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New enediyne derivatives: synthesis of symmetrically and unsymmetrically disubstituted 4,5-dialkynyl-3(2*H*)-pyridazinones

Omar R'kyek, Bert U. W. Maes, Tim H. M. Jonckers, Guy L. F. Lemière* and Roger A. Dommisse

Department of Chemistry, University of Antwerp (RUCA), Groenenborgerlaan 171, B-2020 Antwerp, Belgium

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Abstract—4,5-Dialkynyl-2-(methyl or phenyl)-3(2*H*)-pyridazinones (**2a**–**c**) were efficiently prepared via Sonogashira cross-coupling reaction on 4,5-dichloro-2-(methyl or phenyl)-3(2*H*)-pyridazinones (**1a**,**b**). Selective Sonogashira reactions were successfully achieved on 4-chloro-2-methyl-5-trifluoromethanesulfonyloxy- (**6**) and 5-chloro-2-methyl-4-trifluoromethanesulfonyloxy-3(2*H*)-pyridazinone (**11**), yielding 5-alkynyl-4-chloro- (**7a**–**c**) and 4-alkynyl-5-chloro-2-methyl-3(2*H*)-pyridazinones (**3a**,**c**,**e**), respectively. Compounds **7a**–**c** and **3a**,**c**,**e** were subjected to a second Sonogashira reaction giving 4,5-dialkynyl-2-methyl-3(2*H*)-pyridazinones (**8a**–**c**) bearing two different acetylene substituents. Suzuki cross-coupling reaction was also achieved on compounds **7a** and **3a** producing 4-aryl-5-phenylethynyl- and 5-aryl-4-phenylethynyl-2-methyl-3(2*H*)-pyridazinones, respectively, in excellent yield.

Enediynes have attracted considerable interest in the past decades from chemists as well as from medicinal chemists. From a chemical point of view, the enediyne moiety is attractive since it can be transformed into a benzene ring via a Bergman cyclization reaction.[1] From a medicinal point of view, compounds containing an enediyne moiety are well known as antitumour antibiotics.[2] The chemical and medicinal interest for this structural entity prompted us to investigate the preparation of hitherto unknown enediynes based on the 3(2*H*)-pyridazinone core via a palladium catalysed alkynylation approach (Sonogashira reaction).

Several articles have been published dealing with the synthesis of monoalkynylpyridazines via Sonogashira reaction.[3] Igeta,[4] Yamanaka,[5] Bailey,[6] Stanforth[7] and Haider[8] reported palladium catalysed alkynylation of the pyridazine core starting from halopyridazines (chloro- and iodo-). Generally, the most efficient reactions are performed starting from iodopyridazines. Chloropyridazines often give bad results since harsh reaction conditions are usually required. Besides halopyridazines, trifluoromethanesulfonyloxypyridazines have also been used in Sonogashira reactions.[9] These trifluoromethanesulfonyloxypyridazines are very attractive starting materials since they can be easily prepared from the corresponding pyridazinones under mild reaction conditions.[9,16,17] In contrast to the pyridazine core, there is only one report describing Sonogashira reactions on the 3(2*H*)-pyridazinone system. Raviña and co-workers prepared 5-alkynyl-2-methoxymethyl-6-phenyl-3(2*H*)-pyridazinones via palladium catalysed Sonogashira reaction of terminal alkynes with 5-bromo-2-methoxymethyl-6-phenyl-3(2*H*)-pyridazinone.[10]

Recently, our laboratory described that chloro-3(2*H*)-pyridazinones are valuable starting materials for palladium catalysed cross-coupling reactions. Suzuki arylation as well as Buchwald–Hartwig amination can be very efficiently executed on these skeletons using triarylphosphine based palladium catalysts.[11,12] Since 4,5-dichloro-3(2*H*)-pyridazinones are cheap and easily accessible, we decided to investigate Sonogashira reactions on these compounds in order to prepare the hitherto unknown 4,5-dialkynyl-3(2*H*)-pyridazinones.

First we focused our attention on the synthesis of 2-substituted 4,5-dialkynyl-3(2*H*)-pyridazinones with two identical alkynyl substituents (**2**). These compounds were prepared using modified Sonogashira conditions[13] starting from 2-substituted (2-methyl- or 2-phenyl-) 4,5-dichloro-3(2*H*)-pyridazinones and an excess (3 equiv.) of terminal alkyne (phenylacetylene or trimethylsilylacetylene). Efforts to use these reaction conditions to prepare 2-methyl-4,5-di(pent-1-ynyl)-3(2*H*)-pyridazinone (**2e**) gave only incomplete reactions even after 3 days of heating as confirmed by DCI–MS analysis. A mass spectrum of the crude reaction mixture revealed the presence of **2e** and a monopentynylated 3(2*H*)-pyridazinone (**3e**). Gradual increase of the amount of 1-pentyne as well as the amount of catalyst and co-catalyst did not lead to better results. The exact structure of **3e** could only be proven after a selective alkynylation reaction (see later). The data of Table 1 prove that the nature of the acetylene is very important for the success of the Sonogashira reactions and consequently that the oxidative

Keywords: pyridazinones; Sonogashira reaction; alkynes; palladium and compounds.

* Corresponding author. Tel.: +32-3-21-80-226; fax: +32-3-21-80-233; e-mail: lemiere@ruca.ua.ac.be

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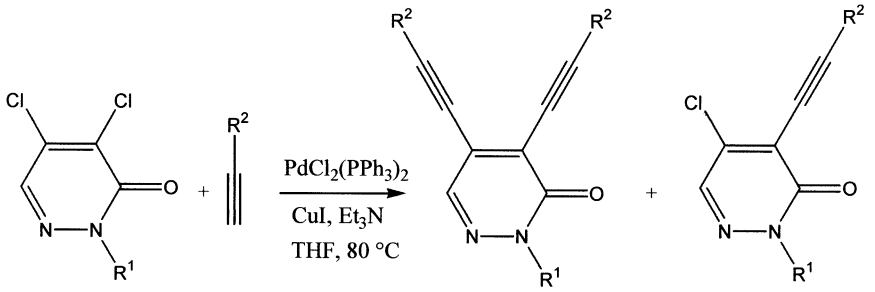
Table 1. Sonogashira cross-coupling reaction on 4,5-dichloro-3(2*H*)-pyridazinones



1a: $R^1 = CH_3$
1b: $R^1 = C_6H_5$

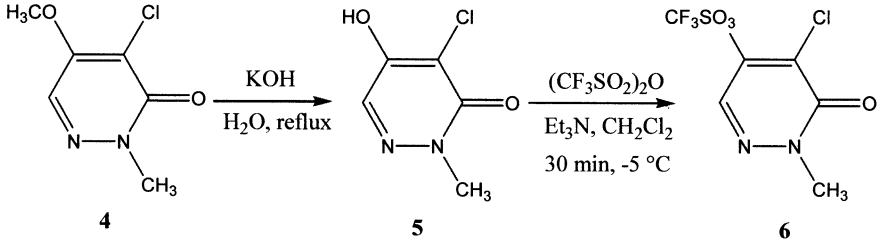
2a-e **3e**

Entry	R^1	R^2	Time (h)	Yield of **2**[a] (%)	Yield of **3**[a] (%)
1	CH_3	C_6H_5	30	82 (**2a**)	0
2	C_6H_5	C_6H_5	16	75 (**2b**)	0
3	CH_3	$(CH_3)_3Si$	50	70 (**2c**)	0
4	C_6H_5	$(CH_3)_3Si$	30	80 (**2d**)	0
5	CH_3	C_3H_7	72	34 (**2e**)	36 (**3e**)

[a] Reaction conditions: 2.5 mmol **1a** or **b**, 3 equiv. 1-alkyne, 3 mol% $PdCl_2(PPh_3)_2$, 3 mol% CuI, Et_3N, THF at 80°C (oil bath) under N_2 atmosphere.

