

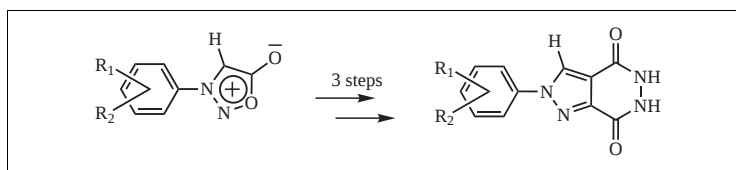
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Dedicated to Dr.G.S.Puranik, P.G.Department of Studies in Chemistry, Karnatak University, Dharwad, on his 75th birthday.

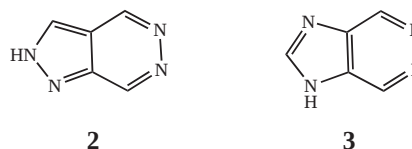


The synthetic utility of 1,3-dipolar cycloaddition of DMAD to sydnones has been exploited in the preparation of new 1-aryl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyridazine-3,6-diones **7a-j** and their aromatic 3,6-dichloro analogues **8a-j**. The lactam-lactim tautomerism of compound **7a** has been studied by the semi empirical (PM3) and *ab initio* methods.

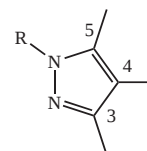
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Introduction.

Sydnones form a class of mesoionic compounds which undergo a wide variety of reactions [1]. In spite of their aromaticity, they behave as potential 1,3-dipolar systems undergoing cycloaddition reactions with different dipolarophiles [1,2]. The ability of sydnone ring to undergo 1,3-dipolar cycloaddition reactions has been extensively used in heterocyclic ring construction [1]. It provides a one-pot facile and convenient means of synthesizing a wide variety of five membered ring nitrogen heterocycles. Many such synthetic uses of sydnones have been reported earlier from this laboratory [3-5]. In continuation of these ongoing studies directed towards the construction of 5-membered 1,2-diaza - Nitrogen heterocycles mediated by sydnones, we thought of further exploiting the 1,3-dipolar cycloaddition chemistry of the sydnone ring for the synthesis of some fused heterocyclic systems, which are difficult and lengthy or inaccessible by routine methods. Now, in the present work, we have used the 1,3-cycloadduct of sydnone with DMAD as an important intermediate in converting some 3-arylsydnonones **1a-j** to the so far unknown 1*H*-pyrazolo[3,4-*d*]pyridazine derivatives **2** – the 1-aryl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyridazine-3,6-diones (**7a-j**). Despite the similarities of the pyrazolo[3,4-*d*]pyridazine system **2** with the purine analogs - 1*H*-imidazo[4,5-*d*]pyridazines **3** [6a], the former have not been extensively studied.



This has been mainly due to the scarcity of synthetic methods and inherent difficulties in the existing ones and so, not much work has been reported on their synthesis. Their biological properties are also not well understood. Only two recent reports [6b,6c] cited in the literature have claimed *in vitro* antimicrobial activities for a series of compound **2** derivatives (the former work is from our laboratory). The key step in obtaining compounds **2** is the synthesis of the precursors - the 3,4-functionalised pyrazoles **4** (only C3-COR & C4-COX; C3-COCH₃ & C4-CO₂Et with C5- CH₃ & C₆H₅ are reported [7]).



The most general synthetic approach to obtain these precursors involves the base (NaOEt) induced reaction of alpha-hydrazinohalides and beta-carbonyl compounds, which in turn are obtained by elaborate processes [7,7a]. Further conversion of these pyrazoles into the pyrazolo-[3,4-*d*]pyridazines follows a simple cyclisation with hydrazine hydrate. However, the hitherto unknown corresponding C-5H compounds are not accessible by this

method and now we demonstrate the use of sydrones for the facile synthesis of such compounds.

Our synthetic strategy, that we have found to be of importance in the design of one-pot, simple and alternate process for the synthesis of these *ortho*-functionalised pyrazoles, involved the cycloaddition of DMAD to 3-arylsydrones **1a-j** to give the dimethyl-1-aryl-1*H*-pyrazole-3,4-dicarboxylates **5a-j** in quantitative yields and high purity. This reaction proceeds smoothly in dry xylene at 120 °C. The synthesis of some such substituted aryl derivatives have been earlier reported from our laboratory [8a,8b,8c]. These compounds are the key intermediates in the synthesis of the title compounds **8a-j**.

This approach provides a shorter route (the 3-arylsydrones are readily obtained by simple procedure from the easily available and inexpensive aromatic amines [9]), useful, practical protocol for the present work and compares favourably in terms of the use of simple reagents and avoids the use of solvent. Hence, it is a cost and time efficient synthesis for the pyrazolo[3,4-*d*]-pyridazine system **2**.

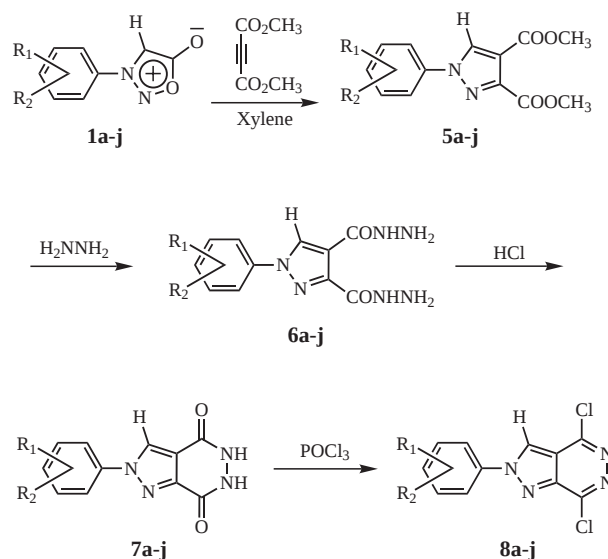
Results and Discussion.

