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A novel conversion of acetylenic 1,2,4-triazoles into 3-alkyl-5-arylpyridazines

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Abstract—Bromination of 2-aryl-1-[1,2,4]triazol-1-ylalk-3-yn-2-ols gives 6-bromo-7-hydroxy-5-alkyl-7-aryl-7,8-dihydro-[1,2,4]triazolo[1,2-*a*]pyridazin-4-ylium salts, which are converted by treatment with strong alkali into novel 3-alkyl-5-arylpyridazines.

1. Introduction

Pyridazines are an important class of heterocycle, which have been the subject of extensive research, particularly in the pharmaceutical and agrochemical areas, and their synthesis and applications have been comprehensively reviewed.[1–4] While there are numerous general methods for the synthesis of pyridazines, there are only few methods for making 3-substituted-5-arylpyridazines. These have usually been based on cycloaddition chemistry, for example, alkyl or alkylstannyl acetylenes undergo [4+2] cycloaddition with 3-aryl-1,2,4,5-tetrazines to give mixtures of regioisomers, which can be manipulated to give a variety of 3,5-diarylpyridazines,[5] and monohaloazodienes react with enamines to give 3-alkyl-5-arylpyridazines in variable yields.[6] In another approach, addition of diazomethane to diarylcyclopropene carboxylates gives diazabicyclohexenes, which lose nitrogen in situ to give diarylpyridazine esters, which are in turn hydrolysed and decarboxylated to give 3,5-diarylpyridazines.[7] In this paper, we wish to report a novel route to 3-alkyl-5-arylpyridazines from 1,2,4-triazolyl alkynols. Our route involves the intramolecular attack of the triazole ring nitrogen on a bromonium ion or bromovinyl cation generated by bromination of an acetylene to give a fused triazolium salt, which then breaks down on treatment with aqueous alkali to give the 3-alkyl-5-arylpyridazines.

Substituted 1,2,4-triazoles have received a great deal of attention owing to their biological activity against both agricultural[8] and human fungi.[9] In particular, tertiary triazolyl alcohols of general type **1** have been of great interest because of their outstanding potency on a wide range of fungal pathogens. In the agrochemical field extensive work by many groups[10] has shown that R and R^1 in **1** can be aryl rings or alkyl chains, which in turn can be substituted by many different groups such as ethers, ketones, esters or even another triazole ring. Important examples of antifungal triazoles are the agricultural fungicide epoxiconazole[11] **2** and the pharmaceutical fungicide fluconazole **3**[9] (Fig. 1).

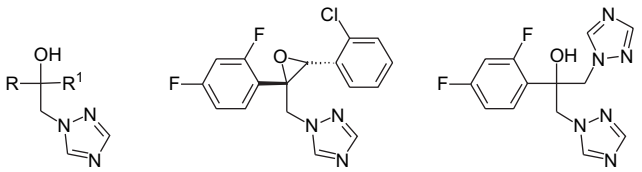

Figure 1. Structures of fungicidal 1,2,4-triazoles **1**–**3**.

2. Results

During our research into fungicides for agricultural use we found that triazoles **1** where R was a substituted phenyl group and R^1 was an alkenyl or alkynyl group, showed high fungicidal activity. We developed a simple synthesis of acetylenic triazoles **6a**–**f**[12] (Scheme 1). Lithium acetylides, generated from the acetylenes by treatment with *n*-butyl lithium, were added smoothly to chloroacetophenones **4a**–**f** to give moderate to excellent yields of the chlorohydrins **5a**–**f**. The crude chlorohydrins were reacted directly with the anion of 1,2,4-triazole, generated with sodium hydride in DMF, to give the 1,2,4-triazolyl alkynols **6a**–**f** in moderate to good yields. For the synthesis of the ethynyl compound **6a**, the trimethylsilyl acetylene chlorohydrin **5a** was used and the trimethylsilyl group was removed by acidic work-up after reaction with 1,2,4-triazole.

Keywords: Pyridazines; Triazoles; Acetylenes; Triazolium; Cyclisation.
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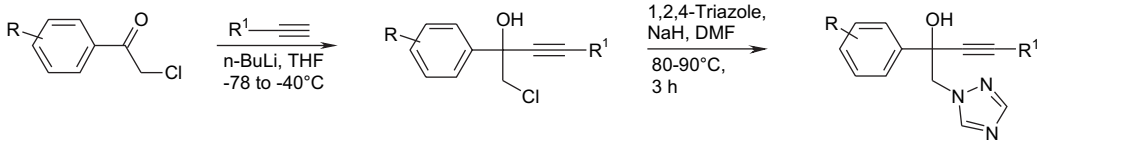


4a R = 2,4-di-Cl
4b R = 4-Cl
4c R = 2,4-di-F

	crude yield
5a R = 2,4-di-Cl, R^1 = $Si(CH_3)_3$,	88%
5b R = 2,4-di-Cl, R^1 = CH_3,	92%
5c R = 2,4-di-Cl, R^1 = C_2H_5,	37%
5d R = 2,4-di-Cl, R^1 = n-C_5H_{11},	100%
5e R = 4-Cl, R^1 = C_2H_5,	100%
5f R = 2,4-di-F, R^1 = C_2H_5	85%

	yield from **4a-e**
6a R = 2,4-di-Cl, R^1 = H,	41%
6b R = 2,4-di-Cl, R^1 = CH_3,	20%
6c R = 2,4-di-Cl, R^1 = C_2H_5,	58%
6d R = 2,4-di-Cl, R^1 = n-C_5H_{11},	59%
6e R = 4-Cl, R^1 = C_2H_5,	41%
6f R = 2,4-di-F, R^1 = C_2H_5,	55%

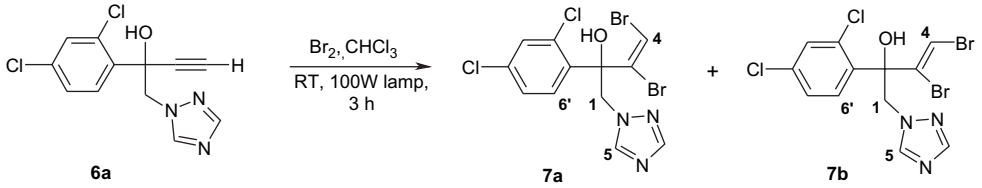
Scheme 1. Synthesis of triazolyl alkynols **6a–f**.

We wished to make some triazoles of type **1** where R was a substituted phenyl group and R^1 was a halogenated alkyl group, and it seemed likely that with the alkynyl analogues **6a–f** in hand, simple addition of halogens would quickly give examples for biological testing. Accordingly bromine was added to the ethynyl compound **6a** in chloroform at room temperature, but gave no reaction. However, in the presence of light (100 W tungsten lamp) smooth bromination took place and after 3 h a nearly quantitative yield of *E*- and *Z*-isomers **7a** and **7b** in an approximately 2:5 ratio was obtained (Scheme 2). The stereochemistry of **7a** and **7b** was assigned by ^{1}H NMR. In the *Z*-isomer **7b** the protons H-1, H-5 and H-6′ showed an NOE when olefinic proton H-4 was irradiated, whereas in the *E*-isomer **7a**, when proton H-4 was irradiated no NOEs were detected.