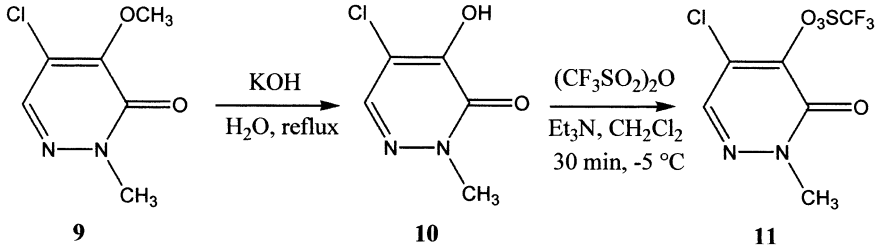
addition is not the rate determining step as often observed for this type of reaction.[14]

Secondly, we investigated the synthesis of 2-substituted 4,5-dialkynyl-3(2*H*)-pyridazinones bearing two different acetylenes. Attempts to use 1 equiv. of the terminal alkyne at room temperature or at reflux to replace selectively one of the chlorine atoms of **1a** failed, and a mixture of mono and dialkynylated products was obtained as indicated by DCI–MS analysis. Since it is well known that the C–I, C–Br and C–OTf bonds readily undergo oxidative addition with different reactivity order, we envisaged the possibility of replacing one of the chlorine atoms in compound **1a** with a different halogen or a pseudohalogen. In this way, selective palladium-catalysed cross-coupling reactions can be achieved and hence disubstitution problems might be avoided. Because of its ease of preparation, the triflate group was our substituent of choice. Starting from 4-chloro-5-methoxy-2-methyl-3(2*H*)-pyridazinone (**4**) or from 5-chloro-4-methoxy-2-methyl-3(2*H*)-pyridazinone (**9**),[11] which were hydrolysed in aqueous KOH solution,[15] the hydroxy products **5** and **10** were transformed with trifluoromethanesulfonic anhydride in CH_2Cl_2 and Et_3N to hitherto unknown 4-chloro-2-methyl-5-trifluoromethanesulfonyloxy-3(2*H*)-pyridazinone (**6**) and 5-chloro-2-methyl-4-trifluoromethanesulfonyloxy-3(2*H*)-pyridazinone (**11**), respectively (Schemes 1 and 2).[16] As illustrated in Tables 2 and 4, selective Sonogashira reactions starting from **6** or **11** were achieved successfully. 5-Alkynyl-4-chloro-(**7a–c**) and 4-alkynyl-5-chloro-2-methyl-3(2*H*)-pyridazinones



4 **5** **6**

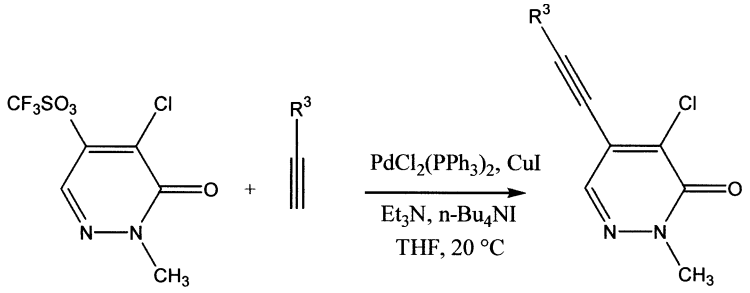
Scheme 1. Preparation of 4-chloro-2-methyl-5-trifluoromethanesulfonyloxy-3(2*H*)-pyridazinone (**6**).



9 **10** **11**

Scheme 2. Preparation of 5-chloro-2-methyl-4-trifluoromethanesulfonyloxy-3(2*H*)-pyridazinone (**11**).

Table 2. Selective cross-coupling reaction on **6**

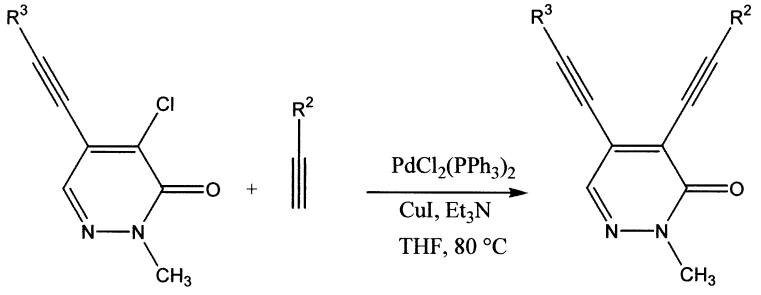


6 **7a-c**

Entry	R^3	Time (h)	Yield[a] (%)
1	C_6H_5	2	83 (**7a**)
2	$(CH_3)_3Si$	2	72 (**7b**)
3	C_3H_7	24	60 (**7c**)

[a] Reaction conditions: 2 mmol **6**, 1.01 equiv. 1-alkyne, 3 mol% $PdCl_2(PPh_3)_2$, 30 mol% CuI, 3 equiv. *n*-Bu_4NI, 3 equiv. Et_3N, THF at room temperature under N_2 atmosphere.

Table 3. Introduction of a second alkynyl group on **7a–c**

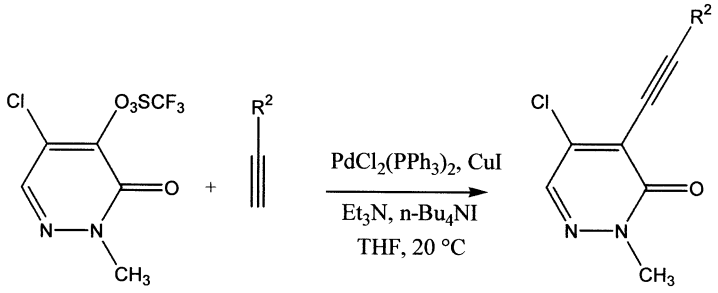


7a-c **8a-c**

Entry	R^2	R^3	Time (h)	Yield of **8**[a] (%)
1	C_6H_5	$(CH_3)_3Si$	7	79 (**8a**)
2	C_6H_5	C_3H_7	45	51 (**8b**)
3	$(CH_3)_3Si$	C_6H_5	24	50 (**8c**)

[a] Reaction conditions: 1.12 mmol **7a–c**, 1.3 equiv. 1-alkyne, 3 mol% $PdCl_2(PPh_3)_2$, 5 mol% CuI, Et_3N, THF at 80°C (oil bath) under N_2 atmosphere.