The dimethyl-1-aryl-1*H*-pyrazole dicarboxylates **5a-j** when refluxed with hydrazine hydrate (99 %) in ethanol gave the bishydrazides **6a-j** instead of the cyclic products **7a-j**. There have been conflicting reports on the hydrazinolysis products of pyrazole diesters. While some workers have reported the formation of bishydrazides [10], others have reported the direct cyclisation to the pyrazolo[3,4-*d*]pyridazine system [6c,7]. However, we have observed the formation of only the bishydrazides **6a-j** for all the pyrazole diesters we have synthesised. The cyclisation to the pyridazine system was not observed even after prolonged heating (~ 40 hrs). The bishydrazides needed refluxing with hydrochloric acid to get the desired 1-aryl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyridazine-3,6-diones **7a-j**. These diones **7a-j** on heating with phosphorous oxychloride aromatised to give the target compounds – 1-aryl-3,6-dichloro-1*H*-pyrazolo[3,4-*d*]pyridazines **8a-j** (Scheme 1).

Conclusions.

The synthetic utility of 1,3-dipolar cycloaddition of sydnone provides a short and efficient route for the 5-substituted / unsubstituted pyrazolo[3,4-*d*]pyridazines in good overall yields. Starting from an aromatic amine, the precursor *i.e.* the *ortho*-functionalised pyrazoles **5a-j** – the key intermediates, are obtained in ~ 90 % yield in only four steps *via* sydrones, while the reported method [7], also starting from the primary amines involves the multistep synthesis of substituted hydrazones and then cyclisation to compound **2** with expensive substituted β -diketones. This work underlines the importance of

Scheme 1



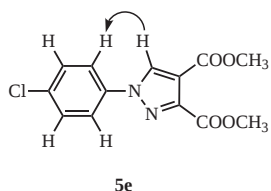
- (a) R_1 & R_2 = H; (b) R_1 = H; R_2 = 4-Br; (c) R_1 = H; R_2 = 4-CH₃;
 (d) R_1 = H, R_2 = 2-Cl; (e) R_1 = H; R_2 = 4-Cl; (f) R_1 = H, R_2 = 2-OCH₃;
 (g) R_1 = H; R_2 = 4-OCH₃; (h) R_1 = H; R_2 = 4-OCH₂CH₃;
 (i) R_1 = 3-Cl; R_2 = 4-CH₃; (j) R_1 = 3-NO₂, R_2 = 4-CH₃.

sydrones as synthons in heterocyclic synthesis and it's 1,3-dipolar cycloaddition reaction which provides a prominent synthetic method for rapid construction of functionalized heterocycles, often which are obtained with difficulty and by lengthy procedures. The synthesis of many more such compounds, with different heterocyclic systems on the phenyl ring is in progress and will be submitted as a separate paper shortly.

Spectral Characterization.

The IR spectra of all the pyrazole dicarboxylates **5a-j** show two intense bands at 1740 and 1702 cm⁻¹ assignable to the two ester carbonyl groups at C3 and C4 positions respectively. The pyrazole ring γ_{C-H} appears as a medium intensity band at 3133 cm⁻¹. The ¹H-NMR (300MHz) spectra of these compounds show two singlets at δ 4.08 and δ 3.85 ppm for the methyl protons of the C-3 and the C-4 ester groups respectively and the assignment of these signals are done on the basis of the low electron density at the 3-position of pyrazoles [11], which is also evidenced by the reported ¹³C -NMR data (C3 at δ 133 & C4 at δ 105 ppm) [11a]. This is also the reason why electrophilic substitution reactions of pyrazoles take place only at 4-position and not at 3 or 5. The pyrazole proton appears at δ 8.45 ppm, while the aryl protons resonate at δ 7.50 - 7.75 ppm. The ¹H-NMR NOE difference spectrum of one compound – the *p*-chlorophenyl derivative **5e**, shows an enhancement in the intensity of the signal for the aromatic proton at δ 7.75 (*ortho* to pyrazole), when the pyrazole ring proton is double irradiated. This indicates a close

proximity between the pyrazole proton and the *ortho*-protons of the phenyl ring. The single crystal X-ray studies of one such compound **5i** which we have been able to document [12] for further structural insight, showed a distance of 2.28 Å between these two protons, which accounts for the above NOE result. In the displacement ellipsoids drawn at the 50% probability level, a low torsional angle of 8.66° was observed between the phenyl and the pyrazole rings.



The IR spectra of the 1-arylpyrazole-3,4-dicarbohydrazides (**6a-j**) show bands at 3395 cm⁻¹ and 3300 cm⁻¹ due to $\gamma_{\text{N-H}}$ stretching vibrations. The pyrazole $\gamma_{\text{C-H}}$ band is observed at 3180 cm⁻¹. The amide carbonyl stretching bands appear at 1644 and 1581 cm⁻¹ while the $\delta_{\text{N-H}}$ bending bands are at 1521 and 1500 cm⁻¹.

The ¹H-NMR (300 MHz) spectra of all these compounds show a broad signal at δ 3.90 corresponding to four protons of NH₂, while the two NH protons resonate at δ 10.01 and δ 11.40 ppm. All these signals disappeared in the D₂O exchange spectrum. The pyrazole proton appears at δ 8.95 and the aromatic protons resonate at δ 7.50 δ - 7.95 ppm.

The IR spectra of the corresponding diones (**7a-j**) show only one band at 1672 cm⁻¹ assignable to CO and a broad band in the region 3200-3450 cm⁻¹ which could be due to the NH and probably the OH stretchings also. These data indicate the existence of the mono lactam form **7-II** or **7-III** and not the dione **7-I** or the diol **7-IV** for these compounds (Figure 1).

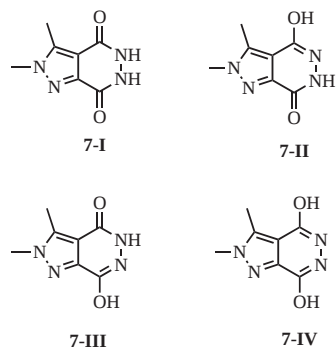


Figure 1

This lactam-lactim tautomer (**7-II** or **7-III**) was also evident from the ¹H-NMR spectra which show signals at δ

8.01 and another at δ 11.15 ppm which are both D₂O exchanged. The large differences in these chemical shifts indicate that both are neither due to the two NH (**7-I**) or two OH (**7-IV**). Hence, these two signals could be assigned to a lactam NH and a lactim OH group. Based on the extent of dehieling, the former signal was assigned to the NH and the latter to the OH. Such lactam-lactim tautomers have been reported for similar types of diones [7]. A more detailed consideration of the tautomerism in these systems has been studied by computational methods. The pyrazole C-5H in these compounds is slightly deshielded due to the proximity of OH /C=O and resonates at δ 9.15.