In the expectation that the alkyl acetylenes **6b–f** would undergo similar radical bromination, we were surprised to find that when bromine was added to the compounds in chloroform at room temperature preparatory to carrying out the light reaction, an exothermic reaction occurred, leading to a rapid decolourisation followed by gradual precipitation of white crystalline solids. After treatment with aqueous alkali to neutralise the reaction these solids yielded new compounds, identified as the novel pyridazines **8b–f** (Scheme 3).

The mass spectra for each of **8b–f** showed a major ion for the loss of two carbon atoms, one nitrogen atom and water from the starting materials **6b–f**, with no incorporation of bromine. There was no alcohol present in their IR spectra. In the ^{1}H NMR spectrum, the triazole protons, typically as singlets at around 7.80 and 8.20 ppm, were replaced by new singlets at around 7.30 and 9.30 ppm. An ^{1}H–^{13}C HMBC study of compound **8e** confirmed all the key connectivities. Pyridazine proton H-4 correlated with carbons C-6 and C-1′, pyridazine proton H-6 correlated with C-4 and C-5 and the ethyl CH_2 protons correlated with C-3 and C-4. Additionally, when pyridazine proton H-6 was irradiated an NOE was shown by the benzene proton H-2′ and when the ethyl CH_2 protons were irradiated an NOE was shown by H-4. The microanalyses were in agreement with the proposed structures.

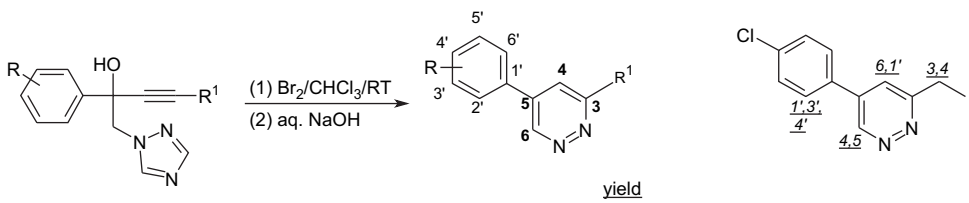
Having identified the final products we then turned our attention to the precipitates formed in the bromination



6a **7a** **7b**

7a:**7b**, 2:5

Scheme 2. Reaction of triazolyl alkynol **6a** with bromine.



6b R = 2,4-di-Cl, R^1 = CH_3
6c R = 2,4-di-Cl, R^1 = C_2H_5
6d R = 2,4-di-Cl, R^1 = n-C_5H_{11}
6e R = 4-Cl, R^1 = C_2H_5
6f R = 2,4-di-F, R^1 = C_2H_5

	yield
8b R = 2,4-di-Cl, R^1 = CH_3	89%
8c R = 2,4-di-Cl, R^1 = C_2H_5	26%
8d R = 2,4-di-Cl, R^1 = n-C_5H_{11}	40%
8e R = 4-Cl, R^1 = C_2H_5	57%
8f R = 2,4-di-F, R^1 = C_2H_5	80%

8e
^{1}H-^{13}C correlations

Scheme 3. Bromination of triazolyl alkynols **6b–f** to give pyridazines **8b–f**.

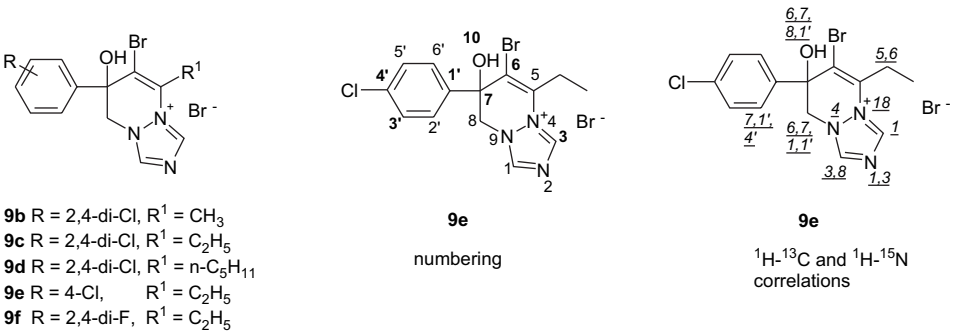


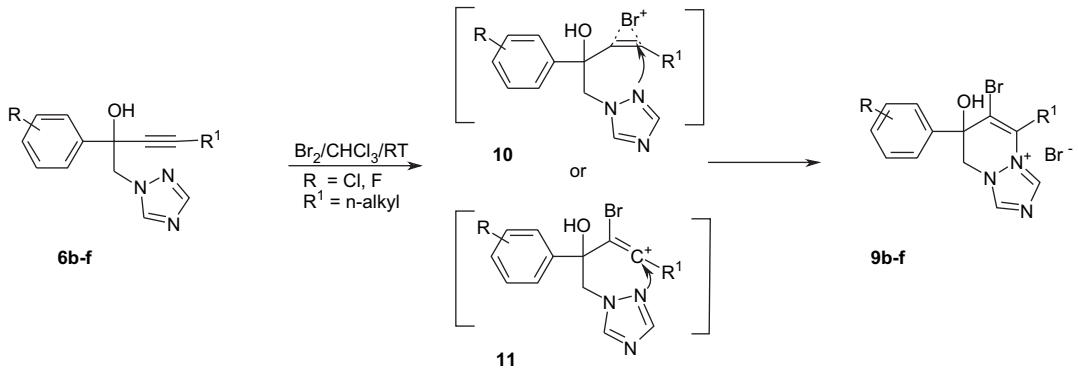
Figure 2. Structures and NMR correlations for triazolium salts **9b–f**.

reaction before work-up, which were found to be extremely soluble in water and to have very high melting points. The electrospray mass spectra showed strong ions corresponding to the addition of one bromine atom and the microanalyses were consistent with the addition of two bromine atoms to the starting materials **6b–f**. Bearing in mind the structures of the pyridazine final products and the putative mechanisms for their formation, it seemed possible that the precipitates could be the novel triazolium salts of structures **9b–f**. In the ^{1}H NMR the signals for the triazole protons, typically singlets at around 7.80 and 8.20 ppm in the starting materials **6b–f**, were replaced by two very low field singlets at around 9.5 and 10.00 ppm, which was consistent with the structures being highly electron deficient triazolium salts (Fig. 2).