Table 4. Selective cross-coupling reaction on **11**

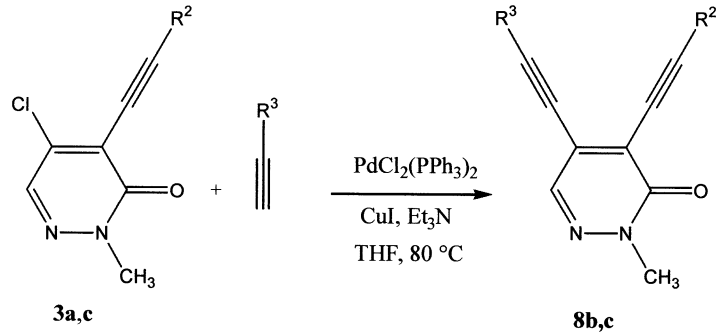


11 **3a,c,e**

Entry	R^2	Time (h)	Yield of **3**[a] (%)
1	C_6H_5	2	95 (**3a**)
2	$(CH_3)_3Si$	24	55 (**3c**)
3	C_3H_7	8	82 (**3e**)

[a] Reaction conditions: 1.4 mmol **11**, 1.01 equiv. 1-alkyne, 3 mol% $PdCl_2(PPh_3)_2$, 30 mol% CuI, 3 equiv. *n*-Bu_4NI, Et_3N/THF (1:1) at room temperature under N_2 atmosphere.

Table 5. Introduction of a second alkynyl group on **3a**,**c**

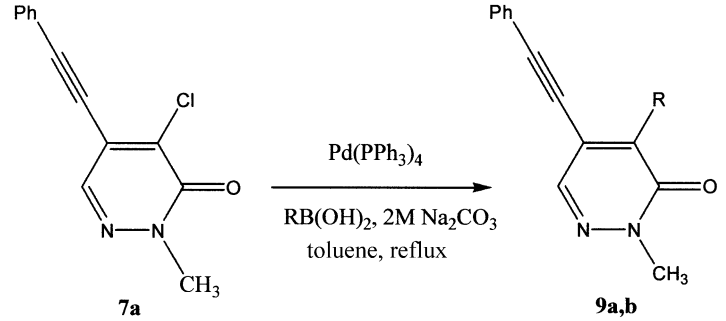


3a,**c** **8b**,**c**

Entry	R^2	R^3	Time (h)	Yield of **8**[a] (%)
1	C_6H_5	C_3H_7	46	97 (**8b**)
2	$(CH_3)_3Si$	C_6H_5	20	52 (**8c**)

[a] Reaction conditions: 1.12 mmol **3a**,**c**, 1.3 equiv. 1-alkyne, 3 mol% $PdCl_2(PPh_3)_2$, 5 mol% CuI, Et_3N, THF at 80°C (oil bath) under N_2 atmosphere.

Table 6. Suzuki cross-coupling reaction on **7a**



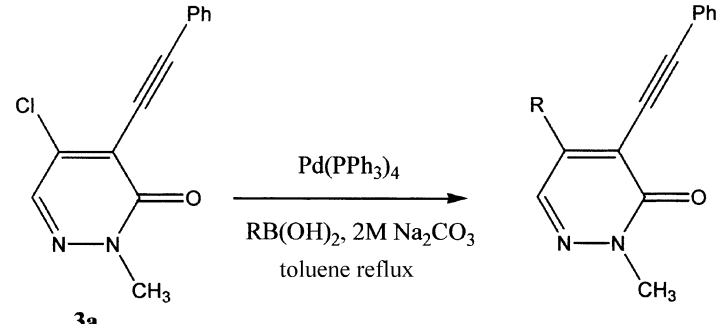
7a **9a,b**

Entry	R	Time (h)	Yield of **9**[a] (%)
1	C_6H_5	15	86 (**9a**)
2	3-$CF_3(C_6H_4)$	16	78 (**9b**)

[a] Reaction conditions: 0.7 mmol **7a**, 1.5 equiv. $RB(OH)_2$, 3 mol% $Pd(PPh_3)_4$, aq. Na_2CO_3 (2 M, 1.1 mL) at 120°C (oil bath) under N_2 atmosphere.

(**3a**,**c**,**e**) were obtained in moderate to good yield. Under our optimised conditions, no dialkynylated products were observed. In contrast, increasing the amount of the terminal alkyne, and using higher reaction temperatures or longer reaction times were not suitable for the selectivity and only favoured the formation of the disubstituted products. All the spectral data of the previously obtained product (**3e**, see Table 1, entry 5) were identical to those of the pentynyl

Table 7. Suzuki cross-coupling reaction on **3a**



3a **10a,b**

Entry	R	Time (h)	Yield of **10**[a] (%)
1	C_6H_5	6	99 (**10a**)
2	3-$CF_3(C_6H_4)$	6	94 (**10b**)

[a] Reaction conditions: 0.7 mmol **3a**, 1.5 equiv. $RB(OH)_2$, 3 mol% $Pd(PPh_3)_4$, aq. Na_2CO_3 (2 M, 1.1 mL) at 120°C (oil bath) under N_2 atmosphere.

derivative synthesised from **11**, confirming that **3e** is the 5-chloro-2-methyl-4-(pent-1-ynyl)-3(2*H*)-pyridazinone. The exact structure of the monoalkynylated pyridazinones was proved using 2D-NMR spectroscopy. Especially the use of the long-range HETCOR experiment turned out to be valuable since we were able to detect a three-bond correlation (^3J) between the proton H-6 of the pyridazinones and the carbon atom C-1′ of the alkynyl group in the case of the 5-alkynylated compounds. Such a coupling was absent when performing the same experiment on the 4-alkynylated isomers.

Finally, a second Sonogashira reaction on the remaining chlorine atom of **7a**–**c** and **3a**,**c** was investigated. In fact, each monoalkynyl precursor was smoothly coupled with a different terminal alkyne yielding the desired dialkynylated 3(2*H*)-pyridazinones in moderate to good yield (Tables 3 and 5). To the best of our knowledge, there are no reports dealing with the preparation of 2-substituted 3(2*H*)-pyridazinone compounds bearing identical or different acetylenic groups at C-4 and C-5 positions, neither with an alkynyl substituent at C-4 and a chlorine atom at C-5 nor vice versa.

Encouraged by these results, and since we know from previous results that the Suzuki cross-coupling reaction works well on the chloro-3(2*H*)-pyridazinone skeleton,[11] we investigated the introduction of an aryl group in C-4 and C-5 positions. Thus, the compounds **7a** and **3a** were reacted with phenylboronic acid and 3-trifluoromethylbenzeneboronic acid to produce a new class of 3(2*H*)-pyridazinone based compounds (Tables 6 and 7).