The IR spectra of the dichloro compounds (**8a-j**) show the absence of CO, NH or OH bands indicating the aromatisation of the ring. The ¹H-NMR spectra show the pyrazole proton resonating at δ 8.64 ppm and other signals only for the aromatic protons.

Computational Studies.

The phenomenon of tautomerism is thought to play a major role in determining the chemical and biological activity of several compounds and in particular the N-heterocycles related to the nucleic acid bases. We thought that these newly synthesized compounds – 1-aryl-4,5-dihydro-1H-pyrazolo[3,4-*d*]pyridazine-3,6-diones **7a-j** would be ideal for the theoretical investigations since they can theoretically exist in four tautomeric forms - the dilactam form **PP-1**, two monolactam forms **PP2** and **PP3a** and its rotamer **PP3b** and the dilactim rotamers **PP4a** and **PP4b** (Figure 2).

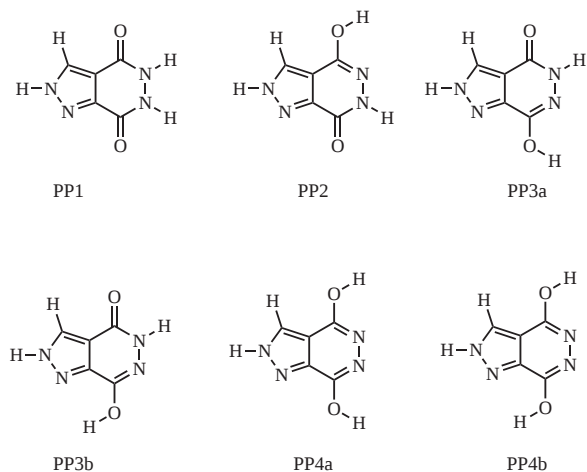
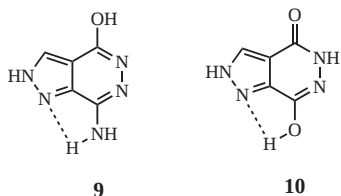


Figure 2

Such pyridazine diones have been reported [7] to exist in the monolactam form **PP3b**, based on their UV, IR and ¹H-NMR spectral studies. Structure **PP3b** was proposed as the preferred tautomer based solely on the resemblance

of the UV and ^1H -NMR spectra with that of compound **9**. There being a possibility of hydrogen bonding in structure **PP3b** as shown in **10**, this would be relatively more stable than the monolactam form **PP3a**.



However, we found these studies inadequate for such molecules, so we have used the Molecular Orbital methods – Semiempirical (PM3) and *ab initio* methods to study the tautomeric preference in these diones and we find that our calculations to be more accurate compared to the qualitative treatment reported earlier [7]. To our knowledge, this appears to be the first documentation of computational studies for such a system.

The spectral data of the pyridazine diones synthesized in the present work, also indicate the existence of the monolactam forms. However, the spectral studies alone do not reveal which of the two monolactam forms is preferred. In the present work we have used both semi empirical (PM3) and *ab initio* methods to study the tautomerism in the parent system and restricted ourselves to a PM3 study of 1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyridazine-3,6-dione **7a**.

All the structures considered in this study were first optimized using the PM3 [13] method as implemented in MOPAC [14]. The PM3 optimized structures were then subjected to energy minimization at the Restricted Hartree-Fock (RHF) level using the standard split valence 6-31G basis set, augmented with a d polarization function on the heavy atom [15]. All the stationary points were characterized as minima (NIMG = 0) by their vibrational analysis at the same level. Second order Moller-Plesset [16] (MP2) calculations were then carried out on the HF/6-31G* geometries to get improved energy comparison. The zero point energy obtained at the HF/6-31G* level were scaled by 0.9135 [17] to account for the systematic overestimation of ZPE at this level. All the *ab initio* calculations were carried out using the PC [18] version of GAMESS [19].

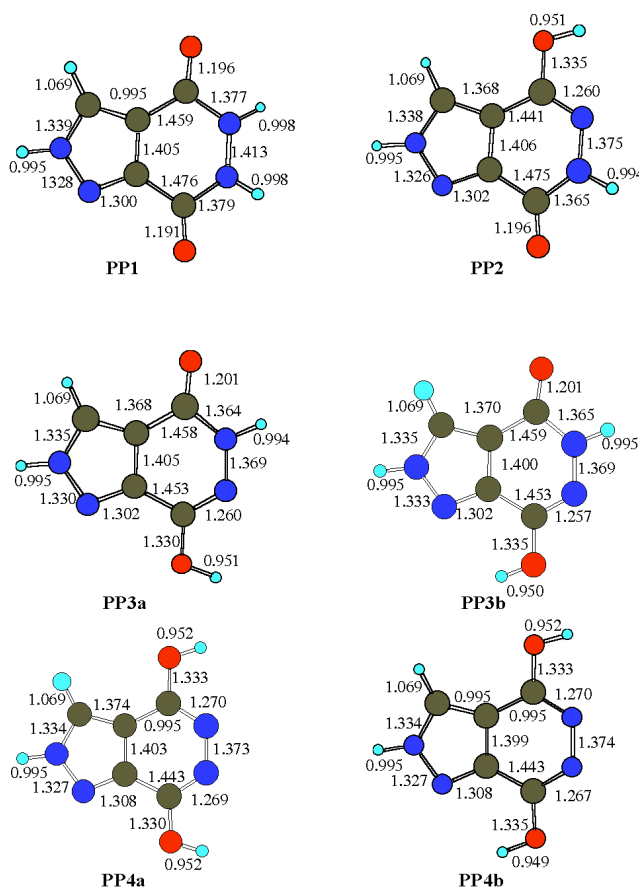
Results.

A) Tautomerism in 1*H*-pyrazolo[3,4-*d*]pyridazine-3,6-dione.

Geometries of the six equilibrium structures we have located are shown in Scheme 2. The relative energies in kcal mol⁻¹ and absolute energies in Hartrees are given in Table 1. All the minimized structures have C_s symmetry

except the dilactam form **PP1**, where both the pyridazine nitrogens are puckered from the plane of the ring. The bond distances and the bond angles are depicted in Scheme 2 and 3 respectively.

