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A Facile Method for the Synthesis of 6-Aryl-1-(3-Chloropropanoyl)-4-[(*E*)-1-(2-Furyl)Methylidene)]-1,2,3,4-Tetrahydro-3-Pyridazinones and 2-(2-Chloroethyl)-5-[*a*-Aracyl-*b*-(2-Furyl)]-(*E*)-Vinyl-1,3,4-Oxadiazoles

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Abstract: The 6-aryl-1-(3-chloropropanoyl)-4-[(*E*)-1-(2-furyl)methylidene)]-1,2,3,4-tetrahydro-3-pyridazinones (**6a-d**) were synthesized by the reaction of acid chloride **3** with *a*-aracyl(*b*-2-furyl)acrylic acid hydrazides (**2a-d**) in a high yield, one pot reaction. On the other hand, 2-(2-chloroethyl)-5-[*a*-aracyl-*b*-(2-furyl)]-(*E*)-vinyl-1,3,4-oxadiazoles (**7a-d**) were also prepared by cyclodehydration of N^1[*a*-aracyl-*b*–(2-furyl)acroyl-N^2[3-chloro-propanoyl] hydrazine derivatives (**4a-d**). The proposed structures of the products were confirmed by elemental analysis, spectral data and chemical evidence.

Keywords: 2(3*H*)-Furanone, 3-Oxopyridazines, dihydropyridazines, 1,3,4-Oxadiazoles.

Introduction

We have previously reported [1,2] a synthetic approach to 5-aryl-3-furfurylidene-2-(3*H*)-furanones (**1**) *via* the condensation reactions of furan-2-carboxaldehyde with 3-aroylpropionic acids under Perkin conditions, which yield the corresponding *E*-lactones as the only product, with no detectable amount of the *Z*-isomers being identified by TLC and ^{1}H NMR [3]. This result was consistent with the reports of Awad *et al*. [5] and others' [6,7] concerning the condensation reaction of 5-methyl-furan-2-carboxaldehyde and/or 5-methyl thiophene-2-carboxaldehyde with 3-aroylpropionic acids under Perkin condi-

tions. The conversion of these 2(3*H*) furanones into benzofuran derivatives [1] and 5-oxo-2-pyrrolines [4] have also been described by one of us.

Dihydropyridazinone rings are of chemical and biological interest, having been reported as having antihypertensive activity [8]. In addition, Nannini et al. [9] has established that the pyridazinones display analgesic and anti-inflammatory activities. On the other hand, 1,3,4-oxadiazoles and N^2(acyl)-benzoic hydrazides are reported to exhibit carcinostatic activity against several types of tumors [10] and antimicrobial effects against *Mycobacterium tuberculosis* and *Mycobacterium lapreae* [11]. The amino-3-substituted propyl functionality is found in many compounds having vasodilator, antispasmodic, blood platelet aggregation inhibition [12], antiarrhythmic [13] and anticholesterolesmic [14] activities.

This reported biological importance of 2(3*H*)-furanones, 4,5-dihydropyridazinones and 1,3,4-oxadiazoles prompted us to attempt the conversion of 2(3*H*)-furanones (**1a-d**) into heterocyclic systems of potential synthetic and biological importance, for example, the acrylic acid hydrazides (**2a-d**), 3-pyridazinones (**6a-d**), N^1[*a*-aracyl-*b*–(2-furyl)acroyl-N^2[3-chloro propanoyl]hydrazine (**4a-d**) and 1,3,4-oxadiazole derivatives (**7a-d**), dihydropyridazinones (**8a-d**).

Results and Discussion

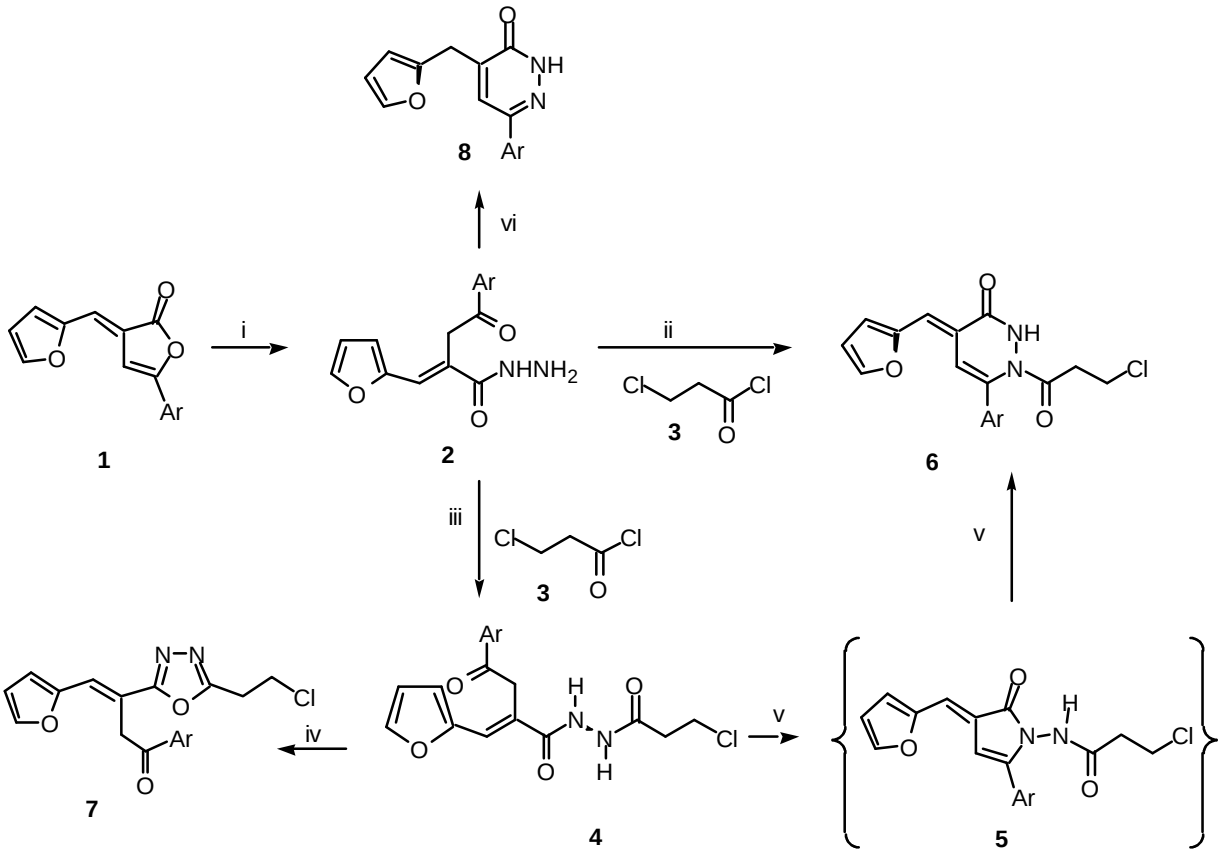
We report here a simple method for the synthesis of 6-aryl-1-(3-chloropropanoyl)-4-[(*E*)-1-(2-furyl)methylidene)]-1,2,3,4-tetrahydro-3-pyridazinones (**6a-d**) and 2-(2-chloroethyl)-5-[*a*-aracyl-*b*-(2-furyl)]-(*E*)-vinyl-1,3,4-oxadiazoles (**7a-d**) in good yields via the interaction of hydrazides (**2a-d**) with acid chloride (**3**) and $POCl_3$ in a one pot reaction.