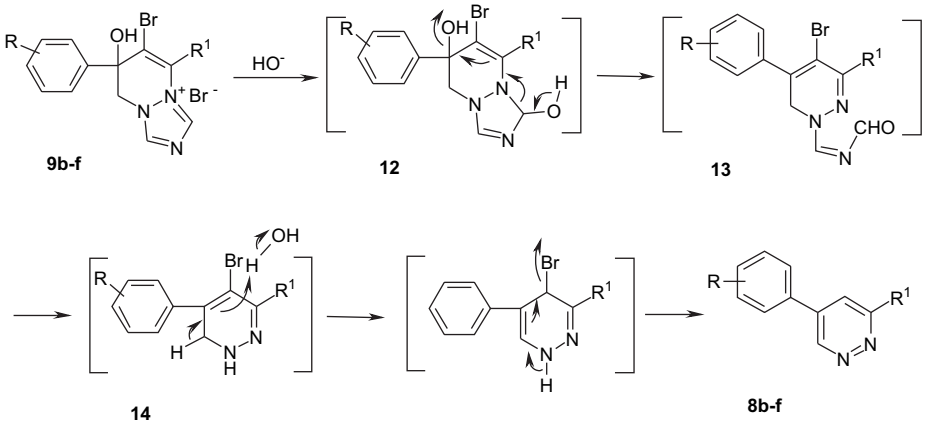
The structures were confirmed as **9b–f** by an ^{1}H–^{13}C HMBC experiment on compound **9e**, which showed that triazole H-1 correlated to triazole C-3 and methylene C-8, triazole proton H-3 correlated to triazole C-1, quaternary benzylic carbon C-7 correlated to benzene ring protons H-2′/H-6′ and methylene protons H-8 and the hydroxyl proton correlated to methylene carbon C-8 and vinyl carbon C-6. In addition an ^{1}H–^{15}N HMBC study was carried out. This showed that ethyl CH_2 and ring methylenes H-8 correlated to triazolium N-4, ring methylenes H-8 correlated with triazolium N-9 and triazoliums H-1 and H-3 correlated to triazolium N-2. The chemical shifts of N-4 and N-9 were very similar, as expected for a triazolium salt, while N-2 was at slightly lower field. The yields of the triazolium salts **9b–f** from triazoles **6b–f** were 84–92%.

3. Discussion

The mechanism of formation of triazolium salts **9b–f** was rationalised as addition of bromine to the triple bond to give an ionic intermediate, which is then intercepted by a triazole nitrogen (Scheme 4). The addition of bromine to triple bonds in a range of solvents is known to proceed to give either a cyclic bromonium ion or vinyl cation,[13] which then reacts with an available nucleophile such as a bromide ion or a solvent molecule to give mainly *E*-products. In the case of electron deficient acetylenes, nucleophilic attack by bromine or bromide ion has also been proposed[14] as the first step, but it would seem unlikely in this instance, as the acetylene is not activated. In the present case we therefore, propose that a cyclic bromonium ion **10** or vinyl cation **11** is formed, which reacts in a 6-*endo-trig* attack by the 2-nitrogen of the triazole to form the triazolium salt **9b–f**. 6-*endo-trig* cyclisation is favoured by Baldwin's rules,[15] but seems to have been rather rarely reported for attack of nitrogen nucleophiles onto acetylenes, having been more commonly observed when a nitrogen anion undergoes nucleophilic addition to an electron deficient acetylene[16] or in metal catalysed reactions.[17] However, a useful synthesis of iodo isoquinolines[18] has been developed based on a 6-*endo-trig* cyclisation of *t*-butylimines onto arylacetylenes in the presence of iodine or iodine monochloride and Larock has proposed a similar mechanism to ours, with attack of the imine nitrogen onto an iodonium ion. In the latter case the cyclisation onto alkyl acetylenes proceeded poorly with iodine, but the yields were much higher when silver nitrate or cuprous iodide was used to



Scheme 4. Proposed mechanism of conversion of triazolyl alkynols **6b–f** to triazolium salts **9b–f**.



Scheme 5. Possible mechanism of conversion of triazolium salts **9b–f** to pyridazines **8b–f**.

activate the triple bond. The reaction with the ethynyl compounds was not reported.

The difference between ethynyl compound **6a** and alkyl acetylenes **6b–f** in their mode of reaction with bromine is striking. There is some evidence that terminal acetylenes are less reactive to bromine than disubstituted acetylenes,[19] which is consistent with the lack of reaction of bromine with ethynyl compound **6a**. Additionally, in a recently reported case of competition between disubstituted and monosubstituted acetylenes in reaction with an iminium ion, the only product obtained was from the disubstituted acetylene, with none from the terminal acetylene being found.[20] In our case we presume that the alkyl groups in **6b–f** both impart greater nucleophilicity to the triple bond and provide extra stabilisation of the vinyl cation or bromonium ion by hyperconjugation.

A possible mechanism for conversion of the triazolium salts **9b–f** to the pyridazines **8b–f** is shown in Scheme 5, although the exact order of steps and identity of the intermediates can only be a matter of conjecture, as no intermediates could be isolated. It is likely to start with the known addition of hydroxide ion to triazolium rings[21] to give a pseudo-bases of type **12**, or their regioisomers, followed by ring-opening and elimination of water to give **13**. Cleavage of the formamido methylene group to **14**, followed by a prototropic shift and elimination of HBr could then lead to the pyridazines **8b–f**.

The reaction to form the triazolium salts **9b–f** followed by the transformation to the pyridazines was general for a small selection of acetylenic triazoles tried. The bromination reaction to form the triazolium salts went in high yield, but it was found that conversion to the pyridazines could be considerably improved by dissolving the salts in a small amount of water and adding the subsequent solution to hot 5 N sodium hydroxide, followed by extraction into ethyl acetate after a few minutes (Table 1).

For comparison we attempted chlorination of the acetylenes. With the ethynyl compound **6a** chlorination proceeded to give a mixture of *E*- and *Z*-isomers, but only in the presence of light. No reaction took place at room temperature. With the ethyl acetylene **6c** the reaction with chlorine with or without light gave very messy reactions from which no addition products or triazolium salts could be isolated.

4. Conclusion

In conclusion we have discovered a novel synthesis of 3-alkyl-5-arylpyridazines, which to our knowledge is the first example of formation of a pyridazine from a 1,2,4-triazole, and which constitutes a useful additional approach to specifically substituted examples of these ring systems.