Scheme 2



Bond lengths (in Angstroms) at HF/6-31G8

As Scheme 2 shows, we have found two minima for the monolactam form, one when the N6-O7-O-H dihedral angle is equal to 0 °C (**PP3a**) and another when it is 180 °C (**PP3b**). The dilactim form also shows two equilibrium geometries, **PP4a** and **PP4b** with N6-O7-O-H dihedral angle of 0 °C and 180 °C respectively. The relative energies of the equilibrium geometries calculated by *ab initio* method without electronic correlation (HF) differs from that of the MP2 calculations. The energetic order is **PP1**<**PP3a**<**PP2**<**PP3b**<**PP4a**<**PP4b** at the HF/6-31G* level while at the MP2 level it is **PP3a**<**PP2**<**PP3b**<**PP1**<**PP4a**<**PP4b**. The semi empirical PM3 method also predicts a stability order similar to the MP2 calculations. The dioxo form **PP1** which is predicted to be more stable than **PP3a** at the HF

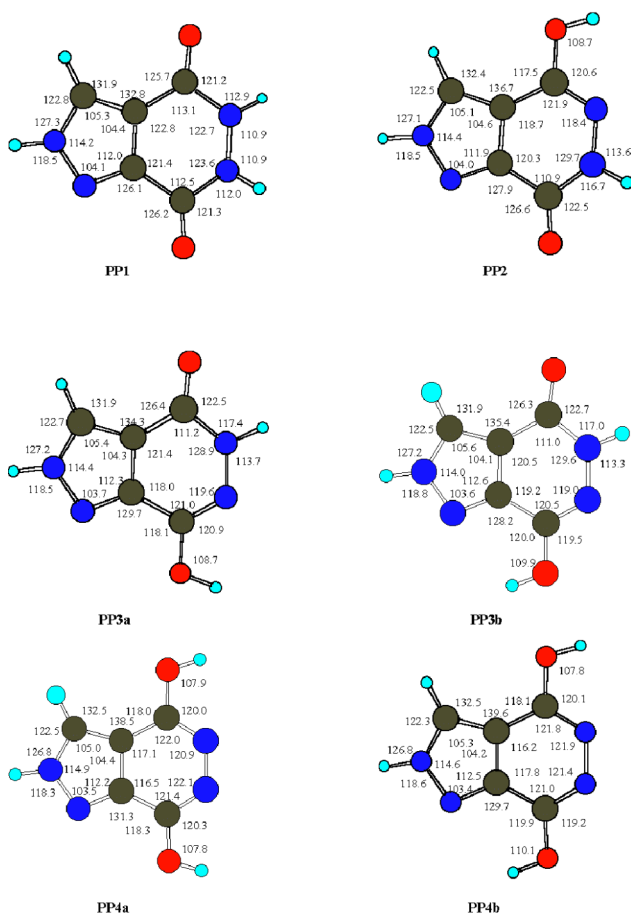
Table 1
Relative Energies (Kcal mol⁻¹) of the Tautomers of 1*H*-Pyrazolo[3,4-*d*]pyridazines-3,6-dione

	PP1	PP2	PP3a	PP3b	PP4a	PP4b
PM3 ^a	5.53	3.87	3.10	3.51	3.38	9.40
HF/6-31G*	-0.45	1.79	0.00	2.26	15.38	19.38
			(-559.147795)			
ZPE ^c	0.104231	0.104239	0.104259	0.104034	0.103812	0.103444
MP2(fc)//HF/6-31G*	2.51	1.02	0.00	1.95	11.62	15.41
			(-560.769710)			
	2.65	1.04	0.00	1.93	11.72	15.49
MP2(full)//HF/6-31G*			(-560.816474)			
HF//HF/6-31G*+ZPE ^c	-0.47	1.78	0.00	2.12	15.10	18.87
MP2(fc)//HF/6-31G*+ZPE ^c	2.49	1.00	0.00	1.81	11.34	14.90
MP2(full)//HF/6-31G*+ZPE	2.64	1.03	0.00	1.79	11.44	14.98

^a PM3 Heat of formation in Kcal mol⁻¹. ^b The values in parentheses are absolute energies(in Hartrees). ^c Zero point energy obtained at the HF/6-31G*level, scaled by 0.9135.

level by 0.47 kcal mol⁻¹, is found to be of higher energy (2.64 kcal mol⁻¹) then **PP3a** at the MP2 (full) level.

Scheme 3



Bond angles(in degree) at HF/6-31G*

Thus, the gas phase *ab initio* calculations indicate a preference of pyrazolo[3,4-*d*]pyridazine diones to exist in the mono lactam form **PP3a**. The other mono lactam form **PP2** is the next most stable tautomer. This tendency of pyrazolo[3,4-*d*]pyridazines to exist in the mono lactam form is not surprising since such a preference has been observed in other cyclic hydrazide compounds like phthalhydrazide [20].

B) Tautomerism in 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyridazine-4,7-dione.

We have used only the computationally less demanding PM3 semi empirical method for studying this compound. The equilibrium geometries located are shown in Scheme 4 & 5.

We have found two minima for each of the structures with identical bond lengths and bond angles; one in which the phenyl ring is coplanar with the pyrazolo[3,4-*d*]pyridazine ring and another in which it is twisted by an angle ranging between 22 to 29°. Both the structures differ slightly in their heat of formation (ΔH_f). The heat of formation of all the geometries are tabulated in Table 2.