In conclusion, by using the Sonogashira cross-coupling reaction and starting from easily accessible starting materials, 2-substituted 4,5-dialkynyl-3(2*H*)-pyridazinones with identical or different acetylenic groups can be prepared. We have also demonstrated that a selective Sonogashira reaction can be achieved by using 2-substituted 4-chloro-5-trifluoromethanesulfonyloxy-3(2*H*)-pyridazinone or its 5-chloro-4-triflate isomer.

1. Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity 400 spectrometer in $CDCl_3$ with TMS as the internal standard. Chemical shifts are given in ppm and *J* values in Hz. HRMS and product ion spectra were recorded on quadrupole-time of flight mass spectrometer (QTof 2, Micromass, Manchester, UK) equipped with a standard electrospray ionisation (ESI) interface. Samples were infused in a 0.1% formic acid/MeOH (10:90) mixture at 5 μL/min. Product ion spectra were recorded selecting the protonated molecule $[M+H]^+$ in the quadrupole. This precursor ion is fragmented in the collision cell using Ar as collision gas and a collision energy of 30 eV. IR spectra were obtained as potassium bromide pellets or as liquid films between two potassium bromide pellets with a Brucker Vector 22 spectrometer. Melting points were recorded using a Büchi B-545 apparatus and are uncorrected. 4,5-Dichloro-2-(methyl and phenyl)-3(2*H*)-pyridazinones (Lancaster, Acros, Avocado), 4-chloro-5-methoxy-2-methyl-3(2*H*)-pyridazinone (Avocado), 1-alkynes (Aldrich, Acros), trifluoromethanesulfonic anhydride (Acros, Aldrich), and $PdCl_2(PPh_3)_2$ (Fluka) were obtained from commercial sources. THF (Acros) was dried over sodium/benzophenone and freshly distilled before use. Flash column chromatography was performed on Kiesel gel 60(Merck), 0.040–0.063 mm.

1.1. General procedure for the preparation of 2-substituted 4,5-dialkynyl-3(2*H*)-pyridazinones (2a–e)

To a solution of 2-substituted 4,5-dichloro-3(2*H*)-pyridazinone (450 mg, 2.5 mmol) in THF (12 mL), $Pd_2Cl_2(PPh_3)_2$ (52 mg, 0.075 mmol), CuI (14 mg, 0.075 mmol), Et_3N (0.95 mL, 7.0 mmol) and the 1-alkyne (7.5 mmol) were added. The mixture was heated at 80°C under a N_2 atmosphere until the starting material had been consumed (TLC analysis and/or DCI–MS). The reaction mixture was then cooled to room temperature, diluted with EtOAc and filtered through a pad of Celite®. The filtrate was concentrated in vacuo and then purified on silica gel. The following products were prepared by this procedure.

1.1.1. 2-Methyl-4,5-bis(phenylethynyl)-3(2*H*)-pyridazinone (2a). Chromatography eluent: heptane/EtOAc (85:15); yield (640 mg, 82%); mp 113°C (brown solid, decomp.); ν_{max} (KBr): 3034, 2944, 2216, 2197, 1644, 1569, 1490, 1383, 1356, 1056, 943, 758, 690, 530 cm^{-1}; δ_H ($CDCl_3$): 7.80 (s, 1H, H-6), 7.66–7.62 (m, 2H, H_{Ph4}-2,6 or H_{Ph5}-2,6), 7.61–7.58 (m, 2H, H_{Ph4}-2,6 or H_{Ph5}-2,6), 7.47–7.34 (m, 6H, H_{Ph4}-3,4,5 and H_{Ph5}-3,4,5), 3.82 (s, 3H, NCH_3); δ_C ($CDCl_3$): 158.70 (C-3), 136.64 (C-6), 132.33, 132.15 (C_{Ph4}-2,6 or C_{Ph5}-2,6), 130.03, 129.67 (C_{Ph4}-4 or C_{Ph5}-4), 128.69, 128.50 (C_{Ph4}-3,5 or C_{Ph5}-3,5), 128.56, 125.62 (C-4 or C-5), 122.36, 121.65 (C_{Ph4}-1 or C_{Ph5}-1), 105.34, 102.21 (C-2′ or C-2″), 83.91, 83.76 (C-1′ or C-1″), 40.62 (NCH_3); MS (ESI) *m*/*z*: 311 (100%), 268, 254, 239; HRMS (ESI) for $C_{21}H_{15}N_2O$ $[M+H]^+$: calcd 311.1184, found 311.1186.

1.1.2. 2-Phenyl-4,5-bis(phenylethynyl)-3(2*H*)-pyridazinone (2b). Chromatography eluent: heptane/EtOAc (85:15); yield (750 mg, 75%); mp 121°C (brown solid, decomp.); ν_{max} (KBr): 3059, 2924, 2201, 1658, 1572, 1492, 1130, 899, 755, 689, 529 cm^{-1}; δ_H ($CDCl_3$): 7.95 (s, 1H, H-6), 7.67–7.61 (m, 6H, H_{Ph4}-2,6 and H_{Ph5}-2,6 and H_{NPh}-2,6), 7.51–7.34 (m, 9H, H_{Ph4}-3,4,5 and H_{Ph5}-3,4,5 and H_{NPh}-3,4,5); δ_C ($CDCl_3$): 158.04 (C-3), 141.44 (C_{NPh}-1), 137.41 (C-6), 132.37, 132.23 (C_{Ph4}-2,6 or C_{Ph5}-2,6), 130.16, 129.76 (C_{Ph4}-4 or C_{Ph5}-4), 128.76, 128.73, 128.53 (C_{Ph4}-3,5 or C_{Ph5}-3,5 or C_{NPH}-3,5), 128.39 (C_{NPh}-4), 128.21, 127.05 (C-5 or C-4), 125.29 (C_{NPh}-2,6), 122.30, 121.61 (C_{Ph4}-1 or C_{Ph5}-1), 105.73, 102.89 (C-2′ or C-2″), 84.05, 83.96 (C-1′ or C-1″); MS (ESI) *m*/*z*: 373 (100%), 330, 268, 240; HRMS (ESI) for $C_{26}H_{17}N_2O$ $[M+H]^+$: calcd 373.1341, found 373.1347.

1.1.3. 2-Methyl-4,5-bis(trimethylsilylethynyl)-3(2*H*)-pyridazinone (2c). Chromatography eluent: heptane/EtOAc (85:15); yield (530 mg, 70%); brownish oil; ν_{max} (liquid film): 2961, 1668, 1251, 1077, 949, 846, 761 cm^{-1}; δ_H ($CDCl_3$): 7.66 (s, 1H, H-6), 3.76 (s, 3H, NCH_3), 0.29 (s, 18H, 2×($(CH_3)_3Si$); δ_C ($CDCl_3$): 158.60 (C-3), 136.60 (C-6), 129.02, 125.75 (C-4 or C-5), 112.55 (C-2′), 109.34

(C-2″), 98.03, 97.31 (C-1″ or C-1′), 40.51 (NCH_3), −0.28 ($(CH_3)_3Si$), −0.43 ($(CH_3)_3Si$); MS (ESI) *m/z*: 303, 231, 73 (100%); HRMS (ESI) for $C_{15}H_{23}N_2OSi_2$ $[M+H]^+$: calcd 303.1349, found 303.1335.