5. Experimental

5.1. General

Melting points were taken using a Büchi B-545 apparatus, and were uncorrected. Infrared Spectra were run on a Perkin–Elmer Spectrum One spectrometer as solid or liquid thin films on a KBr window. ^{1}H and ^{13}C NMR spectra were measured on a Varian Inova-400 (^{1}H, 400 MHz; ^{13}C, 100 MHz), HMBC and HSQC spectra were measured on a Varian Inova-500 NMR spectrometer (^{1}H, 500 MHz). Chemical shifts are in parts per million relative to TMS

Table 1. Reaction of triazoles **6b–f** to form triazolium salts **9b–f** and pyridazines **8b–f**

Starting triazole	R	R^1	Triazolium salt	Isolated yield from **6b–f** (%)	Pyridazine	Isolated yield from **9b–f** (%)
6b	2,4-Di-Cl	CH_3	**9b**	89	**8b**	100
6c	2,4-Di-Cl	C_2H_5	**9c**	92	**8c**	28
6d	2,4-Di-Cl	*n*-C_5H_{11}	**9d**	88	**8d**	45
6e	4-Cl	C_2H_5	**9e**	84	**8e**	68
6f	2,4-Di-F	C_2H_5	**9f**	88	**8f**	91

(^{1}H, ^{13}C 0.0 ppm) and coupling constants (J) are measured in hertz (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet, qd = quartet of doublets, qq = quartet of quartets). Mass spectra were recorded on Micromass PlatformLC. Microanalyses were performed by MEDAC Ltd, Englefield Green, Surrey, UK. All commercially available compounds were used without further purification. Flash chromatography was performed on Merck Kieselgel 60 silica gel, and thin-layer chromatography was performed using Analtech Silica Gel GF 2000 micron plates.

5.2. General procedure for the synthesis of 1-chloro-2-arylalkyn-2-ols (5a–f)

n-Butyl lithium (30 mmol of a 1.6 M solution in hexane) was added dropwise to the alkyne (30 mmol) in 25 mL dry THF at −78 °C, and after completion of the addition the reaction mixture was stirred for 1 h. The haloacetophenone (20 mmol) in 50 mL dry THF was added dropwise keeping the temperature below −70 °C. After completion of the addition the reaction mixture was stirred for 1 h and then warmed to −40 °C, and then poured carefully into water and extracted four times with 50 mL diethyl ether. The ethereal extracts were combined, washed with dilute hydrochloric acid followed by water, and then dried over magnesium sulfate. After evaporation the products **5a–f** were obtained as oils, which were characterised by ^{1}H NMR, IR and MS, and were used for the next step without further purification.

5.2.1. 1-Chloro-2-(2,4-dichlorophenyl)-4-trimethylsilanylbut-3-yn-2-ol (5a). Pale yellow oil, crude yield 88%: IR (cm^{-1}) 3480, 2170, 1580, 1490, 1373, 840. ^{1}H NMR ($CDCl_3$): δ 7.88 (d, 1H, J=8.7 Hz), 7.47 (d, 1H, J=2.15 Hz), 7.36 (dd, 1H, J=8.7, 2.15 Hz), 4.25 (d, 2H, J=11.0 Hz), 4.02 (d, 2H, J=11.0 Hz), 3.36 (s, OH), 0.20 (s, 9H).

5.2.2. 1-Chloro-2-(2,4-dichlorophenyl)-pent-3-yn-2-ol (5b). Pale yellow oil, crude yield 92%: IR (cm^{-1}) 3460, 2244, 1585, 1467, 1376, 1048, 823, 795. ^{1}H NMR ($CDCl_3$): δ 7.85 (d, 1H, J=8.6 Hz), 7.43 (d, 1H, J=2.15 Hz), 7.31 (dd, 1H, J=8.6, 2.15 Hz), 4.19 (d, 1H, J=11.15 Hz), 3.96 (d, 1H, J=11.15 Hz), 1.91 (s, 3H).

5.2.3. 1-Chloro-2-(2,4-dichlorophenyl)-hex-3-yn-2-ol (5c). Pale yellow oil, crude yield 37%: IR (cm^{-1}) 3460, 2239, 1586, 1467, 1377, 1048, 823, 793. ^{1}H NMR ($CDCl_3$): δ 7.85 (d, 1H, J=8.7 Hz), 7.31 (dd, 1H, J=8.7, 2.15 Hz), 4.17 (d, 1H, J=11.1 Hz), 3.97 (d, 1H, J=11.1 Hz), 3.11 (s, OH), 2.28 (q, 2H, J=7.5 Hz), 1.16 (t, 3H, J=7.5 Hz).

5.2.4. 1-Chloro-2-(2,4-dichlorophenyl)-non-3-yn-2-ol (5d). Pale yellow oil, crude yield 100%: IR (cm^{-1}) 3460, 2230, 1586, 1467, 1377, 1049, 780. ^{1}H NMR ($CDCl_3$): δ 7.85 (d, 1H, J=8.6 Hz), 7.31 (dd, 1H, J=8.6, 2.15 Hz), 4.19 (d, 1H, J=11.1 Hz), 3.96 (d, 1H, J=11.1 Hz), 2.26 (t, 2H, J=7.1 Hz), 3.10 (s, OH), 1.49–1.59 (m, 4H), 1.25–1.41 (m, 2H), 0.89 (t, 3H, J=7.0 Hz).

5.2.5. 1-Chloro-2-(4-chlorophenyl)-hex-3-yn-2-ol (5e). Pale yellow oil, crude yield 100%: IR (cm^{-1}) 3420, 2232, 1489, 1091, 1014, 828. ^{1}H NMR ($CDCl_3$): δ 7.60 (d, 2H, J=8.7 Hz), 7.37 (d, 2H, J=8.7 Hz), 3.74 (d, 1H, J=11.0 Hz), 3.68 (d, 1H, J=11.0 Hz), 2.98 (s, OH), 2.32 (q, 2H, J=7.5 Hz), 1.20 (t, 3H, J=7.5 Hz).

5.2.6. 1-Chloro-2-(2,4-difluorophenyl)-hex-3-yn-2-ol (5f). Pale yellow oil, crude yield 85%: IR (cm^{-1}) 3454, 2238, 1614, 1499, 1272, 1139, 1097, 971, 849. ^{1}H NMR ($CDCl_3$): δ 7.75 (td, J=8.8, 6.5 Hz), 6.92 (qq, 1H, J=8.8, 2.5, 1.0 Hz), 6.84 (qd, 1H, J=8.6, 2.6 Hz), 4.00 (d, 1H, J=11.0 Hz), 3.91 (d, 1H, J=11.0 Hz), 3.02 (s, OH), 2.28 (q, 2H, J=7.5 Hz), 1.17 (t, 3H, J=7.5 Hz).

5.3. General procedure for the synthesis of 2-aryl-1-[1,2,4]triazol-1-ylalkyn-2-ols (6a–f)

1,2,4-Triazole (28 mmol) was added portionwise to a suspension of sodium hydride (29 mmol of a 50% dispersion in oil) in dry DMF. After stirring at room temperature for 30 min, the crude 1-chloro-2-arylalkyn-2-ol (14 mmol) in 10 mL dry DMF was added dropwise. After completion of the addition the reaction mixture was heated to 80–90 °C for 3 h. The reaction mixture was cooled and poured into 300 mL water and extracted with 100 mL diethyl ether three times. The combined extracts were washed with water, dried over magnesium sulfate and evaporated to give residues, which were either recrystallised or purified by flash column chromatography on silica gel to give the products **6a–f**.