The introduction of a phenyl ring does not considerably change the geometrical parameters and the relative order of stability of the tautomers of the pyrazolo[3,4-*d*]pyridazine-4,7-dione system. The order of stability also remain unchanged, with the monolactam form **P3a** predicted to be the most stable structure. The structure **P3b** where there is a possibility of interaction between the pyrazole N2 and lactim hydrogen is also of comparable energy while the other mono lactam form **P2** is of slightly higher energy. The dilactam form **P1** has around 1.6 kcal mol⁻¹ higher ΔH_f than the most stable structure **P3a**. The dilactim forms (**P4a** and **P4b**) have the highest ΔH_f

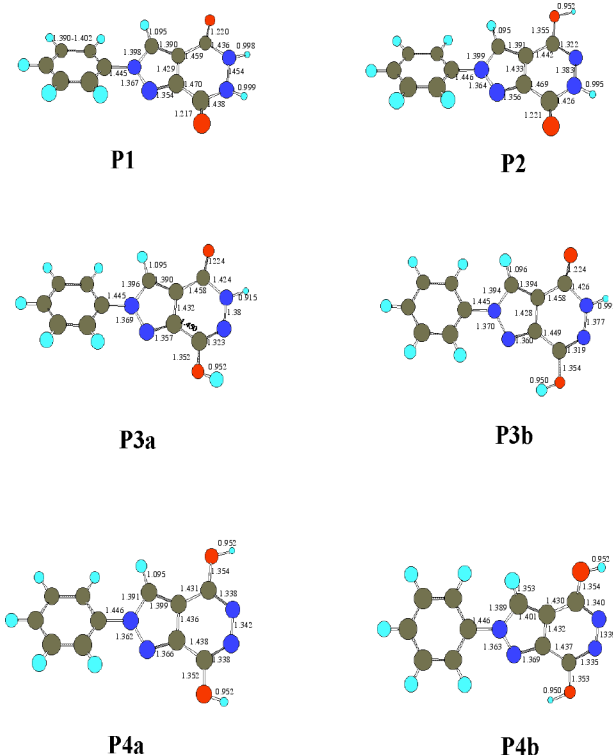
Table 2
PM3 Heat of Formation of 1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyridazine-3,6-dione

	P1	P2	P3a	P3b	P4a	P4b
ΔH_f	34.51 ($\Phi = 00.0$)	32.89 ($\Phi = 00.0$)	32.15 ($\Phi = 00.0$)	32.57 ($\Phi = 00.0$)	37.59 ($\Phi = 00.0$)	38.63 ($\Phi = 00.0$)
	34.61 ($\Phi = 22.1$)	33.02 ($\Phi = 22.3$)	32.26 ($\Phi = 23.6$)	32.64 ($\Phi = 27.6$)	37.71 ($\Phi = 25.9$)	38.70 ($\Phi = 29.1$)

¹ Φ refers to the dihedral angle between the phenyl and the pyrazolo[3,4-*d*]pyridazine ring

values, ~6.5 kcal mol⁻¹ higher than **P3a** (Table 2). These calculations thus indicate a general preference of the pyrazolo[3,4-*d*]pyridazine-4,7-dione to exist in the mono lactam form **P3a**.

Scheme 4



PM3 Geometries of 1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyridazine-3,6-dione (Bond lengths).

EXPERIMENTAL

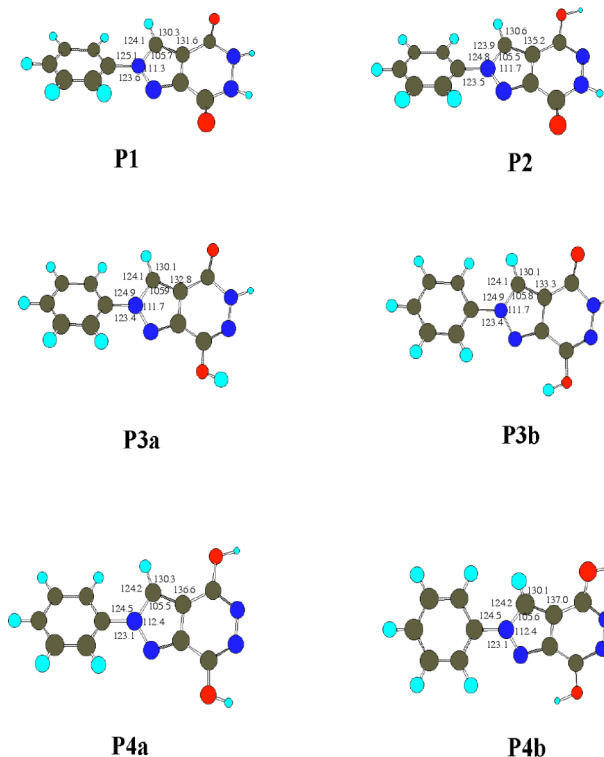
General Procedures.

Dimethyl-1-aryl-1*H*-pyrazole-3,4-dicarboxylates (**5a-j**).

Compounds **5a-g** have been reported earlier [8,8a,8b,8c] and now compounds **5h,i,j** are also prepared by this reported method.

To a solution of 3-arylsydnone **1a-j** (0.005 mol) in dry xylene (4 ml), dimethylacetylenedicarboxylate (0.71 g, 0.005 mol) was added and the reaction mixture heated at 120 °C till

Scheme 5



PM3 Geometries of 1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyridazine-3,6-dione (Bond angles).

the evolution of carbon dioxide ceased (~ 1 hr). The solvent was removed under reduced pressure and the residue triturated with petroleum ether (60-80 °C). The white solid obtained was recrystallised from ethanol. **5h** (yield 94 %). m.p. 102-104 °C. ¹H NMR (CDCl₃): δ 8.40 (s,1H, pyrazole C5-H), 7.50 (d, 2H, J= 8.0 Hz), 7.42 (d, 2H, J= 8.0 Hz), 4.2 (q, 2H) 4.00 (s, 3H), 3.80 (s, 3H), 1.3 (s,3H). Mass calcd. for C₁₅H₁₆N₂O₅; 304; found: 304.

Anal. Calcd. for C₁₅H₁₆N₂O₅ C, 59.21; H, 5.26; N,9.21 %; Found C, 59.01; H, 4.88; N,8.81 %.

5i m.p. 96-98 °C. (yield 99 %). ¹H NMR (CDCl₃): δ 8.40 (s,1H, pyrazole C5-H), 7.50 – 7.30 (m, 3H,Ar), 4.00 (s,3H), 3.80 (s,3H), 2.3 (s,3H). Mass calcd. for C₁₄H₁₃N₂O₄Cl: 308 & 310; Found: 308 & 310.

Anal. Calcd. for C₁₄H₁₃N₂O₄Cl C, 54.54; H,4.22; N,9.09%; Found C, 54.23; H,4.19 N,8.69 %.

5j m.p. 122-124 °C. (yield 96 %). ¹H NMR (CDCl₃): δ 8.40 (s, 1H, pyrazole C5-H), 7.90 (s, 1H, Ar), 7.60 (d, 1H, J=8.1, Ar), 7.82 (d, 1H, J=8.1, Ar), 4.00 (s, 3H), 3.80 (s, 3H), 2.3 (s, 3H). Mass Calcd. for C₁₄H₁₃N₃O₆: 319; found: 319.