1.1.4. 2-Phenyl-4,5-bis(trimethylsilylethynyl)-3(2*H*)-pyridazinone (2d). Chromatography eluent: heptane/EtOAc (85:15); yield (790 mg, 80%); dark brown oil; ν_{max} (liquid film): 3068, 2936, 2901, 1672, 1573, 1490, 1251, 1137, 1036, 846, 763, 693, 629, 588 cm^{-1}; δ_H ($CDCl_3$): 7.81 (s, 1H, H-6), 7.58 (br d, 2H, H_{Ph}-2,6), 7.44 (br t, 2H, H_{Ph}-3,5), 7.37 (br t, 1H, H_{Ph}-4), 0.31 (s, 9H, $(CH_3)_3Si$), 0.29 (s, 9H, $(CH_3)_3Si$); δ_C ($CDCl_3$): 157.94 (C-3), 141.28 (C_{Ph}-1), 137.34 (C-6), 128.75, 127.30 (C-4 or C-5), 128.64 (C_{Ph}-2,6), 128.33 (C_{Ph}-4), 125.16 (C_{Ph}-3,5), 113.02 (C-2′), 110.22 (C-2″), 98.10, 97.42 (C-1′ or C-1″), -0.31 ($(CH_3)_3Si$), −0.42 ($(CH_3)_3Si$); MS (ESI) *m/z*: 365, 293, 73 (100%); HRMS (ESI) for $C_{20}H_{25}N_2OSi_2$ $[M+H]^+$: calcd 365.1505, found 365.1495.

1.1.5. 2-Methyl-4,5-di(pent-1-ynyl)-3(2*H*)-pyridazinone (2e). Chromatography eluent: heptane/EtOAc (85:15); yield (320 mg, 34%); dark yellow oil; ν_{max} (liquid film): 2964, 2935, 2873, 2221, 1658, 1574, 1462, 1378, 1231, 990, 882, 772, 660 cm^{-1}; δ_H ($CDCl_3$): 7.61 (s, 1H, H-6), 3.75 (s, 3H, NCH_3), 2.54 (t, J=7.0 Hz, 2H, H-3′ or H-3″), 2.47 (t, J=7.0 Hz, 2H, H-3′ or H-3″), 1.67 (br hex, $J\approx$7.0 Hz, 2H, H-4′ or H-4″), 1.66 (br hex, $J\approx$7.0 Hz, 2H, H-4′ or H-4″), 1.08 (t, J=7.3 Hz, 3H, H-5′ or H-5″), 1.07 (t, J=7.3 Hz, 3H, H-5′ or H-5″); δ_C ($CDCl_3$): 159.41 (C-3), 137.25 (C-6), 129.21, 126.24 (C-4 or C-5), 107.10, 103.75 (C-2′ or C-2″), 75.88, 75.15 (C-1′ or C-1″), 40.47 (NCH_3), 22.34, 21.89 (C-3′ or C-3″), 21.84, 21.74 (C-4′ or C-4″), 13.45 (C-5′ and C-5″); MS (ESI) *m/z*: 243, 213, 199, 185, 129 (100%), 115; HRMS (ESI) for $C_{15}H_{19}N_2O$ $[M+H]^+$: calcd 243.1497, found 243.1505

1.2. General procedure for the preparation of 4-chloro-2-methyl-5-trifluoromethanesulfonyloxy-3(2*H*)-pyridazinone (6) and its isomer 5-chloro-4-trifluoromethanesulfonyloxy-3(2*H*)-pyridazinone (11)

A solution of compound **5** or **10** (340 mg, 2.125 mmol), Et_3N (0.4 mL, 2.76 mmol) in dichloromethane (10.5 mL), was chilled in an ice-acetone bath (temperature of the bath was −5°C). Under stirring, trifluoromethanesulfonic anhydride (0.4 mL, 2.34 mmol) was added dropwise to the solution. The resulting yellow solution was stirred for 30 min at −5°C. The reaction mixture was then poured into dilute HCl (30 mL, 0.5 M) and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with a 1% $NaHCO_3$ solution (70 mL), brine (70 mL), and then dried ($MgSO_4$). The filtrate was concentrated under reduced pressure.

1.2.1. 4-Chloro-2-methyl-5-trifluoromethanesulfonyloxy-3(2*H*)-pyridazinone (6). Brown oil. Because of its instability, this isomer was used immediately after its preparation, therefore, no spectral data were recorded.

1.2.2. 5-Chloro-2-methyl-4-trifluoromethanesulfonyloxy-3(2*H*)-pyridazinone (11). Yield (910 mg, 90%, crude product); mp 62°C (pale brown solid); ν_{max} (KBr): 3083, 1666, 1431, 1209, 1133, 958, 813, 624, 512 cm^{-1}; δ_H ($CDCl_3$): 7.84 (s, 1H, H-6), 3.85 (s, 3H, NCH_3); δ_C ($CDCl_3$): 155.14 (C-3), 142.47 (C-4), 135.57 (C-6), 130.40 (C-5), 118.45 (q, J_{CF}=321.2 Hz, CF_3), 40.63 (NCH_3); MS (ESI) *m/z*: 160 (^{35}Cl), 162 (^{37}Cl), 104 (100%); HRMS (ESI) for $C_6H_6{}^{35}ClF_3N_2O_4S$ $[M+H]^+$: calcd 292.9611, found 292.9606.

1.3. General procedure for the preparation of 5-alkynyl-4-chloro-2-methyl-3(2*H*)-pyridazinones (7a–c)

To a solution of **6** (600 mg, 2 mmol) in THF (11 mL), $Pd_2Cl_2(PPh_3)_2$ (42 mg, 0.06 mmol), CuI (106 mg, 0.6 mmol) and n-Bu_4NI (2.21 g, 6 mmol) were added. After a few seconds of stirring, Et_3N (0.76 mL, 6 mmol) and the 1-alkyne (2.02 mmol) were added successively. The reaction mixture was stirred under a N_2 atmosphere at room temperature until the starting material had been consumed (TLC analysis and/or DCI–MS). The mixture was diluted with EtOAc and filtered through a pad of Celite®. The filtrate was concentrated in vacuo and the residue obtained was purified on silica gel.