5.3.1. 2-(2,4-Dichlorophenyl)-1-[1,2,4]triazol-1-yl-but-3-yn-2-ol (6a). White solid, yield 41%: mp 129–131 °C (hexanes/ethyl acetate). IR (cm^{-1}) 3263, 3034, 1513, 1137, 1079, 1049, 803. ^{1}H NMR ($CDCl_3$): δ 8.13 (s, 1H), 7.77 (d, 1H, J=8.6 Hz), 7.94 (s, 1H), 7.44 (d, 1H, J=2.15 Hz), 7.26 (dd, 1H, J=8.6, 2.15 Hz), 4.93 (d, 1H, J=14.1 Hz), 4.84 (s, 1H), 4.63 (d, 1H, J=14.1 Hz), 2.56 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 151.84, 144.54, 135.39, 134.89, 131.94, 130.97, 129.13, 127.49, 80.88, 75.94, 70.47, 56.51. MS m/z=282 (2^{35}Cl) $[M]^+$, 284 (^{35}Cl, ^{37}Cl) $[M+2]^+$, 286 (2^{37}Cl) $[M+4]^+$. Anal. Calcd for $C_{12}H_9Cl_2N_3O$: C 51.09; H 3.22; N 14.89. Found: C 51.25; H 3.33; N 14.66.

5.3.2. 2-(2,4-Dichlorophenyl)-1-[1,2,4]triazol-1-ylpent-3-yn-2-ol (6b). White crystalline solid, yield 20% from 2,4-dichloroacetophenone: mp 145–147 °C (hexanes/ethyl acetate). IR (cm^{-1}) 3064, 1510, 1203, 1131, 1074, 1048, 800. ^{1}H NMR ($CDCl_3$): δ 8.02 (s, 1H), 7.84 (s, 1H), 7.65 (d, 1H, J=8.6 Hz), 7.34 (d, 1H, J=2.15 Hz), 7.15 (dd, 1H, J=8.6, 2.15 Hz), 4.75 (d, 1H, J=14.0 Hz), 4.61 (d, 1H, J=14.0 Hz), 4.35 (s, 1H), 1.70 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 151.72, 144.43, 135.93, 134.97, 131.99, 130.89, 129.05, 127.31, 84.47, 76.70, 70.74, 56.82, 3.52. MS m/z=296 (2^{35}Cl) $[M]^+$, 298 (^{35}Cl, ^{37}Cl) $[M+2]^+$, 300 (2^{37}Cl) $[M+4]^+$. Anal. Calcd for $C_{13}H_{11}Cl_2N_3O$: C 52.72; H 3.74; N 14.19. Found: C 52.95; H 3.65; N 13.90.

5.3.3. 2-(2,4-Dichlorophenyl)-1-[1,2,4]triazol-1-ylhex-3-yn-2-ol (6c). White solid, yield 58% from 2,4-dichloroacetophenone: mp 133–134 °C (hexanes/ethyl acetate). IR (cm^{-1}) 3150, 1506, 1463, 1378, 1130, 1048, 798. ^{1}H NMR ($CDCl_3$): δ 8.11 (s, 1H), 7.91 (s, 1H), 7.73 (d, 1H, J=8.6 Hz), 7.41 (d, 1H, J=2.15 Hz), 7.23 (dd, 1H, J=8.6, 2.15 Hz), 4.83 (d, 1H, J=14.0 Hz), 4.65 (d, 1H, J=14.0 Hz), 4.38 (s, 1H), 2.13 (q, 2H, J=7.6 Hz), 1.03 (t, 3H, J=7.6 Hz). ^{13}C NMR ($CDCl_3$): δ 151.78, 144.47,

135.91, 134.72, 132.02, 130.91, 129.07, 127.32, 90.09, 76.80, 70.78, 56.90, 13.21, 12.29. MS *m/z*=310 (2^{35}Cl) $[M]^+$, 312 (^{35}Cl, ^{37}Cl) $[M+2]^+$, 314 (2^{37}Cl) $[M+4]^+$. Anal. Calcd for $C_{14}H_{13}Cl_2N_3O$: C 54.21; H 4.22; N 13.55. Found: C 54.01; H 4.48; N 13.38.

5.3.4. 2-(2,4-Dichlorophenyl)-1-[1,2,4]triazol-1-ylnon-3-yn-2-ol (6d). White crystalline solid, yield 59% from 2,4-dichloroacetophenone: mp 83–84 °C (hexanes/ethyl acetate). IR (cm^{-1}) 3078, 1509, 1463, 1135, 800. ^{1}H NMR ($CDCl_3$): δ 8.01 (s, 1H), 7.83 (s, 1H), 7.65 (d, 1H, *J*=8.7 Hz), 7.33 (d, 1H, *J*=2.15 Hz), 7.14 (dd, 1H, *J*=8.7, 2.15 Hz), 4.75 (d, 1H, *J*=14.0 Hz), 4.55 (d, 1H, *J*=14.0 Hz), 4.28 (2, 1H), 2.02 (t, 2H, *J*=7.0 Hz), 1.32 (t, 2H, *J*=7.0 Hz), 1.13–1.18 (m, 2H), 0.76 (t, 3H, *J*=7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 151.84, 144.45, 135.91, 134.96, 131.99, 130.90, 129.07, 127.33, 89.02, 77.39, 70.85, 56.88, 30.94, 27.77, 22.05, 18.54, 13.90. MS *m/z*=352 (2^{35}Cl) $[M]^+$, 354 (^{35}Cl, ^{37}Cl) $[M+2]^+$. Anal. Calcd for $C_{17}H_{19}Cl_2N_3O$: C 57.96; H 5.44; N 11.93. Found: C 57.70; H 5.71; N 12.19.

5.3.5. 2-(4-Chlorophenyl)-1-[1,2,4]triazol-1-ylhex-3-yn-2-ol (6e). Pale yellow gum, yield 41% from 4-chloroacetophenone: IR (cm^{-1}) 3079, 1508, 1488, 1130, 1084, 831. ^{1}H NMR ($CDCl_3$): δ 8.11 (s, 1H), 7.59 (s, 1H), 7.55 (dt, 2H, *J*=7.8, 2.0 Hz), 7.84 (dt, 2H, *J*=7.8, 2.0 Hz), 4.84 (s, 2H), 4.14 (s, 1H), 2.16 (q, 2H, *J*=7.5 Hz), 1.05 (t, 3H, *J*=7.5 Hz). ^{13}C NMR ($CDCl_3$): δ 151.75, 144.36, 139.43, 134.49, 128.62, 127.21, 90.39, 78.22, 72.19, 60.96, 13.47, 12.24. MS *m/z*=276 (^{35}Cl) $[M]^+$, 278 (^{35}Cl, ^{37}Cl) $[M+2]^+$. Anal. Calcd for $C_{14}H_{14}ClN_3O$: C 60.98; H 5.12; N 15.24. Found: C 61.26; H 4.83; N 15.01.