In this investigation, hydrazides (**2a-d**) proved to be useful precursors in the synthesis of several heterocyclic systems. When the 2(3*H*)furanones (**1a-d**) were allowed to react with hydrazine hydrate in ethanol, ring opening occurs with the formation of the *E*-isomers of *a*-aracyl-*b*–(2-furyl)acrylic acid hydrazides (**2a-d**) as the only products. There was no detectable amount of the corresponding *Z*-isomers according to ^{1}H NMR [3]. The configurational structures of the 2(3*H*)-furanones (**1a-d**) as *E*-isomers were confirmed by ^{1}H and ^{13}C NMR, as illustrated in Tables 2 and 4. The infrared spectra of these products (**2a-d**) (*cf.* Table 1) show an absorption band at 3199.7-3104.2-3331 cm $^{-1}$ (broad band) characteristic of the NH group, and bands at 1648-55 cm^{-1} and 1668-97 cm^{-1} for υC=O, characteristic of the amide carbonyl and ketone groups, respectively. On heating the hydrazides (**2a-d**) in 1.0 N HCl for 30-60 min, ring closure occurs, leading to the formation of the corresponding 3(2*H*)-pyridazinones, namely the 6-aryl-4-furylmethyl-3(2*H*)-pyridazinones (**8a-d**). The infrared spectra of compounds (**8a-d**) (*cf.* Table 1) show a broad absorption band at 3150-3300 cm $^{-1}$ characteristic of the NH group and an absorption band at 1654-60 cm^{-1} for υC=O, characteristic of the amide carbonyl group. The infrared spectra of these compounds are similar to those reported for other pyridazinone derivatives [15-18].

The ^{1}H NMR spectra of compounds (**2a-d**) exhibit singlet signals at 4.41 for (C$\underline{H}_2$COAr), a singlet at δ 6.67 for olefinic protons, triplet signals at δ 7.07 for (-N$\underline{H}$-NH$_2$) and two signals dd for (-NH-N$\underline{H}_2$) due to the strong electrical quadrupole moment effect [19]. In compounds (**8a-d**) the CH_2 adjacent to

the furan ring exhibited a singlet at δ 3.92, the olefinic proton of the unsaturated double bond showed a doublet signal at δ 7.56 and the (-NH-) group a singlet at δ13.23 ppm.

The interaction of *a*-aracyl-*b*-(2-furyl)acrylic acid hydrazides (**2a-d**) with 3-chloropropanoyl chloride (**3**) was studied also under different conditions at 0-15°C and 80°C. When the reaction took place at 0-15°C over 4-5 h, it gave a 85% yield of N^1[*a*-aracyl-*b*–(2-furyl)acroyl-N^2[3-chloropropanoyl]-hydrazine compounds (**4a-d**), but when the reaction took place at 80°C over 30-60 min, HCl was liberated to give an 80-92% yield of 6-aryl-1-(3-chloropropanoyl)-4-[(*E*)-1-(2-furyl)methylidene)]-1,2,3,4-tetrahydro-3-pyridazinones (**6a-d**) as illustrated in Scheme 1.



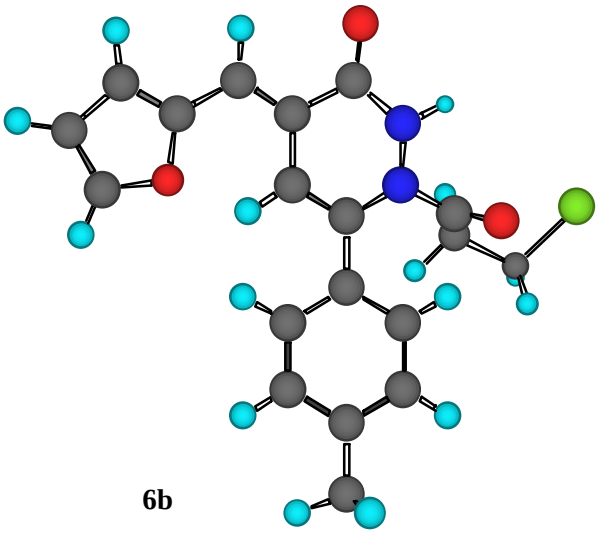
Ar = a = C_6H_5, b = $C_6H_4CH_3$ (P), c = $C_6H_4OCH_3$ (P), d = C_6H_4Cl (P)
Scheme 1. Reagents and conditions: i) NH_2NH_2 . H_2O/ethanol, stirring at RT for 2 days: ii) Benzene, heat/30-60 mins; iii) benzene , stirring at 0-15 °C for 4-5hrs.; iv) heating with $POCl_3$ for 1h.; v) Benzene, heat with 1.0 N HCl for 30-60 mins; vi) Stirred and heating with 1.0 N HCl in benzene for 1h.

Scheme 1.