1.3.1. 4-Chloro-2-methyl-5-phenylethynyl-3(2*H*)-pyridazinone (7a). Chromatography eluent: heptane/EtOAc (85:15); yield (380 mg, 83%); mp 151°C (dark yellow solid); ν_{max} (KBr): 3057, 2218, 1650, 1582, 1444, 1332, 1215, 872, 764, 689, 537 cm^{-1}; δ_H ($CDCl_3$): 7.76 (s, 1H, H-6), 7.57–7.62 (m, 2H, H_{Ph5}-2,6), 7.38–7.48 (m, 3H, H_{Ph5}-3,4,5), 3.83 (s, 3H, NCH_3); δ_C ($CDCl_3$): 157.07 (C-3), 136.79 (C-4), 136.15 (C-6), 132.25 (C_{Ph5}-2,6), 130.27 (C_{Ph5}-4), 128.68 (C_{Ph5}-3,5), 126.17 (C-5), 121.11 (C_{Ph5}-1), 103.27 (C-2″), 81.36 (C-1″), 41.04 (NCH_3); MS (ESI) *m/z*: 245 (^{35}Cl), 247 (^{37}Cl), 154 (100%), 139, 113; HRMS (ESI) for $C_{13}H_{10}{}^{35}ClN_2O$: calcd 245.0482, found 245.0475.

1.3.2. 4-Chloro-2-methyl-5-trimethylsilylethynyl-3(2*H*)-pyridazinone (7b). Chromatography eluent: heptane/EtOAc (85:15); yield (380 mg, 72%); mp 68°C (pale brown solid); ν_{max} (KBr): 3073, 2952, 1655, 1579, 1273, 1252, 1149, 1056, 845, 759, 660, 548 cm^{-1}; δ_H ($CDCl_3$): 7.66 (s, 1H, H-6), 3.81 (s, 3H, NCH_3), 0.29 (s, 9H, $(CH_3)_3Si$); δ_C ($CDCl_3$): 156.97 (C-3), 137.61 (C-4), 136.21 (C-6), 125.72 (C-5), 111.02 (C-2″), 95.64 (C-1″), 40.95 (NCH_3), −0.57 ($(CH_3)_3Si$); MS (ESI) *m/z*: 241 (^{35}Cl), 243 (^{37}Cl), 183, 148, 73 (100%); HRMS (ESI) for $C_{10}H_{14}{}^{35}ClN_2OSi$ $[M+H]^+$: calcd 241.0564, found 241.0567.

1.3.3. 4-Chloro-2-methyl-5-(pent-1-ynyl)-3(2*H*)-pyridazinone (7c). Chromatography eluent: heptane/EtOAc (85:15); yield (300 mg, 60%); yellow oil; ν_{max} (liquid film): 2972, 2939, 2878, 2232, 1652, 1592, 1284, 1166, 871, 753, 657 cm^{-1}; δ_H ($CDCl_3$): 7.61 (s, 1H, H-6), 3.78 (s, 3H, NCH_3), 2.47 (t, J=7.0 Hz, 2H, H-3″), 1.66 (br hex, $J\approx$7.0 Hz, 2H, H-4″), 1.05 (t, J=7.4 Hz, 3H, H-5″); δ_C ($CDCl_3$): 157.19 (C-3), 136.68 (C-6+C-4), 126.77 (C-5), 106.18 (C-2″), 73.66 (C-1″), 40.91 (NCH_3), 21.87, 21.63 (C-3″ or C-4″), 13.45 (C-5″); MS (ESI) *m/z*: 211 (^{35}Cl), 213 (^{37}Cl), 182 (100%), 169, 91; HRMS (ESI) for $C_{10}H_{12}{}^{35}ClN_2O$ $[M+H]^+$: calcd 211.0638, found 211.0635.

1.4. General procedure for the preparation of 4-alkynyl-5-chloro-2-methyl-3(2*H*)-pyridazinones (3a,c,e)

To a solution of 5-chloro-2-methyl-4-trifluoromethanesulfonyloxy-3(2*H*)-pyridazinone **11** (400 mg, 1.4 mmol) in THF (6 mL), $Pd_2Cl_2(PPh_3)_2$ (29 mg, 0.042 mmol), CuI (73 mg, 0.42 mmol) and *n*-Bu_4NI (1.5 g, 4.2 mmol) were added. After a few seconds of stirring, Et_3N (6 mL, 43.4 mmol) and the 1-alkyne (1.41 mmol) were added successively. The reaction mixture was stirred under an N_2 atmosphere at room temperature until the starting material had been consumed (TLC analysis and/or DCI–MS). The mixture was diluted with EtOAc and filtered through a pad of Celite®. The filtrate was concentrated in vacuo and the residue obtained was purified on silica gel.

1.4.1. 5-Chloro-2-methyl-4-phenylethynyl-3(2*H*)-pyridazinone (3a). Chromatography eluent: heptane/EtOAc (85:15); yield (324 mg, 95%); mp 113°C (yellow solid); ν_{max} (KBr): 3075, 2925, 2206, 1647, 1568, 1224, 1033, 934, 756, 689, 530 cm^{-1}; δ_H ($CDCl_3$): 7.78 (s, 1H, H-6), 7.65–7.61 (m, 2H, H_{Ph4}-2,6), 7.35–7.44 (m, 3H, H_{Ph4}-3,4,5), 3.80 (s, 3H, NCH_3); δ_C ($CDCl_3$): 158.53 (C-3), 139.36 (C-5), 135.88 (C-6), 132.40 (C_{Ph4}-2,6), 129.87 (C_{Ph4}-4), 128.48 (C_{Ph4}-3,5), 123.44 (C-4), 121.86 (C_{Ph4}-1), 106.04 (C-2′), 81.16 (C-1′), 40.57 (NCH_3); MS (ESI) *m/z*: 245 (^{35}Cl, 100%), 247 (^{37}Cl), 105, 77; HRMS (ESI) for $C_{13}H_{10}{}^{35}ClN_2O$ $[M+H]^+$: calcd 245.0482, found 245.0476.

1.4.2. 5-Chloro-2-methyl-4-trimethylsilylethynyl-3(2*H*)-pyridazinone (3c). Chromatography eluent: heptane/EtOAc (85:15); yield (180 mg, 55%); mp 98°C (brown solid); ν_{max} (KBr): 3084, 3055, 2963, 1645, 1563, 1248, 1029, 935, 845, 763 cm^{-1}; δ_H ($CDCl_3$): 7.74 (s, 1H, H-6), 3.76 (s, 3H, NCH_3), 0.29 (s, 9H, $(CH_3)_3Si$); δ_C ($CDCl_3$): 158.49 (C-3), 140.36 (C-5), 135.72 (C-6), 122.93 (C-4), 113.89 (C-2′), 94.99 (C-1′), 40.48 (NCH_3), −0.44 ($(CH_3)_3Si$); MS (ESI) *m/z*: 241 (^{35}Cl), 243 (^{37}Cl), 91, 73 (100%); HRMS (ESI) for $C_{10}H_{14}{}^{35}ClN_2OSi$ $[M+H]^+$: calcd 241.0564, found 241.0565.