5.3.6. 2-(2,4-Difluorophenyl)-1-[1,2,4]triazol-1-ylhex-3-yn-2-ol (6f). White crystalline solid, yield 55% from 2,4-difluoroacetophenone: mp 76–78 °C (hexanes/ethyl acetate). IR (cm^{-1}) 3108, 1615, 1600, 1509, 1492, 1269, 964. ^{1}H NMR ($CDCl_3$): δ 8.06 (s, 1H), 7.85 (s, 1H), 7.56 (td, 1H, *J*=9.0, 6.4 Hz), 6.73–6.80 (m, 2H), 4.53 (q, 2H, *J*=11.3 Hz), 4.27 (s, 1H), 2.06 (q, 2H, *J*=7.5 Hz), 0.96 (t, 3H, *J*=7.5 Hz). ^{13}C NMR ($CDCl_3$): δ 163.01 (d, *J*=250 Hz), 159.60 (d, *J*=250 Hz), 151.80, 144.90, 129.06 (dd, *J*=9.6, 4.6 Hz), 123.78 (dd, *J*=11.10, 3.8 Hz), 111.19 (dd, *J*=21.1, 3.4 Hz), 104.58 (t, *J*=25.7 Hz), 89.34, 77.34, 69.51, 58.17, 13.36, 12.22. MS *m/z*=287 $[MH]^+$. Anal. Calcd for $C_{14}H_{13}F_2N_3O$: C 60.65; H 4.73; N 15.15. Found: C 60.35; H 4.89; N 15.42.

5.4. Preparation of (*E*)- and (*Z*)-3,4-dibromo-2-(2,4-dichlorophenyl)-1-[1,2,4]triazol-1-ylbut-3-en-2-ols (7a) and (7b)

2-(2,4-Dichlorophenyl)-1-[1,2,4]triazol-1-yl-but-3-yn-2-ol (0.99 g, 3.5 mmol) was stirred as a slurry in 5 mL chloroform and a few drops of a solution of bromine (0.56 g, 3.5 mmol) in 5 mL chloroform were added. The reaction mixture was irradiated with a 100 W tungsten lamp and after 10 min some decolourisation occurred. The remainder of the bromine in chloroform solution was added and irradiation was continued with stirring until all the colour had disappeared. The reaction mixture was poured into 25 mL water containing a few millilitres of 2 N sodium hydroxide and was extracted twice with 25 mL ethyl acetate. The organic extract was washed with 10 mL water, dried over magnesium sulfate and evaporated to give 1.66 g (100%) of a white foam, shown by ^{1}H NMR to consist of a 2:5 mixture of *E*:*Z* isomers **7a** and **7b**. The isomers were separated by HPLC on elution with 99:1 *t*-butyl ether/methanol, to give 0.41 g of the *E*-isomer **7a** as a white crystalline solid, and 0.90 g of the *Z*-isomer **7b** as a white powdery solid.

5.4.1. (*E*)-3,4-Dibromo-2-(2,4-dichlorophenyl)-1-[1,2,4]triazol-1-ylbut-3-en-2-ol (7a). White crystalline solid, yield 26%: mp 138–141 °C (hexanes/ethyl acetate). IR (cm^{-1}) 3075, 1511, 1466, 1200, 1132, 1080, 1015. ^{1}H NMR ($CDCl_3$): δ 7.84 (s, 1H), 7.81 (s, 1H), 7.38 (d, 1H, *J*=2.15 Hz), 7.82 (d, 1H, *J*=8.7 Hz), 7.09 (dd, *J*=8.7, 2.15 Hz), 6.78 (s, 1H), 5.19 (d, 1H, *J*=13.8 Hz), 4.91 (d, 1H, *J*=13.8 Hz), 4.85 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 151.69, 144.48, 136.59, 135.27, 131.43, 130.49, 129.88, 127.02, 124.81, 105.45, 78.17, 56.45. MS *m/z*=442 $[2^{79}Br]^+$, 444 $[^{79}Br, ^{81}Br]^+$, 446 $[2^{81}Br]^+$. Anal. Calcd for $C_{12}H_9Br_2Cl_2N_3O$: C 32.61; H 2.05; N 9.51. Found: C 32.78; H 2.46; N 9.22.

5.4.2. (*Z*)-3,4-Dibromo-2-(2,4-dichlorophenyl)-1-[1,2,4]triazol-1-ylbut-3-en-2-ol (7b). White powdery solid, yield 58%: mp 162–164 °C (hexanes/ethyl acetate). IR (cm^{-1}) 3031, 1516, 1135, 1020. ^{1}H NMR ($CDCl_3$): δ 7.84 (s, 1H), 7.72 (s, 1H), 7.40 (d, 1H, *J*=8.6 Hz), 7.26 (d, 1H, *J*=2.15 Hz), 7.08 (dd, 1H, *J*=8.6, 2.15 Hz), 6.79 (s, 1H), 5.21 (d, 1H, *J*=14.1 Hz), 4.87 (d, 1H, *J*=14.1 Hz). ^{13}C NMR ($CDCl_3$): δ 151.79, 144.41, 135.72, 135.25, 131.97, 131.19, 130.14, 127.56, 114.21, 80.15, 55.00. MS *m/z*=442 $[2^{79}Br]^+$, 444 $[^{79}Br, ^{81}Br]^+$, 446 $[2^{81}Br]^+$. Anal. Calcd for $C_{12}H_9Br_2Cl_2N_3O$: C 32.61; H 2.05; N 9.51. Found: C 32.40; H 2.31; N 9.28.

5.5. General procedure for the synthesis of 6-bromo-7-aryl-7-hydroxy-5-alkyl-7,8-dihydro-[1,2,4]triazolo-[1,2-*a*]pyridazine-4-ylium bromides (9b–f)

Bromine (18 mmol) in chloroform (10 mL) was added dropwise to a stirred solution of the triazolyl acetylene (18 mmol) in chloroform (50 mL) at a rate sufficient to allow decolourisation and to maintain the temperature at 30 °C or less. After all the bromine had been added the resultant yellow mixtures were stirred for 1 h and the white precipitates were filtered, washed well with chloroform and air dried to give the products **9b–f** as white solids, which were analysed without further purification.