In a parallel experiment using benzene solvent in the presence of acid catalyst (1.0 N HCl) at 80°C the hydrazine compounds (**4a-d**) cyclised and only formation of products (**6a-d**) was noted, as evidenced by TLC after 1h. We believe the liberation of HCl aided the ring closure of the hydrazine derivatives compounds (**4a-d**) under the reaction conditions at 80°C to provide compounds (**6a-d**). These

compounds were shown by direct comparison (m.p and mixed m.p) and also by TLC to be identical in all aspects with the authentic products obtained by the action of 1.0 N HCl in benzene solvent with N^1[*a*-aracyl-*b*–(2-furyl)acroyl-N^2[3-chloropropionyl]hydrazine compounds (**4a-d**). Acid catalysis proved to be essential and reaction was essentially complete after 30-60 min at 80°C (ca. 92% yield). The ^{1}H NMR spectra of (**4a-d**) exhibited singlet signals for the CH_2 protons at δ 4.41 ppm and also show two doublet signals at 9.8 and 10.11 ppm for the hydrazine (-NH-NH-) group.

The alternative mode of ring closure of N^1[*a*-aracyl-*b*–(2-furyl)acroyl-N^2[3-chloropropionyl]-hydrazine compounds (**4a-d**), that is attack by the N^1, would lead to the formation of the corresponding *N*-(3-chloropropionyl)aminopyrrolines (**5a-d**) as intermediates. But these *N*-aminopyrrolines (**5**) are not formed, and the pyridazinones (**6a-d**) are the only isolable products obtained from this reaction. We believe that the *N*-aminopyrrolines (**5a-d**) are unstable under the acid catalyzed reaction conditions and if formed, they might undergo ring expansion [1b] yielding the corresponding 3(2*H*) pyridazinones (**6a-d**). This behavior is in accordance with the reported rearrangements of *N*-aminophthalimides in acid medium to the corresponding phthalaza-1,4-diones [15]. The structure of compounds (**6a-d**) was confirmed by ^{1}H NMR (300 MHz), microanalysis and infrared spectral data. The IR spectra show an absorption band for the υC=O stretching vibrations of cyclic carboxamides at 1666-1678 cm^{-1}, characteristic of the 3(2*H*) pyridazinone ring, and in the 1725-1733 cm^{-1} region for the C=O of the open alkylcarboximide, as well as a broad band at 3227-3337 cm^{-1} characteristic of the NH group. The spectra of compounds (**6a-d**) (*cf*, Table 1) are similar to those of 1-benzoyl-6-aryl-4-thienylidene-1,6-dihydropyridazin-3-(2*H*)ones [20]. The ^{1}H and ^{13}C NMR data showed evidence for the formation of a bicyclic structure as shown in Tables 2 and 3. In compounds (**6a-d**), as expected, the two olefins (=C-H) have different chemical shifts both in the ^{1}H and ^{13}C NMR spectra. These highly conjugated structures show a typical two singlet signal for the C-H in the ^{1}H NMR spectrum at δ 6.6-6.7 and 7.08-7.13 for CH=C-Ar and Fur-CH=C- respectively, because in the case of Fur-CH=C- there is a long range coupling with the furan-H and this evidence can be obtained from the coupling constants between H(7) and furan-H(9) as illustrated in Table 2. Further evidence to support our assignments was obtained from the ^{13}C NMR spectrum of compound (**6b**) that showed the carbons of the highly conjugated system at C(5) and C(7) to be at δ 118.7 and 126.25 respectively as shown in Table 3. It is clear also from the ^{1}H NMR spectrum of the compounds (**6a-d**) that in the $ClCH_2CH_2CO$- system, the CH_2 adjacent to the carbonyl appears as a triplet at δ 3.722 ppm and the other CH_2 adjacent to the chlorine nuclei are completely decoupled from directly attached protons, and appear as two triplet signals at 2.54-2.77 ppm, due to the strong electrical quadrupole moment effect [19].



6b

Figure 1. MM2 Calculations for compound **6b**.

Steric Energy		Minimize Energy	
Stretch:	14.1377	Stretch:	0.7590
Bend:	14.7873	Bend:	15.6902
Stretch-Bend:	-0.7962	Stretch-Bend:	0.0215
Torsion:	-3.2895	Torsion:	-6.0891
Non-1,4 VDW:	37.3133	Non-1,4 VDW:	-5.2474
1,4 VDW:	10.1824	1,4 VDW:	9.1168
Dipole/Dipole:	-3.8562	Dipole/Dipole:	-5.3897

Total steric energy for structure (**6b**): 68.479 kcal/mole

Total of the minimum energy for the structure (**6b**): 8.8612 kcal/mol

Another piece of evidence to support our assignment the structure of compound (**6b**) was obtained through MM2 calculations for the minimum and total steric energy, as illustrated in Figure 1. It is important to point out that we have examined steric energies from 68.479 kcal/mole to the lowest energy structure at 8..86 kcal/mole over 392 iterations. Minimization terminated normally because the gradient norm was less than the minimum gradient norm.

The interaction of hydrazides (**2a-d**) with $POCl_3$ provided 2-(*b*-chloroethyl)-5-[*a*-aracyl-*b*-(2-furyl)](*E*)-vinyl-1,3,4-oxadiazoles (**7a-d**) as the only products in 75-83% yield.. The infrared spectra (IR) of these products (*cf.* Table 1) show an absorption band at 1695-1698 cm^{-1} for υC=O, characteristic of the ketone carbonyl group, and 1578-1617 cm^{-1} for υC=N. The ^1H NMR spectrum of compounds (**7a-d**) exhibit singlet signals at δ 4.37 for ($C\underline{H}_2COAr$) and a singlet signal at δ 6.65 for the olefinic proton and the disappearance the signals of the hydrazo group as illustrated in Table 2.

Table 1. Infrared (IR) and ^{1}H NMR (300 MHz) spectral data for compounds **1a**-**8d**.