1.4.3. 5-Chloro-2-methyl-4-(pent-1-ynyl)-3(2*H*)-pyridazinone (3e). Chromatography eluent: heptane/EtOAc (85:15); yield (235 mg, 82%); mp 38°C (yellow solid); ν_{max} (KBr): 3090, 2963, 2875, 2225, 1651, 1567, 1207, 955, 712, 628 cm^{-1}; δ_H ($CDCl_3$): 7.73 (s, 1H, H-6), 3.76 (s, 3H, NCH_3), 2.55 (t, J=7.0 Hz, 2H, H-3′), 1.68 (br hex, $J\approx$7.3 Hz, 2H, H-4′), 1.08 (t, J=7.3 Hz, 3H, H-5′); δ_C ($CDCl_3$): 159.08 (C-3), 139.25 (C-5), 135.88 (C-6), 123.98 (C-4), 109.19 (C-2′), 72.98 (C-1′), 40.51 (NCH_3), 22.29 (C-3′), 21.72 (C-4′), 13.45 (C-5′); MS (ESI) *m/z*: 211 (^{35}Cl), 213 (^{37}Cl), 182, 157, 128, 100 (100%); HRMS (ESI) for $C_{10}H_{12}{}^{35}ClN_2O$ $[M+H]^+$: calcd 211.0638, found 211.0643.

1.5. General procedure for the introduction of a second alkynyl group (8a–c)

To a solution of **7a–c** or **3a**,**c** (270 mg, 1.12 mmol) in THF (6 mL), $Pd_2Cl_2(PPh_3)_2$ (25 mg, 0.034 mmol), CuI (111 mg, 0.06 mmol), Et_3N (1.44 mL, 10.1 mmol) and the 1-alkyne (1.46 mmol) were added. The reaction mixture was heated at 80°C under an N_2 atmosphere until the starting material had been consumed (TLC analysis and/or DCI–MS). The reaction mixture was then cooled to room temperature, diluted with EtOAc and filtered through a pad of Celite®. The solvent was removed under reduced pressure and the residue obtained was purified on silica gel.

1.5.1. 2-Methyl-4-phenylethynyl-5-trimethylsilylethynyl-3(2*H*)-pyridazinone (8a). Chromatography eluent: heptane/EtOAc (8:2); yield (270 mg, 79%); brown oil; ν_{max} (liquid film): 3062, 2960, 2901, 2206, 2160, 1658, 1569, 1250, 1159, 1070, 942, 847, 758, 690, 529 cm^{-1}; δ_H ($CDCl_3$): 7.70 (s, 1H, H-6), 7.61 (br dd, 2H, H_{Ph}-2,6), 7.37 (m, 3H, H_{Ph}-3,4,5), 3.79 (s, 3H, NCH_3), 0.30 (s, 9H, $(CH_3)_3Si$); δ_C ($CDCl_3$): 158.57 (C-3), 136.72 (C-6), 132.37 (C_{Ph}-2,6), 129.61 (C_{Ph}-4), 128.37 (C_{Ph}-3,5), 128.07, 126.37 (C-4 or C-5), 122.29 (C_{Ph}-1), 109.26 (C-2″), 105.31 (C-2′), 98.26 (C-1″), 83.58 (C-1′), 40.55 (NCH_3), −0.42 ($(CH_3)_3Si$); MS (ESI) *m/z*: 307, 221, 73 (100%); HRMS (ESI) for $C_{18}H_{19}N_2OSi$ $[M+H]^+$: calcd 307.1267, found 307.1250.

1.5.2. 2-Methyl-5-(pent-1-ynyl)-4-phenylethynyl-3(2*H*)-pyridazinone (8b). Chromatography eluent: heptane/EtOAc (7:3); yields (135 mg, 51% from **7c**; 210 mg, 97% from **3a**); brown oil; ν_{max} (liquid film): 3063, 2964, 2933, 2873, 2204, 1657, 1572, 1379, 1245, 1026, 758, 690, 529 cm^{-1}; δ_H ($CDCl_3$): 7.66 (s, 1H, H-6), 7.61–7.58 (m, 2H, H_{Ph4}-2,6), 7.39–7.32 (m, 3H, H_{Ph4}-3,4,5), 3.78 (s, 3H, NCH_3), 2.52 (t, J=7.0 Hz, 2H, H-3″), 1.68 (br hex, $J\approx$ 7.0 Hz, 2H, H-4″), 1.07 (t, J=7.3 Hz, 3H, H-5″); δ_C ($CDCl_3$): 158.75 (C-3), 137.10 (C-6), 132.22 (C_{Ph4}-2,6), 129.36 (C_{Ph4}-4), 129.19, 125.41 (C-4 or C-5), 128.29 (C_{Ph4}-3,5), 122.36 (C_{Ph4}-1), 104.75, 104.10 (C-2′ or C-2″), 83.53 (C-1′), 75.80 (C-1″), 40.41 (NCH_3), 21.86 (C-3″), 21.70 (C-4″), 13.42 (C-5″); MS (ESI) *m/z*: 277, 248, 220, 178 (100%), 165; HRMS (ESI) for $C_{19}H_{15}N_2O$ $[M+H]^+$: calcd 277.1341, found 277.1329.

1.5.3. 2-Methyl-5-phenylethynyl-4-trimethylsilylethynyl-3(2*H*)-pyridazinone (8c). Chromatography eluent: heptane/EtOAc (8:2); yields (194 mg, 50% from **7a**; 100 mg, 52% from **3c**); mp 96°C (yellow solid); ν_{max} (KBr): 2957, 2899, 2212, 1650, 1568, 1250, 1056, 948, 846, 762, 688 cm^{-1}; δ_H ($CDCl_3$): 7.75 (s,1H, H-6), 7.55–7.60 (m, 2H, H_{Ph}-2,6), 7.38–7.46 (m, 3H, H_{Ph}-3,4,5), 3.78 (s, 1H, NCH_3), 0.30 (s, 9H, $(CH_3)_3Si$); δ_C ($CDCl_3$): 158.66 (C-3), 136.41 (C-6), 132.18 (C_{Ph}-2,6), 129.97 (C_{Ph}-4), 129.49, 125.01 (C-4 or C-5), 128.57 (C_{Ph}-3,5), 121.55 (C_{Ph}-1), 112.44 (C-2″), 102.15 (C-2′), 97.59 (C-1″), 83.72 (C-1′), 40.51 (NCH_3), −0.28 ($(CH_3)_3Si$); MS (ESI) *m/z*: 307, 305, 291, 165, 73 (100%); HRMS (ESI) for $C_{18}H_{19}N_2OSi$ $[M+H]^+$: calcd 307.1267, found 307.1269.

1.6. General procedure for the Suzuki reaction on compounds 7a and 3a (9a,b and 10a,b)

A mixture of **7a** or **3a** (170 mg, 0.7 mmol), $Pd(PPh_3)_4$ (250 mg, 0.021 mmol), boronic acid (0.13 g, 1.05 mmol) and aqueous 2 M Na_2CO_3 (1.1 mL) in toluene (4 mL) was flushed with N_2 for 5 min under stirring. Then the reaction mixture was heated at 120°C until the starting material had been consumed (TLC analysis and/or DCI–MS). After cooling to room temperature, the reaction mixture

was evaporated to dryness under reduced pressure. EtOAc was added and the suspension was placed in an ultrasonic bath for a few minutes. The mixture was filtered through a pad of Celite® and then concentrated under reduced pressure. The residue obtained was purified on silica gel.