5.5.1. 6-Bromo-7-(2,4-dichlorophenyl)-7-hydroxy-5-methyl-7,8-dihydro-[1,2,4]triazolo[1,2-*a*]pyridazine-4-ylium bromide (9b). White solid, yield 89%: mp 324–325 °C (dec). IR (cm^{-1}) 3148, 2179, 1351, 1089. ^{1}H NMR (DMSO-d_6): δ 9.85 (s, 1H), 9.51 (s, 1H), 7.93 (d, 1H, *J*=8.6 Hz), 7.77 (d, 1H, *J*=2.15 Hz), 7.64 (dd, 1H, *J*=8.6, 2.15 Hz), 5.19 (d, 1H, *J*=14.2 Hz), 5.11 (d, 1H, *J*=14.2 Hz), 2.61 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 149.69, 145.39, 135.88, 131.84, 130.63, 130.25, 128.85, 127.81, 120.16, 71.72, 53.78, 17.15. MS *m/z*=374 (^{79}Br, 2^{35}Cl) $[M]^+$, 376 (^{81}Br, 2^{35}Cl) $[M+2]^+$, 378 (^{81}Br, ^{35}Cl, ^{37}Cl) $[M+4]^+$. Anal. Calcd for $C_{13}H_{12}Br_2ClN_3O$: C 34.24; H 2.43; N 9.22. Found: C 33.98; H 2.57; N 8.89.

5.5.2. 6-Bromo-7-(2,4-dichlorophenyl)-5-ethyl-7-hydroxy-7,8-dihydro-[1,2,4]triazolo[1,2-*a*]pyridazin-4-ylium bromide (9c). White solid, yield 92%: mp 323–324 °C (dec). IR (cm^{-1}) 3158, 2256, 1349. ^1H NMR (DMSO-d_6): δ 9.95 (s, 1H), 9.52 (s, 1H), 7.95 (d, 1H, J=8.6 Hz), 7.77 (d, 1H, J=2.15 Hz), 7.64 (dd, 1H, J=8.6, 2.15 Hz), 7.54 (s, OH), 5.19 (d, 1H, J=14.4 Hz), 5.09 (d, 1H, J=14.4 Hz), 3.04 (q, 2H, J=7.5 Hz), 1.50–1.70 (m, 2H), 1.44–1.21 (m, 4H), 1.23 (q, 1H, J=11.0 Hz). ^{13}C NMR (DMSO-d_6): δ 149.86, 145.11, 135.95, 134.69, 133.14, 131.85, 130.59, 130.28, 127.83, 119.87, 71.67, 53.80, 23.83, 10.36. MS m/z=388 (^{79}Br, $2^{35}Cl$) $[M]^+$, 390 (^{81}Br, $2^{35}Cl$) $[M+2]^+$, 392 (^{81}Br, ^{35}Cl, ^{37}Cl) $[M+4]^+$. Anal. Calcd for $C_{14}H_{13}Br_2Cl_2N_3O$: C 35.78; H 2.79; N 8.94. Found: C 35.56; H 2.52; N 8.67.

5.5.3. 6-Bromo-7-(2,4-dichlorophenyl)-7-hydroxy-5-pentyl-7,8-dihydro-[1,2,4]triazolo[1,2-*a*]pyridazin-4-ylium bromide (9d). White solid, yield 88%: mp 272–273 °C (dec). IR (cm^{-1}) 3118, 3048, 2163, 1352, 1084. ^1H NMR (DMSO-d_6): δ 9.96 (s, 1H), 9.53 (s, 1H), 7.95 (d, 1H, J=8.6 Hz), 7.77 (d, 1H, J=2.15 Hz), 7.64 (dd, 1H, J=8.6, 2.15 Hz), 7.52 (s, OH), 5.19 (d, 1H, J=14.2 Hz), 5.11 (d, 1H, J=14.2 Hz), 3.03 (t, 2H, J=7.5 Hz), 1.65 (octet, 2H, J=7.5, 7.0 Hz), 1.50–1.30 (m, 4H), 0.89 (t, 3H, J=7.25 Hz). ^{13}C NMR (DMSO-d_6): δ 149.84, 145.15, 135.99, 134.69, 132.25, 131.73, 130.57, 130.24, 127.83, 120.49, 71.74, 53.70, 30.31, 29.73, 25.47, 21.81. MS m/z=430 (^{79}Br, $2^{35}Cl$) $[M]^+$, 432 (^{81}Br, $2^{35}Cl$) $[M+2]^+$, 434 (^{81}Br, ^{35}Cl, ^{37}Cl) $[M+4]^+$. Anal. Calcd for $C_{17}H_{19}Br_2Cl_2N_3O$: C 39.87; H 3.74; N 8.21. Found: C 39.66; H 3.59; N 8.05.

5.5.4. 6-Bromo-7-(4-chlorophenyl)-5-ethyl-7-hydroxy-7,8-dihydro-[1,2,4]triazolo[1,2-*a*]pyridazin-4-ylium bromide (9e). Pale yellow solid, yield 84%: mp 285–286 °C (dec). IR (cm^{-1}) 3195, 2162, 1491, 1347, 1090. ^1H NMR (DMSO-d_6): δ 9.94 (s, 1H), 9.47 (s, 1H), 7.54 (d, 1H, J=8.6 Hz), 7.48 (d, 1H, J=8.6 Hz), 7.27 (s, OH), 5.11 (d, 1H, J=14.0 Hz), 5.01 (d, 1H, J=14.0 Hz), 3.03 (q, 2H, J=7.5 Hz), 1.25 (q, 3H, J=7.5 Hz). ^{13}C NMR (DMSO-d_6): δ 149.15, 145.05, 139.13, 133.75, 133.37, 128.45, 128.17, 121.52, 71.81, 56.49, 24.07, 10.80. MS m/z=354 (^{79}Br, $2^{35}Cl$) $[M]^+$, 356 (^{81}Br, $2^{35}Cl$) $[M+2]^+$, 358 (^{81}Br, ^{35}Cl, ^{37}Cl) $[M+4]^+$. Anal. Calcd for $C_{14}H_{14}Br_2ClN_3O$: C 38.60; H 3.24; N 9.65. Found C 38.30; H 3.06; N 9.30.

5.5.5. 6-Bromo-7-(2,4-difluorophenyl)-5-ethyl-7-hydroxy-7,8-dihydro-[1,2,4]triazolo[1,2-*a*]pyridazin-4-ylium bromide (9f). White solid, yield 88%: mp 294–295 °C (dec). IR (cm^{-1}) 3185, 2162, 1501, 1114. ^1H NMR (DMSO-d_6): δ 9.95 (s, 1H), 9.53 (s, 1H), 7.79 (td, 1H, J=8.8, 6.5 Hz), 7.45 (s, OH), 7.42 (qd, 1H, J=9.0, 2.6 Hz), 7.26 (td, 1H, J=8.6, 2.5 Hz), 5.21 (d, 1H, J=14.2 Hz), 4.82 (d, 1H, J=14.2 Hz), 3.03 (qd, 2H, J=7.5, 1.2 Hz), 1.23 (t, 3H, J=7.5 Hz); ^{13}C NMR (DMSO-d_6): δ 163.0 (d, J=248 Hz), 158.5 (d, J=248 Hz), 149.69, 144.94, 132.96, 129.72, 123.52 (d, J=14.20 Hz), 120.42, 111.72 (d, J=28.4 Hz), 104.77 (t, J=26.50 Hz), 70.40, 54.43, 23.97, 10.69; MS m/z=354 (^{79}Br, $2^{35}Cl$) $[M]^+$, 356 (^{81}Br, $2^{35}Cl$) $[M+2]^+$, 358 (^{81}Br, ^{35}Cl, ^{37}Cl) $[M+4]^+$. Anal. Calcd for $C_{14}H_{13}BrF_2N_3O$; C 38.44; H 2.97; N 9.61. Found C 38.60; H 2.94; N 9.69.