Cpd No	Aryl group	Infrared bands (IR)υ_{max} (Nujol)/ cm^{-1} $u_{C=O}$ $u_{-C=N}$ u_{-NH}	^{1}H NMR (300 MHz, DMSO); δH [$^2H_6$] DMSO
1a	C_6H_5	1754.0	δ = 6.78 (dd, 1H, J = 1.8, 3.6 Hz, furan-H4), 7.20 (s, 1H, -CH=C-Ar), 7.25 (d, 1H, J = 3.3 Hz, furan-H3), 7.40 (d, 1H, J = 0.6 Hz, fur-C=CH-), 7.48-7.50 (m, 3H, Ph-H), 7.80-7.84 (dd, 2H, J = 2.1, 7.8 Hz, Ph-Ho), 8.04 (d, J = 1.5 Hz, furan-H5) ppm.
1b	$C_6H_5OCH_3$	1783.1	δ = 2.32 (s, 3H, Ar-Me), 6.72 (q, 1H, J = 1.8, 3.6 Hz, furan-H4), 7.08 (s, 1H, -CH=C-Ar), 7.17 (d, 1H, J = 3 Hz, furan-H3), 7.22 (d, 2H, J = 8.7 Hz, Ar-H), 7.27 (s, 1H, fur-C=CH-), 7.48 (d, 2H, J = 8.7 Hz, Ar-H), 7.98 (d, 1H, J = 1.5 Hz, furan-H5) ppm.
1c	$C_6H_5OCH_3$	1786.0	δ = 3.82 (s, 3H, Ar-OMe), 6.76 (q, 1H, J = 1.8, 3.6 Hz, furan-H4), 7.07 (d, 2H, J = 9 Hz, Ar-H), 7.11 (s, 1H, -CH=C-Ar), 7.20 (d, 1H, J = 3.3 Hz, furan-H3), 7.25 (s, 1H, fur-C=CH-), 7.78 (d, 2H, J = 9 Hz, Ar-H), 8.00 (d, 1H, J = 1.5 Hz, furan-H5) ppm.
1d	C_6H_5Cl	1752.0	δ = 6.66 (dd, 1H, J = 1.8, 3.6 Hz, furan-H4), 6.73 (d, 1H, J = 1.2 Hz,-CH=C-fur), 6.99 (d, 1H, J = 3.6 Hz, furan-H3), 7.13 (s, 1H, CH=C-Ar), 7.46 (d, 2H, J = 9 Hz, Ar-H), 7.57 (d, 2H, J = 8.7 Hz, Ar-H), 7.76 (d, 1H, J = 2.1 Hz, furan-H5) ppm.
2a	C_6H_5	1655-1697 3199.7-3331	δ = 3.01-3.08 (dd, 2H, J = 2.4, 2.7 Hz, -NHNHa_2), 3.17-3.24 (dd, 2H, J = 2.4, 2.7 Hz, -NHNHb_2), 4.41 (s, 2H, -CH_2COPh), 6.57 (dd, 1H, J = 1.8, 3.3 Hz, furan-H4), 6.67 (s, 1H, fur-CH=C-), 6.74 (d, 1H, J = 3.3 Hz, furan-H3), 7.07 (t, 1H, J = 2.4 Hz,-CO-NHNH_2), 7.27-7.29 (m, 3H, Ph-H), 7.35 (d, 2H, J = 4.5 Hz, Ph-Ho), 7.76 (d, J = 1.8 Hz, furan-H5) ppm.
2b	$C_6H_5OCH_3$	1648-1687 3104.3-3325	δ = 2.32 (s, 3H, Ar-Me), 3.015-3.085 (dd, 2H, J = 2.4, 2.7 Hz, -NHNHa_2), 3.17-3.24 (dd, 2H, J = 2.4, 2.7 Hz, -NHNHb_2), 4.38 (s, 2H, -CH2COAr), 6.57 (dd, 1H, J = 1.8, 3.3 Hz, furan-H4), 6.67 (s, 1H, Fur-CH=C-), 6.74 (d, 1H, J = 3.3 Hz, furan-H3), 7.07 (t, 1H, J = 2.4 Hz,-CO-NHNH_2), 7.22 (d, 2H, J = 8.7 Hz, Ar-H), 7.35 (d, 2H, J = 8.7 Hz, Ar-H), 7.78 (d, J = 1.8 Hz, furan-H5) ppm.
2c	$C_6H_5OCH_3$	1648-1672 3242.3-3324	δ = 3.82 (s, 3H, Ar-OMe), 3.10 (dd, 2H, J = 2.4, 2.7 Hz, -NHNHa_2), 3.22 (dd, 2H, J = 2.4, 2.7 Hz, -NHNHb_2), 4.32 (s, 2H, -CH_2-COAr), 6.57 (dd, 1H, J = 1.8, 3.3 Hz, furan-H4), 6.7 (s, 1H, fur-CH=C-), 6.74 (d, 1H, J = 3.3 Hz, furan-H3), 7.1 (t, 1H, J = 2.4 Hz,-CO-NHNH_2), 7.22 (d, 2H, J = 8.7 Hz, Ar-H), 7.30 (d, 2H, J = 8.7 Hz, Ar-H), 8.0 (d, J = 1.8 Hz, furan-H5) ppm.
2d	C_6H_5Cl	1652-1668 3235.6-3317	δ = 3.01-3.08 (dd, 2H, J = 2.4, 2.7 Hz, -NHNHa_2), 3.17-3.24 (dd, 2H, J = 2.4, 2.7 Hz, -NHNHb_2), 4.48 (s, 2H, -CH2-COAr), 6.57 (dd, 1H, J = 1.8, 3.3 Hz, furan-H4), 6.67 (s, 1H, fur-CH=C-), 7.07 (t, 1H, J = 2.4 Hz,-CO-NHNH_2), 7.38 (d, 2H, J = 8.7 Hz, Ar-H), 7.48 (d, 2H, J = 8.7 Hz, Ar-H), 7.74 (d, 1H, J = 3.3 Hz, furan-H3), 7.76 (d, J = 1.8 Hz, furan-H5) ppm.

Continuation of the Table 1.