Anal. Calcd. for C₁₄H₁₃N₃O₆ C, 52.67; H, 4.10; N, 13.16 %; Found C, 52.39; H, 4.00; N, 12.79 %.

1-Arylpyrazole-3,4-dicarbohydrazides (**6a-j**).

To a solution of **5a-j** (0.003 mol) in 10 ml of ethanol, hydrazine hydrate (99-100%, 1.46 ml, 0.03 mol) was added and the reaction mixture refluxed for 5 hours. The white solid that separated on cooling was collected by filtration, washed with water and dried. Recrystallisation was done from ethanol/DMF.

6a m.p. 210-213 °C. (yield 79 %). ¹H NMR (CDCl₃): δ 11.37 (br, 1H), 10.11 (br, 1H), 8.91 (s, 1H, pyrazole C5-H), 7.80-7.70 (m, 5H, Ar), 3.67 (br, 4H).

Anal. Calcd. for C₁₁H₁₂N₆O₂ C, 50.77; H, 4.65; N, 32.29 %; Found C, 50.46; H, 4.22; N, 31.71 %.

6b m.p. 225-227 °C. (yield 87 %). ¹H NMR (CDCl₃): δ 11.37 (br, 1H), 10.11 (br, 1H), 8.91 (s, 1H, pyrazole C5-H), 7.50 (d, 2H, J= 8.1 Hz, Ar), 7.42 (d, 2H, J= 8.1 Hz, Ar), 3.67 (br, 4H).

Anal. Calcd. for C₁₁H₁₁N₆O₂Br C, 38.96; H, 3.27; N, 24.78 %; Found C, 38.60; H, 3.01; N, 24.35 %.

6c m.p. 201-204 °C. (yield 88 %). ¹H NMR (CDCl₃): δ 11.37 (br, 1H), 10.11 (br, 1H), 8.91 (s, 1H, pyrazole C5-H), 7.40 (d, 2H, J= 8.0 Hz, Ar), 7.35 (d, 2H, J= 8.0 Hz, Ar), 3.66 (br, 4H), 2.35 (s, 3H).

Anal. Calcd for C₁₂H₁₄N₆O₂ C, 52.55; H, 5.14; N, 30.64 %; Found C, 52.15; H, 5.09; N, 30.26 %.

6d m.p. 226-229 °C. (yield 90 %). ¹H NMR (CDCl₃): δ 11.37 (br, 1H), 10.11 (br, 1H), 8.91 (s, 1H, pyrazole C5-H), 7.65- 7.40 (m, 4H, Ar), 3.68 (br, 4H).

Anal. Calcd. for C₁₁H₁₁N₆O₂Cl C, 44.90; H, 3.74; N 28.57 %. Found C, 44.56; H, 3.66; N, 28.09 %.

6e m.p. >300 °C. (yield 92%). ¹H NMR (CDCl₃): δ 11.37 (br, s, 1H), 10.11 (br, s, 1H), 8.91 (s, 1H, pyrazole C5-H), 7.42 (d, 2H, J= 8.0 Hz, Ar), 7.40 (d, 2H, J= 8.0 Hz, Ar), 3.69 (br, 4H).

Anal. Calcd. for C₁₁H₁₁N₆O₂Cl C, 44.90; H, 3.74; N, 28.57 %; Found C, 44.78; H, 3.63; N, 28.21 %.

6f m.p. 193 °C (decomp). (yield 72 %). ¹H NMR (CDCl₃): δ 11.37 (br, s, 1H), 10.11 (br, s, 1H), 8.91 (s, 1H, pyrazole C5-H), 7.38-7.30 (m, 4H, Ar), 3.67 (br, 4H), 3.9 (s, 3H).

Anal. Calcd. for C₁₂H₁₄N₆O₃ C, 49.65; H, 4.82; N, 28.95 %; Found C, 49.22; H, 4.51; N, 28.59 %.

6g m.p. 225-228 °C. (yield 91%). ¹H NMR (CDCl₃): δ 11.37 (br, 1H), 10.11 (br, 1H), 8.91 (s, 1H, pyrazole C5-H), 7.38 (d, 2H, J= 7.9 Hz, Ar), 7.30 (d, 2H, J= 7.9 Hz, Ar), 3.67 (br, 4H), 3.95 (s, 3H).

Anal. Calcd. for C₁₂H₁₄N₆O₃ C, 49.65; H, 4.82; N, 28.95 %; Found C, 49.26; H, 4.81; N, 28.59 %.

6h m.p. 210-214 °C. (yield 78%). ¹H NMR (CDCl₃): δ 11.37 (br, 1H), 10.11 (br, 1H), 8.91 (s, 1H, pyrazole C5-H), 7.40 (d, 2H, J= 7.9 Hz, Ar), 7.35 (d, 2H, J= 7.9 Hz, Ar), 4.2 (q, 2H), 1.4 (t, 3H), 3.67 (br, 4H).

Anal. Calcd. for C₁₃H₁₆N₆O₃ C, 51.31; H, 5.26; N, 27.62 %; Found C, 50.75; H 5.05; N, 27.41 %.

6i m.p. 241-244 °C. (yield 88%). ¹H NMR (CDCl₃): δ 11.37 (br, 1H), 10.11 (br, 1H), 8.91 (s, 1H, pyrazole C5-H), 7.40-7.30 (m, 3H, Ar), 3.67 (br, 4H), 2.25 (s, 3H).

Anal. Calcd. for C₁₂H₁₃N₆O₂Cl C, 46.75; H, 4.22; N, 27.22 %; Found C, 46.48; H, 4.07; N, 26.79 %.

6j m.p. 281-285 °C. (yield 84%). ¹H NMR (CDCl₃): δ 11.37 (br, 1H), 10.11 (br, 1H), 8.91 (s, 1H, pyrazole C5-H), 7.65-7.40 (m, 3H, Ar), 3.67 (br, 4H), 2.25 (s, 3H).

Anal. Calcd. for C₁₂H₁₃N₇O₄ C, 45.14; H, 4.07; N, 30.72 %; Found C, 45.09; H, 4.02; N 30.39 %.