5.6. General procedure for the synthesis of 5-aryl-3-alkylpyridazines (8b–f)

The triazolium salt (1.1 mmol) was stirred in water (20 mL) and warm 5 N sodium hydroxide (20 mL) was added quickly. The mixture was shaken for a few minutes and then extracted with ethyl acetate, and the ethyl acetate extracts were washed with water, dried over magnesium sulfate and evaporated. The residues were purified by flash column chromatography (hexane/ethyl acetate, 3:7) to give the pyridazines **8b–f** as solids.

5.6.1. 5-(2,4-Dichlorophenyl)-3-methylpyridazine (8b). White solid, yield 100%: mp 153–155 °C (hexanes/ethyl acetate). IR (cm^{-1}) 1596, 1475, 1359, 1105, 861, 822. ^1H NMR ($CDCl_3$): δ 9.13 (s, 1H), 7.57 (d, 1H, J=1.9 Hz), 7.42 (s, 1H), 7.41 (dd, 1H, J=8.3, 1.9 Hz), 7.29 (d, 1H, J=8.3 Hz), 2.81 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 159.78, 149.17, 136.67, 136.18, 133.26, 132.79, 131.57, 130.38, 127.92, 126.60, 22.37. MS m/z=238 ($2^{35}Cl$) $[M]^+$, 240 (^{35}Cl, ^{37}Cl) $[M+2]^+$. Anal. Calcd for $C_{11}H_8Cl_2N_2$: C 55.25; H 3.37; N 11.72. Found C 54.88; H 3.50; N 11.45.

5.6.2. 5-(2,4-Dichlorophenyl)-3-ethylpyridazine (8c). Beige solid, yield 28%: mp 98–100 °C (hexanes/ethyl acetate). IR (cm^{-1}) 1597, 1477, 1106, 861, 818. ^1H NMR ($CDCl_3$): δ 9.14 (s, 1H), 7.57 (d, 1H, J=1.9 Hz), 7.42 (s, 1H), 7.41 (dd, 1H, J=8.3, 1.9 Hz), 7.30 (d, 1H, J=8.3 Hz), 3.10 (q, 2H, J=7.6 Hz), 1.43 (t, 3H, J=7.6 Hz). ^{13}C NMR ($CDCl_3$): δ 164.45, 149.31, 136.70, 136.09, 133.28, 132.97, 131.58, 130.37, 127.90, 125.51, 29.51, 13.62. MS m/z=252 ($2^{35}Cl$) $[M]^+$, 256 (^{35}Cl, ^{37}Cl) $[M+2]^+$. Anal. Calcd for $C_{12}H_{10}C_{l2}N_2$: C 56.91; H 3.95; N 11.07. Found C 56.80; H 3.79; N 11.05.

5.6.3. 5-(2,4-Dichlorophenyl)-3-pentylpyridazine (8d). White solid, yield 45%: mp 60–64 °C (hexanes/ethyl acetate). IR (cm^{-1}) 1598, 1476, 1104, 864, 820. ^1H NMR ($CDCl_3$): δ 9.13 (s, 1H), 7.57 (d, 1H, J=2.15 Hz), 7.41 (dd, 1H, J=8.3, 2.15 Hz), 7.40 (s, 1H), 7.30 (d, 1H, J=8.3 Hz), 3.05 (d, 1H, J=7.8 Hz), 1.83 (quintet, 2H, J=7.5 Hz), 1.40 (m, 4H), 0.91 (t, 3H, J=7.25 Hz). ^{13}C NMR ($CDCl_3$): δ 163.58, 149.23, 136.56, 136.09, 133.30, 132.96, 131.57, 130.37, 127.89, 125.97, 36.28, 31.40, 29.66, 29.31, 22.40, 13.93. MS m/z=294 ($2^{35}Cl$) $[M]^+$, 296 (^{35}Cl, ^{37}Cl) $[M+2]^+$. Anal. Calcd for $C_{15}H_{16}Cl_2N_2$: C 61.02; H 5.46; N 9.49. Found C 61.27; H 5.60; N 8.99.

5.6.4. 5-(4-Chlorophenyl)-3-ethylpyridazine (8e). Pale yellow solid, yield 68%: mp 108–109 °C (hexanes/ethyl acetate). IR (cm^{-1}) 1596, 1493, 1090, 822. ^1H NMR ($CDCl_3$): δ 9.28 (d, 1H, J=2.15 Hz), 7.61 (d, 1H, J=8.7 Hz), 7.52 (d, 1H, J=8.7 Hz), 7.47 (d, 1H, J=2.15 Hz), 3.09 (q, 2H, J=7.6 Hz), 1.43 (t, 3H, J=7.6 Hz). ^{13}C NMR ($CDCl_3$): δ 164.84, 147.58, 137.65, 136.36, 133.26, 129.72, 128.35, 122.57, 29.48, 13.74. MS m/z=218 ($2^{35}Cl$) $[M]^+$, 220 (^{35}Cl, ^{37}Cl) $[M+2]^+$. Anal. Calcd for $C_{12}H_{11}ClN_2$: C 65.90; H 5.07; N 12.81. Found C 65.72; H 5.33; N 12.52.

5.6.5. 5-(2,4-Difluorophenyl)-3-ethylpyridazine (8f). Pale yellow solid, yield 91%: mp 53–54 °C (hexanes/ethyl acetate). IR (cm^{-1}) 1595, 1504, 1139, 843. ^1H NMR ($CDCl_3$): δ

9.22 (s, 1H), 7.51 (td, 1H, J=7.5, 6.4 Hz), 7.49 (s, 1H), 7.06 (qq, 1H, J=7.0, 2.4, 1.0 Hz), 7.01 (qd, 1H, J=8.6, 2.4 Hz), 3.09 (q, 2H, J=7.5 Hz), 1.43 (t, 3H, J=7.5 Hz). ^{13}C NMR ($CDCl_3$): δ 164.66, 163.79 (dd, J=253, 11.9 Hz), 160.44 (dd, J=253, 11.9 Hz), 148.72 (d, J= 4.0 Hz), 133.43, 131.08 (dd, J=9.6, 4.6 Hz), 124.57 (d, J=4 Hz), 119.30 (d, J=13 Hz), 112.65 (q, J=21, 4 Hz), 105.15 (t, J=25 Hz), 29.52, 13.67. MS m/z=220 $[M]^+$. Anal Calcd for $C_{12}H_{10}F_2N_2$: C 65.44; H 4.58; N 12.72; Found C 65.09; H 4.68; N 12.51.

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