Cpd No	Aryl group	Infrared bands (IR)υ_{max} (Nujol)/ cm^{-1} $u_{C=O}$	$u_{-C=N}$	u_{-NH}	^1H NMR (300 MHz, DMSO); δH [$^2H_6$] DMSO
4a	C_6H_5	1633-1705		3100-3287	δ = 2.57-2.67 (pentet, 1H, J = 6.6 Hz, ClC$\underline{Ha}_2CH_2CO$-) 2.69-2.78 (pentet, 1H, J = 6 Hz, ClC$\underline{Hb}_2CH_2CO$-), 3.71 (t, 2H, J = 6 Hz, $ClCH_2C\underline{H}_2CO$-), 3.84 (s, 2H, -C$\underline{H}$2CO Ph), 6.64 (dd, 1H, J = 1.8, 3.6 Hz, furan-H4), 6.70 (d, 1H, J = 0.9Hz, fur-CH=C-), 6.96 (d, 1H, J = 3.3 Hz, furan-H3), 7.44-7.61 (m, 5H, Ph-H), 7.76 (d, J = 1.5 Hz, furan-H5), 9.40 (d, 1H, J = 3.3 Hz,-CONHNHCO-), 10.18 (d, 1H, J = 3.9 Hz,-CONHNH CO-), ppm.
4b	$C_6H_5OCH_3$	1628-1672		3140-3250	δ = 2.32 (s, 3H, Ar-Me), δ = 2.48-2.64 (pentet, 1H, J = 6.6Hz, ClC$\underline{Ha}$2CH2CO-), 2.68-2.77 (pentet, 1H, J= 6Hz, ClC$\underline{Hb}_2CH_2CO$-), 3.72 (t, 2H, J = 6Hz, $ClCH_2C\underline{H}_2CO$-), 3.84 (s, 2H, -C$\underline{H}_2$COAr), 6.72 (dd, 1H, J = 1.8, 3.6 Hz, furan-H4), 7.1 (s, 1H, Fur-CH=C-), 7.17 (d, 1H, J = 3 Hz, furan-H3), 7.22 (d, 2H, J = 8.7 Hz, Ar-H), 7.51 (d, 2H, J = 8.7 Hz, Ar-H), 7.98 (d, J = 1.8 Hz, furan-H5), 9.41 (d, 1H, J = 3.3 Hz,-CONHNH CO-), 10.68 (d, 1H, J = 3.9 Hz,-CONHNHCO-), ppm.
4c	$C_6H_5OCH_3$	1633-1688		3150-3245	δ = 3.81 (s, 3H, Ar-Me), 2.48-2.64 (pentet, 1H, J = 6.6 Hz, ClC$\underline{Ha}_2CH_2CO$-), 2.68-2.77 (pentet, 1H, J = 6 Hz, ClC$\underline{Hb}_2CH_2CO$-), 3.72 (t, 2H, J = 5.7 Hz, $ClCH_2C\underline{H}_2$ CO-), 3.85 (s, 2H, -C$\underline{H}_2$COAr), 6.72 (dd, 1H, J = 1.8, 3.6 Hz, furan-H4), 7.1 (s, 1H, Fur-CH=C-) 7.17 (d, 1H, J = 3 Hz, furan-H3), 7.22 (d, 2H, J = 8.7 Hz,Ar-H), 7.51 (d, 2H, J = 8.7 Hz, Ar-H), 7.98 (d, J = 1.8 Hz, furan-H5), 9.45 (d, 1H, J = 3.3 Hz, -CONHNHCO-), 10.61 (d, 1H, J = 3.9 Hz,-CONHNHCO-), ppm.
4d	C_6H_5Cl	1600-1708		3150-3333	δ =2.66 (pentet, 1H, J = 7.2 Hz, ClC$\underline{Ha}_2CH_2CO$-), 2.71 (pentet, 1H, J = 6 Hz, ClC$\underline{Hb}_2CH_2CO$-), 3.72 (t, 2H, J = 5.7 Hz, $ClCH_2C\underline{H}_2CO$-), 3.85 (s, 2H, -C$\underline{H}_2$COAr), 6.65 (dd, 1H, J = 1.8, 3.6 Hz, furan-H4), 6.99 (d, 1H, J = 3 Hz, furan-H3), 7.13 (s, 1H, fur-CH=C-), 7.48 (d, 2H, J = 9 Hz,Ar-H), 7.58 (d, 2H, J = 8.7 Hz, Ar-H), 7.77 (d, J = 2.1 Hz, furan-H5), 9.41 (d, 1H, J = 3.3 Hz,-CONHNHCO-), 10.68 (d, 1H, J = 3.9 Hz,-CONHNH CO-), ppm.
6a	C_6H_5	1666-1715		3227-3337	δ = 2.57-2.67 (pentet, 1H, J = 6.6 Hz, ClC$\underline{Ha}_2CH_2CO$-) 2.69-2.78 (pentet, 1H, J = 5.7 Hz, ClC$\underline{Hb}_2CH_2CO$-), 3.71 (t, 2H, J = 6 Hz, $ClCH_2C\underline{H}_2CO$-), 6.65 (dd, 1H, J = 1.8, 3.6 Hz, furan-H4), 6.7 (d, 1H, J = 0.9 Hz, -CH=C-Ar), 6.97 (d, 1H, J = 3.3 Hz, furan-H3), 7.1 (s, 1H, Fur-CH=C-), 7.44-7.61 (m, 5H, Ph-H), 7.76 (d, J = 1.5 Hz, furan-H5), 8.76 (s, 1H, -CONH-) ppm.
6b	$C_6H_5OCH_3$	1672-1728.3		3287.8	δ = 2.32 (s, 3H, Ar-Me), 2.62 (pentet, 1H, J = 6.6 Hz, ClC$\underline{Ha}_2CH_2CO$-), 2.70 (pentet, 1H, J = 6 Hz, ClC$\underline{Hb}_2$ CH_2CO-), 3.722 (t, 2H, J = 6 Hz, $ClCH_2C\underline{H}_2$ CO-), 6.59 (s, 1H, -CH=C-Ar), 6.72 (dd, 1H, J = 1.8, 3.6 Hz, furan-H4), 7.08 (s, 1H, furan-CH=C-), 7.17 (d, 1H, J = 3 Hz, furan-H3), 7.22-7.25 (d, 2H, J = 8.7 Hz,Ar-H), 7.48-7.51 (d, 2H, J = 8.7 Hz, Ar-H), 7.98 (d, J = 1.8 Hz, furan-H5), 10.68 (s, 1H, -CONH-) ppm.

Continuation of the Table 1.