1.6.1. 2-Methyl-4-phenyl-5-phenylethynyl-3(2*H*)-pyridazinone (9a). Chromatography eluent: heptane/EtOAc (8:2); yield (171 mg, 86%); mp 147°C (light yellow solid); ν_{max} (KBr): 3057, 2925, 2214, 1646, 1443, 1347, 1038, 754, 687, 579 cm^{-1}; δ_H ($CDCl_3$): 7.86 (s, 1H, H-6), 7.74 (br d, 2H, H_{Ph4}-2,6), 7.49–7.40 (m, 3H, H_{Ph4}-3,4,5), 7.39–7.29 (m, 5H, H-5Ph), 3.83 (s, 3H, NCH_3); δ_C ($CDCl_3$): 159.55 (C-3), 140.41 (C-4), 137.78 (C-6), 132.64 (C-1′), 131.95 (C_{Ph5}-2,6), 130.10 (C-2′,6′), 129.67, 129.43 (C_{Ph5}-4 or C-4′), 128.53 (C_{Ph5}-3,5), 127.75 (C-3′,5′), 124.07 (C-5), 121.71 (C_{Ph5}-1), 99.23 (C-2″), 84.29 (C-1″), 40.69 (NCH_3); MS (ESI) *m/z*: 287, 230, 202 (100%); HRMS (ESI) for $C_{19}H_{15}N_2O$ $[M+H]^+$: calcd 287.1184, found 287.1170.

1.6.2. 2-Methyl-5-phenylethynyl-4-(3-trifluoromethylphenyl)-3(2*H*)-pyridazinone (9b). Chromatography eluent: heptane/EtOAc (8:2); yield (193 mg, 78%); mp 139°C (pale yellow solid); ν_{max} (KBr): 2922, 2213, 1644, 1349, 1171, 1130, 1071, 1035, 882, 809, 753, 689 cm^{-1}; δ_H ($CDCl_3$): 8.07 (br s, 1H, H-2′), 7.96 (br d, J=7.8 Hz, 1H, H-6′), 7.90 (s, 1H, H-6), 7.70 (br d, J=7.8 Hz, 1H, H-4′), 7.59 (br t, J=7.8 Hz, 1H, H-5′), 7.41–7.30 (m, 5H, H_{Ph5}-2,6), 3.85 (s, 3H, NCH_3); δ_C ($CDCl_3$): 159.19 (C-3), 138.42 (C-4), 137.74 (C-6), 133.59, 133.38 (C-1′ or C-6′), 132.01 (C_{Ph5}-2,6), 130.39 (q, J_{CF}=32.8 Hz, C-3′), 130.00 (C_{Ph5}-4), 128.60 (C_{Ph5}-3,5), 128.30 (C-5′), 127.11 (q, J_{CF}= 3.8 Hz, C-2′), 126.08 (q, J_{CF}=3.8 Hz, C-4′), 124.68 (C-5), 124.12 (q, J_{CF}=272.4 Hz, CF_3), 121.23 (C_{Ph5}-1), 100.30 (C-2″), 83.54 (C-1″), 40.77 (NCH_3); MS (ESI) *m/z*: 355, 335, 292, 264 (100%), 258, 202; HRMS (ESI) for $C_{20}H_{14}F_3N_2O$ $[M+H]^+$: calcd 355.1058, found 355.1052.

1.6.3. 2-Methyl-5-phenyl-4-phenylethynyl-3(2*H*)-pyridazinone (10a). Chromatography eluent: heptane/EtOAc (8:2); yield (200 mg, 99%); mp 107°C (yellow solid); ν_{max} (KBr): 3054, 2924, 2207, 1648, 1600, 1443, 1353, 1248, 1023, 928, 757, 697, 526 cm^{-1}; δ_H ($CDCl_3$): 7.88 (s, 1H, H-6), 7.73 (br d, 2H, H-2″,6″), 7.51 (m, 3H, H-3″,4″,5″), 7.44 (br d, 2H, H_{Ph4}-2,6), 7.32 (m, 3H, H_{Ph4}-3,4,5), 3.87 (s, 3H, NCH_3); δ_C ($CDCl_3$): 159.72 (C-3), 144.10 (C-5), 136.72 (C-6), 134.42 (C-1″), 132.14 (C_{Ph4}-2,6), 129.90 (C-4″), 128.73, 128.62, 128.37 (C_{Ph4}-3,5 or C_{Ph5}-2,6 or C_{Ph5}-3,5), 122.43, 120.86 (C_{Ph4}-1 or C-4), 102.75 (C-2″), 83.53 (C-1″), 40.63 (NCH_3); MS (ESI) *m/z*: 287, 230 (100%), 202; HRMS (ESI) for $C_{19}H_{15}N_2O$ $[M+H]^+$: calcd 287.1184, found 287.1176.

1.6.4. 2-Methyl-4-phenylethynyl-5-(3-trifluoromethylphenyl)-3(2*H*)-pyridazinone (10b). Chromatography eluent: heptane/EtOAc (8:2); yield (218 mg, 94%); mp 127°C (light yellow solid); ν_{max} (KBr): 3062, 2926, 2204, 1645, 1322, 1171, 1113, 1078, 936, 804, 750, 686, 525 cm^{-1}; δ_H ($CDCl_3$): 8.06 (br s, 1H, H-2″), 7.88 (br d, 1H, H-6″), 7.87 (s, 1H, H-6), 7.77 (br d, 1H, H-4″), 7.67 (br t, 1H, H-5″), 7.43 (br d, 2H, H_{Ph4}-2,6), 7.39–7.29 (m, 3H, H_{Ph4}-3,4,5), 3.89 (s, 3H, NCH_3); δ_C ($CDCl_3$): 159.40 (C-3), 142.28 (C-5), 135.96 (C-6), 135.26 (C-1″), 132.18 (C_{Ph4}-2,6), 131.90 (C-6″), 131.35 (q, J_{CF}=32.8 Hz, C-3″), 129.66, 129.31, 121.96, 121.56 (C-4 or C_{Ph4}-1 or C-5″ or C_{Ph4}-4), 128.44 (C_{Ph4}-3,5), 126.54 (q, J_{CF}=3.8 Hz, C-2″), 125.72 (q, J_{CF}=3.8 Hz, C-4″), 123.84 (q, J_{CF}=272.4 Hz, CF_3), 103.84 (C-2′), 82.84 (C-1′), 40.76 (NCH_3); MS (ESI) *m/z*: 355 (100%), 298, 278, 258, 202; HRMS (ESI) for $C_{20}H_{14}F_3N_2O$ $[M+H]^+$: calcd 355.1058, found 355.1044.

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