1-Aryl-4,5-dihydro-1H-pyrazolo[3,4-*d*]pyridazine-3,6-diones (**7a-j**).

1-Arylpyrazole-3,4-dicarbohydrazides (**6a-j**) (0.003 mol) were suspended in 30 ml of water and the pH adjusted to 2 with 2 N hydrochloric acid. The resulting mixture was refluxed for 2 hours on a heating mantle during which time the pyridazine-diones separated as white solids. The reaction mixture was cooled and the solid collected by filtration, washed with water until the washings were neutral, and dried. Recrystallisation was done from DMF. **7a** [8] m.p. 284-286 °C. (yield 70%). ¹H NMR (DMSO-*d*₆): δ 11.15 (s, 1H, OH), 9.14 (s, 1H, pyrazole C-5H), 7.98 (s, 1H, NH), 8.02 - 7.56 (m, 5H, Ar). Mass calcd. for C₁₁H₈N₄O₂: 228. Found: 228.

Anal. Calcd. for C₁₁H₈N₄O₂ C, 57.89; H, 3.53; N, 24.55 %; Found C, 57.79; H, 3.46; N 24.19 %.

7b m.p. >300 °C. (yield 74%). ¹H NMR (DMSO-*d*₆): δ 11.15 (s, 1H, OH), 9.14 (s, 1H, pyrazole C-5H), 7.98 (s, 1H, NH), 8.02 (d, 2H, J=8.6 Hz, Ar), 7.50 (d, 2H, J=8.6 Hz, Ar). Mass calcd. for C₁₁H₇N₄O₂Br :306 & 308. Found: 306 & 308.

Anal. Calcd. for C₁₁H₇N₄O₂Br C, 42.96; H, 2.28; N, 18.24 %; Found C, 42.59; H, 1.96; N 17.89%.

7c m.p. 294 °C.(decomp) (yield 78 %). ¹H NMR (DMSO-*d*₆): δ 11.15 (s, 1H, OH), 9.14 (s, 1H, pyrazole C-5H), 7.98 (s, 1H, NH), 8.12 (d, 2H, J=8.6, Ar), 7.60 (d, 2H, J=8.6, Ar), 2.35 (s, 3H, CH₃). Mass calcd. for C₁₂H₁₀N₄O₂: 242. Found: 242.

Anal. Calcd. for C₁₂H₁₀N₄O₂ C, 59.50; H, 4.16; N, 23.13 %; Found C, 59.16; H, 4.02; N 22.83 %.

7d m.p. 272 °C.(decomp) (yield 78%). ¹H NMR (DMSO-*d*₆): δ 11.15 (s, 1H, OH), 9.14 (s, 1H, pyrazole C-5H), 7.98 (s, 1H, NH of lactam), 8.22 - 7.80 (m, 4H, Ar). Mass calcd. for C₁₁H₇N₄O₂Cl :262 & 264. Found: 262 & 264.

Anal. Calcd. for C₁₁H₇N₄O₂Cl C, 50.38; H, 2.61; N, 21.37 %; Found C, 50.01; H, 2.41 N, 20.91 %.

7e m.p. >3000 °C (yield 79%). ¹H NMR (DMSO-*d*₆): δ 11.15 (s, 1H, OH), 9.14 (s, 1H, pyrazole C-5H), 7.98 (s, 1H, NH), 8.12 (d, 2H, J=8.5, Ar), 7.60 (d, 2H, J=8.5, Ar). Mass calcd. for C₁₁H₇N₄O₂Cl :262 & 264. Found: 262 & 264.

Anal. Calcd. for C₁₁H₇N₄O₂Cl C, 50.38; H, 2.61; N, 21.37 %; Found C, 50.00; H, 2.28; N, 20.98 %.

7f m.p. 292 °C (decomp). (yield 69 %). ¹H NMR (DMSO-*d*₆): δ 11.15 (s, 1H, OH), 9.14 (s, 1H, pyrazole C-5H), 7.98 (s, 1H, NH of lactam), 8.10- 7.70 (m, 4H, Ar), 4.05 (s, 3H, CH₃). Mass calcd. for C₁₂H₁₀N₄O₃: 258. Found: 258.

Anal. Calcd. for C₁₂H₁₀N₄O₃ C, 55.81; H, 3.90; N, 21.70 %; Found C, 55.55; H, 3.68; N, 21.35 %.

7g >300 °C. (yield 76%). ¹H NMR (DMSO-*d*₆): δ 11.15 (s, 1H, OH), 9.14 (s, 1H, pyrazole C-5H), 7.98 (s, 1H, NH), 8.32 (d, 2H, J=8.7, Ar), 7.80 (d, 2H, J=8.7, Ar), 4.01 (s, 3H, CH₃). Mass calcd. for C₁₂H₁₀N₄O₃: 258. Found: 258.

Anal. Calcd for C₁₂H₁₀N₄O₃ C, 55.81; H, 3.90; N, 21.70 %; Found C, 55.45; H, 3.45; N, 21.37 %.

7h m.p. 252-254 °C. (yield 72 %). ¹H NMR (DMSO-*d*₆): δ 11.15 (s, 1H, OH), 9.14 (s, 1H, pyrazole C-5H), 7.98 (s, 1H, NH), 8.34 (d, 2H, J=8.7, Ar), 7.85 (d, 2H, J=8.7, Ar), 4.15 (q, 2H), 1.55 (t, 3H). Mass calcd. for C₁₃H₁₂N₄O₃: 272. Found: 272.

Anal. Calcd. for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.41; N, 20.58 %; Found C, 57.19; H, 4.04; N, 20.23 %.

7i m.p. 258-260 °C. (yield 78%). 1H NMR (DMSO- d_6): δ 11.15 (s, 1H, OH), 9.14 (s, 1H, pyrazole C-5H), 7.98 (s, 1H, NH), 8.34 -7.85 (m, 3H, Ar), 2.45 (s, 3H). Mass calcd. for $C_{12}H_9N_4O_2Cl$: 276. Found: 276.

Anal. Calcd. for $C_{12}H_9N_4O_2Cl$: C, 52.17; H, 3.26; N, 20.28 %; found C, 51.98; H, 3.02; N, 19.88 %.