Cpd. No	Aryl group	Infrared bands (IR)υ_{max} (Nujol)/ cm^{-1} $u_{C=O}$ $u_{-C=N}$ u_{-NH}	^1H NMR (300 MHz, DMSO); δH [$^2H_6$] DMSO
6c	$C_6H_5OCH_3$	1668-1733 3278	δ = 2.60-2.68 (pentet, 1H, J = 6 Hz, ClC<u>Ha</u>$_2$CH$_2$CO-), 2.69-2.76 (pentet, 1H, J = 6 Hz, ClC<u>Hb</u>$_2$CH$_2$CO-), 3.72 (t, 2H, J = 6 Hz, ClCH$_2$C<u>H</u>$_2$CO-), 3.85 (s, 3H, Ar-OMe), 6.59 (s, 1H, -CH=C-Ar), 6.72 (dd, 1H, J = 1.8, 3.6 Hz, furan-H4), 7.08 (s, 1H, fur-CH=C-), 7.17 (d, 1H, J = 3 Hz, furan-H3), 7.22-7.25 (d, 2H, J = 8.7 Hz,Ar-H), 7.48-7.51 (d, 2H, J = 8.7 Hz, Ar-H), 7.98 (d, J = 1.8 Hz, furan-H5), 10.66 (s, 1H, -CONH-) ppm.
6d	C_6H_5Cl	1678-1722 3257.3-3311	δ =2.60-2.68 (pentet, 1H, J = 6 Hz, ClC<u>Ha</u>$_2$CH$_2$CO-), 2.69-2.76 (pentet, 1H, J = 6 Hz, ClC<u>Hb</u>$_2$CH$_2$CO-), 3.72 (t, 2H, J = 6 Hz, ClCH$_2$C<u>H</u>$_2$CO-), 6.66 (dd, 1H, J = 1.8, 3.6 Hz, furan-H4), 6.74 (d, 1H, J = 1.2 Hz, -CH=C-Ar), 6.99 (d, 1H, J = 3.6 Hz, furan-H3), 7.13 (s, 1H, furan-CH=C-), 7.46 (d, 2H, J = 9 Hz,Ar-H), 7.57 (d, 2H, J = 8.7 Hz, Ar-H), 7.77 (d, J = 2.1 Hz, furan-H5), 8.78 (s, 1H, -CONH-) ppm.
7a	C_6H_5	1695 1578-1612	δ = 2.49 (t, 1H, J = 6.6 Hz, ClC<u>H</u>$_2$CH$_2$CO-), 3.53 (t, 1H, J = 6.6 Hz, ClCH$_2$C<u>H</u>$_2$CO), 4.37 (s, 2H, -C<u>H</u>$_2$CO Ph), 6.65 (dd, 1H, J = 1.8, 3.6 Hz, furan-H4), 6.97 (d, 1H, J = 3.3 Hz, furan-H3), 7.13 (s, 1H, furan-CH=C-), 7.44-7.61 (m, 5H, Ph-H), 7.76 (d, J = 1.5 Hz, furan-H5) ppm.
7b	$C_6H_5OCH_3$	1692.3 1588-1611	δ = 2.32 (s, 3H, Ar-Me), 2.62-2.70 (t, 1H, J = 6.6 Hz, ClC<u>H</u>$_2$CH$_2$CO), 3.722 (t, 1H, J = 6 Hz, ClCH$_2$C<u>H</u>$_2$CO-) 4.41 (s, 2H, -C<u>H</u>$_2$COAr), 6.71 (dd, 1H, J = 1.8, 3.6 Hz, furan-H4), 7.08 (s, 1H, furan-CH=C-), 7.17 (d, 1H, J = 3 Hz, furan-H3), 7.22-7.25 (d, 2H, J = 9 Hz,Ar-H), 7.48-7.51 (d, 2H, J = 9 Hz, Ar-H), 7.98 (d, J = 1.8 Hz, furan-H5) ppm.
7c	$C_6H_5OCH_3$	1693.2 1589-1609	δ = 2.60-2.76 (t, 1H, J = 6 Hz, ClC<u>H</u>$_2$CH$_2$CO-), 3.72 (t, 1H, J = 6 Hz, ClCH$_2$C<u>H</u>$_2$CO-), 4.42 (s, 2H, -C<u>H</u>2COAr), 3.85 (s, 3H, Ar-OMe), 6.72 (dd, 1H, J = 1.8, 3.6 Hz, furan-H4), 7.08 (s, 1H, furan-CH=C-), 7.17 (d, 1H, J = 3 Hz, furan-H3), 7.22-7.25 (d, 2H, J = 8.7 Hz,Ar-H), 7.48-7.51 (d, 2H, J = 8.7 Hz, Ar-H), 7.98 (d, J = 1.8 Hz, furan-H5) ppm.
7d	C_6H_5Cl	1698 1590-1617	δ = 2.75 (t, 2H, J = 6 Hz, ClC<u>H</u>$_2$CH$_2$CO-), 3.72 (t, 1H, J = 6 Hz, ClCH$_2$C<u>H</u>$_2$CO-), 4.36 (s, 1H, -C<u>H</u>$_2$COAr), 6.66 (dd, 1H, J = 1.8, 3.6 Hz, furan-H4), 6.99 (d, 1H, J = 3.6 Hz, furan-H3), 7.13 (s, 1H, furan-CH=C-), 7.46 (d, 2H, J = 9 Hz,Ar-H), 7.57 (d, 2H, J = 8.7 Hz, Ar-H), 7.77 (d, J = 2.1 Hz, furan-H5) ppm.
8a	C_6H_5	1655 1605 2150-3300	δ = 3.90 (s, 2H, -furan-C<u>H</u>$_2$-), 6.22 (d, 1H, J = 3 Hz, furan-H3), 6.39 (dd, 1H, J = 1.8, 3 Hz, furan-H4), 7.42-7.49 (m, 3H, Ph-H), 7.56 (d, 1H, J = 0.9 Hz, -CH=C-Ar), 7.42-7.76 (dd, 2H, J = 1.2, 5.1 Hz, Ph-H), 7.79 (d, J = 1.8 Hz, furan-H5), 13.23 (s, 1H, -CONH-) ppm.

Continuation of the Table 1.

