 (3H, s, CH_3), 2.62 (3H, s, CH_3), 5.57 (1H, s, H-2), 7.23−7.49 (2H, m, H-9 and H-10), 7.64 (1H, s, H_7); ^{13}C NMR ppm 14.7 (q), 20.0 (q), 93.5 (d), 113.5 (d), 122.7 (s), 125.3 (s), 128.2 (s), 129.1 (d), 134.9 (d), 144.9 (s), 156.7 (s).

1-Methyl-8-methoxy-3*H*-pyrazolo[1,2-*a*]benzo[1,2,3,4]-tetrazin-3-one (**4c**) (yield 90%): mp 155 °C (dec); IR 1660 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.63 (3H, s, CH_3), 3.87 (3H, s, OCH_3), 5.51 (1H, s, H-2), 7.03 (1H, dd, J = 8.8, 2.9 Hz, H-9), 7.25 (1H, d, J = 8.8 Hz, H-10), 7.37 (1H, d, J = 2.9 Hz, H-7); ^{13}C NMR ($CDCl_3$) ppm 15.3 (q), 55.9 (q), 85.0 (d), 98.8 (s), 113.4 (d), 113.7 (d), 116.8 (s), 120.5 (d), 125.5 (s), 142.4 (s), 157.4 (s).

8-Hydroxy-1-methyl-3*H*-pyrazolo[1,2-*a*]benzo[1,2,3,4]-tetrazin-3-one (**4d**) (yield 60%): mp >290 °C; IR 3160 (broad OH), 1597 (CO) cm^{-1}; ^1H NMR δ 2.16 (3H, s, CH_3), 5.50 (1H, s, H-2), 6.84−7.63 (3H, m, H_7, H-9 and H-10), 9.79 (1H, broad OH); ^{13}C NMR ppm 18.6 (q), 92.5 (d), 115.4 (d), 125.5 (d), 128.5 (d), 131.6 (s), 139.3 (s), 140.5 (s), 156.1 (s), 160.9 (s).

8-Chloro-1-methyl-3*H*-pyrazolo[1,2-*a*]benzo[1,2,3,4]-tetrazin-3-one (**4e**) (yield 80%): mp 158 °C (dec); IR 1680 (CO) cm^{-1}; ^1H NMR δ 2.67 (3H, s, CH_3), 5.70 (1H, s, H-2), 7.69 (1H, d, J = 8.8 Hz, H-10), 7.58 (1H, d, J = 8.8 Hz, H-9), 7.96 (1H, s, H-7); ^{13}C NMR ppm 15.5 (q), 96.2 (d), 113.3 (d), 129.8 (d), 129.9 (s), 133.7 (d), 135.5 (s), 143.5 (s), 157.1 (s), 197.3 (s).

8-Fluoro-1-methyl-3*H*-pyrazolo[1,2-*a*]benzo[1,2,3,4]-tetrazin-3-one (**4f**) (yield 77%): mp 143 °C (dec); IR 1672 (CO) cm^{-1}; ^1H NMR δ 2.62 (3H, s, CH_3), 5.60 (1H, s, H-2), 7.48 (1H, ddd, J_{HH} = 8.8, 2.9 Hz, J_{FH} = 9.8 Hz, H-9), 7.57 (1H, dd, J_{HH} = 8.8 Hz, J_{FH} = 4.9 Hz, H-10), 7.75 (1H, dd, J_{HH} = 2.9 Hz, J_{FH} = 8.8 Hz, H-7); ^{13}C NMR ppm 14.7 (q), 93.5 (d), 115.5 (d, J_{CF} = 18.3 Hz), 115.7 (d, J_{CF} = 15.3 Hz), 121.1 (d, J_{CF} = 23.3 Hz), 124.6 (s, J_{CF} = 3.1 Hz), 129.3 (s, J_{CF} = 9.0 Hz), 145.6 (s), 156.5 (s), 161.3 (s, J_{CF} = −238.8 Hz).

1,9-Dimethyl-3*H*-pyrazolo[1,2-*a*]benzo[1,2,3,4]tetrazin-3-one (**4g**) (yield 77%): mp 151 °C (dec); IR 1680 (CO) cm^{-1}; ^{1} H NMR δ 2.40 (3H, s, CH_3), 2.65 (3H, s, CH_3), 5.59 (1H, s, H-2), 7.15 (1H, d, J = 7.8 Hz, H-8), 7.36 (1H, s, H-10), 7.67 (1H, d, J = 7.8 Hz, H-7);^{13}C NMR ppm 14.9 (q), 21.7 (q), 94.2 (d), 113.6 (d), 126.4 (d), 127.4 (s), 128.9 (d), 145.0 (s), 145.9 (2s), 156.7 (s).

9-Chloro-1-methyl-3*H*-pyrazolo[1,2-*a*]benzo[1,2,3,4]-tetrazin-3-one (**4h**) (yield 60%): mp 137 °C (dec); IR 1663 (CO) cm^{-1}; ^1H NMR δ 2.66 (3H, s, CH_3), 5.66 (1H, s, H_2), 7.38 (1H, d, J = 7.8 Hz, H-8), 7.49 (1H, s, H-10), 7.78 (1H, d, J = 7.8 Hz, H-7); ^{13}C NMR ppm 14.5 (q), 94.9 (d), 113.4 (d), 125.7 (d), 126.1 (s), 128.6 (s), 130.4 (d), 138.4 (s), 145.9 (s), 156.5 (s).

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Supporting Information Available: Elemental analyses and tables of full biological data. This material is available free of charge via the Internet at http://pubs.acs.org

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