7j m.p. >300 °C. (yield 75%). 1H NMR (DMSO- d_6): δ 11.15 (s, 1H, OH), 9.14 (s, 1H, pyrazole C-5H), 7.98 (s, 1H, NH), 8.1 - 7.8 (m, 3H, Ar), 2.48 (s, 3H). Mass calcd. for $C_{12}H_9N_5O_4$: 287. Found: 287.

Anal. Calcd. for $C_{12}H_9N_5O_4$: C, 50.18; H, 3.13; N, 24.38 %; Found C, 49.78; H, 2.82; N, 23.99 %.

1-Aryl-3,6-dichloro-1H-pyrazolo[3,4-d]pyridazines (**8a-j**).

1-Aryl-4,5-dihydro-1H-pyrazolo[3,4-d]pyridazine-3,6-diones **7a-j** (0.002 mol) were refluxed with $POCl_3$ (8 ml) for 5- 8 hours. Excess $POCl_3$ was removed under reduced pressure and the residue obtained was treated with an ice-cold solution of $NaHCO_3$. The white solid was then collected by filtration, washed with water and dried. Recrystallisation was done from chloroform. **8a** m.p. 155-157 °C. (yield 62 %). 1H NMR (DMSO- d_6): δ 8.59 (s, 1H, pyrazole C-5H), 7.98 -7.22 (m, 5H, Ar). Mass calcd. for $C_{11}H_6N_4Cl_2$: 264, 266 & 268. Found: 264, 266 & 268.

Anal. Calcd. for $C_{11}H_6N_4Cl_2$: C, 50.00; H, 2.28; N, 21.21 %; Found C, 49.60; H, 2.04; N, 20.76 %.

8b m.p. 125-127 °C. (yield 67 %). 1H NMR (DMSO- d_6): δ 8.59 (s, 1H, pyrazole C-5H), 8.12 (d, 2H, J=8.5, Ar), 7.90 (d, 2H, J=8.5, Ar).

Anal. Calcd. for $C_{11}H_5N_4Cl_2Br$: C, 38.48; H, 1.47; N, 16.36 %; Found C, 38.08; H, 1.15; N, 15.91 %.

8c m.p. 162-164 °C. (yield 70 %). 1H NMR (DMSO- d_6): δ 8.59 (s, 1H, pyrazole C-5H), 7.90 (d, 2H, J=8.5, Ar), 7.20 (d, 2H, J=8.5, Ar), 2.4 (s, 3H). Mass Calcd. for $C_{12}H_8N_4Cl_2$: 278, 280 & 282. Found: 278, 280 & 282.

Anal. Calcd. for $C_{12}H_8N_4Cl_2$: C, 51.79; H, 2.89; N, 20.14 %; Found C, 51.50; H, 2.49; N, 19.84 %.

8d m.p. 179-181 °C. (yield 69 %). 1H NMR (DMSO- d_6): δ 8.59 (s, 1H, pyrazole C-5H), 8.10 - 7.95 (m, 4H, Ar).

Anal. Calcd. for $C_{11}H_5N_4Cl_3$: C, 44.29; H, 1.68; N, 18.70 %; Found C, 44.00; H, 1.35; N, 18.25 %.

8e m.p. 170-172 °C. (yield 70 %). 1H NMR (DMSO- d_6): δ 8.59 (s, 1H, pyrazole C-5H), 7.90 - 7.20 (m, 4H, Ar).

Anal. Calcd. for $C_{11}H_5N_4Cl_3$: C, 44.29; H, 1.68; N, 18.70 %; Found C, 44.01; H, 1.22; N, 18.31 %.

8f m.p. 142-144 °C. (yield 69 %). 1H NMR (DMSO- d_6): δ 8.59 (s, 1H, pyrazole C-5H), 8.10 - 7.95 (m, 4H, Ar), 4.05 (s, 3H). Mass Calcd. for $C_{12}H_8N_4OCl_2$: 294, 296 & 298. Found: 294, 296 & 298.

Anal. Calcd. for $C_{12}H_8N_4OCl_2$: C, 48.84; H, 2.73; N, 18.98 %; Found C, 48.37; H, 2.67; N, 18.62 %.

8g m.p. 158 (decomp) °C. (yield 68 %). 1H NMR (DMSO- d_6): δ 8.59 (s, 1H, pyrazole C-5H), 7.85 (d, 2H, J=8.5, Ar), 7.25 (d, 2H, J=8.5, Ar), 4.15 (s, 3H). Mass Calcd. for $C_{12}H_8N_4OCl_2$: 294, 296 & 298. Found: 294, 296 & 298.

Anal. Calcd. for $C_{12}H_8N_4OCl_2$: C, 48.84; H, 2.73; N, 18.98 %; found C, 48.55; H, 2.43; N, 18.55 %.

8h m.p. 128-130° (yield 72 %). 1H NMR (DMSO- d_6): δ 8.59 (s, 1H, pyrazole C-5H), 7.90 (d, 2H, J=8.5, Ar), 7.20 (d, 2H,

J=8.5, Ar), 4.20 (q, 2H), 1.42 (t, 3H). Mass Calcd. for $C_{13}H_{10}N_4OCl_2$: 308, 310 & 312. Found: 308, 310 & 312.

Anal. Calcd. for $C_{13}H_{10}N_4OCl_2$: C, 50.64; H, 3.24; N, 18.18 %; Found C, 50.22; H, 2.95; N, 17.83 %.

8i m.p. 121-123 °C. (yield 78 %). 1H NMR (DMSO- d_6): δ 8.59 (s, 1H, pyrazole C-5H), 7.50 - 7.20 (m, 3H, Ar), 2.72 (s, 3H).

Anal. Calcd. for $C_{12}H_7N_4Cl_3$: C, 46.15; H, 2.24; N, 17.94 %; Found C, 45.81; H, 2.02; N, 17.57 %.

8j m.p. 182 (decomp) °C. (yield 75 %). 1H NMR (DMSO- d_6): δ 8.59 (s, 1H, pyrazole C-5H), 7.80 - 7.40 (m, 3H, Ar), 2.80 (s, 3H). Mass Calcd. for $C_{12}H_7N_5O_2Cl_2$: 323, 325 & 327.

Anal. Calcd. for $C_{12}H_7N_5O_2Cl_2$: C, 44.58; H, 2.16; N, 21.67 %; Found C, 44.21; H, 2.01; N, 21.35 %.

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