Cpd. No	Aryl group	Infrared bands (IR)υ_{max} (Nujol)/ cm^{-1}			^{1}H NMR (300 MHz, DMSO); δH [$^2H_6$] DMSO
		uC=O	*u-C=N*	*u-NH*	
8b	$C_6H_5OCH_3$	1660	1610	2850-3300	δ = 2.32 (s, 3H, Ar-Me), 3.92 (s, 2H, -furan-C$\underline{H}_2$-), 6.23 (d, 1H, J = 3 Hz, furan-H3), 6.42 (dd, 1H, J = 1.8, 3.6 Hz, furan-H4), 7.25 (d, 2H, J = 8.7 Hz,Ar-H), 7.47 (s, 1H, -CH=C-Ar), 7.51 (d, 2H, J = 8.7 Hz, Ar-H), 7.98 (d, J = 1.8 Hz, furan-H5), 13.46 (s, 1H, -CONH-) ppm.
8c	$C_6H_5OCH_3$	1660	1610	3800-3400	δ = 3.85 (s, 3H, Ar-OMe), 3.93 (s, 2H, -furan-C$\underline{H}_2$-), 6.72 (d, 1H, J = 3 Hz, furan-H3), 7.17 (dd, 1H, J = 1.8, 3.6 Hz, furan-H4), 7.08 (s, 1H, furan-CH=C-), 7.26 (d, 2H, J = 8.7 Hz,Ar-H), 7.49 (d, 1H, J = 0.9 Hz, -CH=C-Ar), 7.51 (d, 2H, J = 8.7 Hz, Ar-H), 7.48 (d, J = 1.8 Hz, furan-H5), 13.65 (s, 1H, -CONH-) ppm.
8d	C_6H_5Cl	1660	1613	3900-3400	δ =3.95 (s, 2H, -furan-C$\underline{H}_2$-), 6.66 (d, 1H, J = 3.6 Hz, furan-H3), 7.1 (dd, 1H, J = 1.8, 3.6 Hz, furan-H4), 7.44 (d, 1H, J = 1.2 Hz, -CH=C-Ar), 7.46 (d, 2H, J = 9 Hz,Ar-H), 7.57 (d, 2H, J = 8.7 Hz, Ar-H), 7.97 (d, J = 1.8 Hz, furan-H5), 13.38 (s, 1H, -CONH-) ppm.

Experimental

General

^{1}H NMR spectra were recorded on Varian Plus 300 (300 MHz) or Bruker XL 300 (300 MHz) instruments, the ^{13}C NMR spectra (with DEPT 135) on a Bruker WP80 or XL 300 instrument. Infrared spectra listed as recorded 'neat' refer to a thin film of material on NaCl disks, and were taken on a Perkin Elmer 1600 FT-IR spectrometer. Mass spectra were recorded on a Kratos Concept instrument. Melting points were measured on an Electrothermal digital melting point apparatus and are uncorrected. The TLC analyses were carried out using Macherey-Nagel 0.25mm layer fluorescent UV_{254} plates with the indicated solvent system. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ) at University of Minho, Braga, Portugal.

*a-(2-Furyl)methylidene-(E)-g-aryl-2(3H)-furanones (***1a-d***)*

2(3*H*)-Furanones (**1a-d**) were prepared following the literature method [2]. The structures of the products were confirmed by ^{1}H and ^{13}C NMR spectral data as listed in Tables 1 and 2.

*a-Aracycl-b-(2-furyl)acrylic acid hydrazides (***2a-d***) [2]*

Hydrazine hydrate (1 mol) was added to a suspension of the 2-(3*H*)-furanones (**1a-d**) (1 mol) in absolute ethanol (20 mL). The reaction mixture was allowed to stand at room temperature with occasional

shaking from time to time and then left overnight. The reaction was monitored by TLC and was shown to be complete after 2 days. Evaporation of the solvent by rotatory evaporator gave a colorless solid that was filtered off and recrystallized from a suitable solvent to give colorless crystals in 75-85% yield, as listed in Table 2.

*4-Furylmethyl-6-aryl-3(2H)pyridazin-3-ones (***8a-d***)*

1.0 N HCl (5 mL) was added dropwise with stirring at 25-35°C over 30-60 min to a solution of the *a*-aracycl-*b*-(2-furyl)acrylic acid hydrazides (**2a-d**) (1 mole) in benzene (20 mL); after completion of the addition the solid was continue stirring for 1h, then filtered off and washed thoroughly with water. The product obtained was recrystallized from a suitable solvent as shown in Table 2.

*N^1[a-Aracyl-b-(2-furyl)acroyl- N^2[3-chloropropionyl]hydrazine (***4a-d***)*

To a solution of the *a*-aracycl-*b*-(2-furyl)acrylic acid hydrazides (**2a-d**) (1 mol) in benzene (50 mL) was added 3-chloro-propionyl chloride (**3**) (1.01 mol) and the mixture stirred at 0-15° C for 5 h. The progress of the reaction was monitored by TLC and shown to be complete after 5-6 hrs and when the color become yellow. The solid separated out were collected and re-crystallized from ethanol to yield the title compounds in 80-92% yield (*cf.* Table 2).

*6-Aryl-1-(3-chloropropanoyl)-4-[(E)-1-(2-furyl)methylidene)]-1,2,3,4-tetrahydro-3-pyridazinones (***6a-d***)*

To a solution of the *a*-aracycl-*b*-(2-furyl)acrylic acid hydrazides (**2a-d**) (1 mol) in benzene (50 mL) was added 3-chloropropionyl chloride (**3**) (1.1 mol) and the reaction mixture was refluxed at 80°C for 30-60 min. The progress of the reaction was monitored by TLC during this time and the reaction was shown to be complete after 1h when the color become yellow. The solvent was removed by rotatory evaporator and the solids which separated out were collected and then recrystallized from ethanol to yield the products in 80-92% yield (*cf.* Table 2). In a parallel experiment with hydrazine derivatives (**4a-d**) in benzene solvent in the presence of acid catalyst (1.0 N HCl) using the same reaction conditions previously mentioned, the only products which could be identified by TLC after 30-60 min. were compounds (**6a-d**). These compounds were shown by direct comparison of m.p and mixed m.p, TLC and spectral data to be identical in all aspects with authentic samples.

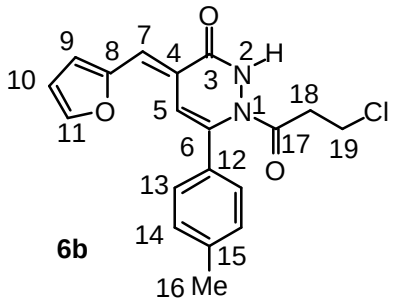
*2-(b-Chloroethyl)-5-[a-aracyl-b-(2-furyl)]-(E)-vinyl-1,3,4-oxadiazoles (***7a-d***)*

A mixture of the N^1[*a*-aracyl-*b*-(2-furyl)acroyl-N^2[3-chloropropionyl]hydrazine compounds (**4a-d**) (1 mol) and $POCl_3$ (10 mL) were stirred and heated at 106°C for 1 h., then allowed to cool, poured onto crushed ice and washed with aqueous 1.0 N $NaHCO_3$. The yellowish solid precipitate was filtered off, washed with water and recrystallized from benzene-petroleum ether (b.p. 100-120°C) mixture to produce compounds (**7a-d**) (*cf.* Table 2). These experiments were repeated using Ac_2O as dehydrating agent instead of $POCl_3$ and there is no indication for any change in the yields.

Table 2. Physical data for compounds **1a-8d**.

Cpd. No.	*Aryl Group*	*m.p* ^{o}C	*Yield*	*Recryst. Solvent*	*MF*	*Analysis [Calc./Found]* C	H	N
1a	C_6H_5	195-198	78%	EtOH	$C_{15}H_{10}O_3$	75.63/75.56	4.20/4.19	
1b	$C_6H_5CH_3$	205-207	88%		$C_{16}H_{12}O_3$	76.19/76.20	4.76/4.63	
1c	$C_6H_5OCH_3$	215-217	91%		$C_{16}H_{12}O_4$	71.64/71.42	4.47/4.56	
1d	C_6H_5Cl	235-238 dec.	75%		$C_{15}H_9ClO_3$	66.05/66.24	3.30/3.42	
2a	C_6H_5	134-135	76%	EtOH	$C_{15}H_{14}N_2O_3$	66.67/66.85	5.18/5.07	10.37/10.53
2b	$C_6H_5CH_3$	172-173	72%		$C_{16}H_{16}N_2O_3$	67.60/67.56	5.63/5.54	9.86/9.71
2c	$C_6H_5OCH_3$	125-126	78%		$C_{16}H_{16}N_2O_4$	64.00/63.88	5.33/5.23	9.33/9.12
2d	C_6H_5Cl	216-217	73%		$C_{15}H_{13}ClN_2O_3$	59.11/59.01	4.27/4.19	9.19/9.32
4a	C_6H_5	135-136	82%	MeOH	$C_{18}H_{17}N_2O_4Cl$	59.91/60.10	4.71/4.82	7.76/7.55
4b	$C_6H_5CH_3$	173-175	85%		$C_{19}H_{19}N_2O_4Cl$	60.88/60.92	5.07/4.99	7.47/7.67
4c	$C_6H_5OCH_3$	110-112	83%		$C_{19}H_{19}N_2O_5Cl$	58.38/58.12	4.86/4.77	7.17/7.27
4d	C_6H_5Cl	215-217	80%		$C_{18}H_{16}N_2O_4Cl_2$	54.68/54.33	4.05/4.25	7.08/7.20
6a	C_6H_5	160-162	80%	EtOH	$C_{18}H_{15}N_2O_3Cl$	63.06/63.02	4.37/4.16	8.17/8.28
6b	$C_6H_5CH_3$	182-183	92%		$C_{19}H_{17}N_2O_3Cl$	63.95/63.69	4.76/4.47	7.85/7.55
6c	$C_6H_5OCH_3$	173-175	92%		$C_{19}H_{17}N_2O_4Cl$	61.20/61.15	4.56/4.45	7.51/7.57
6d	C_6H_5Cl	205-206	89%		$C_{18}H_{14}N_2O_3Cl_2$	57.29/57.25	3.71/3.22	7.42/7.76
7a	C_6H_5	157-158	75%	Benz.	$C_{18}H_{15}N_2O_3Cl$	63.06/63.02	4.37/4.16	8.17/8.28
7b	$C_6H_5CH_3$	175-177	83%		$C_{19}H_{17}N_2O_3Cl$	63.95/63.69	4.76/4.47	7.85/7.55
7c	$C_6H_5OCH_3$	180-182	82%		$C_{19}H_{17}N_2O_4Cl$	61.20/61.15	4.56/4.45	7.51/7.57
7d	C_6H_5Cl	165-167	79%		$C_{18}H_{14}N_2O_3Cl_2$	57.29/57.25	3.71/3.22	7.42/7.76
8a	C_6H_5	207-210	75%	EtOH	$C_{15}H_{12}N_2O_2$	71.42/71.53	4.76/4.87	11.11/10.95
8b	$C_6H_5CH_3$	239-240	79%		$C_{16}H_{14}N_2O_2$	72.1872.13	5.26/5.00	10.52/10.60
8c	$C_6H_5OCH_3$	172-173	80%		$C_{16}H_{14}N_2O_3$	68.08/68.38	4.96/5.14	9.92/10.13
8d	C_6H_5Cl	210-212	77%		$C_{15}H_{11}N_2O_2Cl$	62.82/62.64	3.83/3.80	9.77/9.80

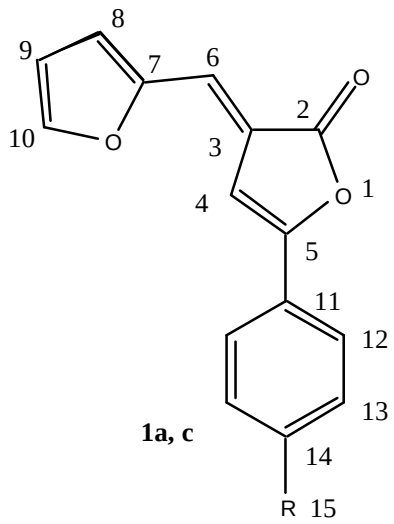
Table 3. ^{13}C Chemical shifts ($\delta C[^2H_6]DMSO$) for 6-(4-methylphenyl)-1-(3-chloropropanoyl)-4-[(*E*)-1-(2-furyl)methylidene)]-1,2,3,4-tetrahydro-3-pyridazinones (**6a-d**).



6b

C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11
168.74	123.53	118.7	151.86	126.25	147.1	113.4	99.24	117.14
C-12	C-13	C-14	C-15	C-16	C-17	C-18	C-19	
146.4	129.2	126.9	139.3	20.9	168.2	53.4	36.1	

Table 4. ^{13}C Chemical shifts (δC[$^{2}H_6$]DMSO) for *a*-(2-furyl)methylidene-(*E*)-*g*-aryl-2(3*H*)-furanones **1a** and **1c**.



Cpd No.	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13	C-14	C-15
1a	168.58	130.4	119.7	154.6	121.1	151.4	113.9	99.24	120.27	147.8	125.1	129.1	127.84	----
1c	168.74	144.8	118.8	154.8	121.4	151.5	113.7	99.97	120.25	147.4	126.9	114.64	161.04	55.4

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Samples Availability: Available from the authors.