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From *N*-sulfonyl,*C*-homoallyl-hydrazones to pyrazole and pyridazine (N_2)-heterocycles: the ultimate aromatization process

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ABSTRACT

Isomeric six- and five-membered (N_2)-aromatics, 6-methylpyridazines and 5-vinylpyrazoles, which energetic topological aromaticity is comparable to that of benzene, are shown to be efficiently produced by sequential isomerization–elimination processes from the corresponding 6-methylidene-1,4,5,6-tetrahydropyridazines and 5-vinylpyrazolines, respectively. The latter precursors are available from the same *N*-sulfonyl,*C*-homoallyl-hydrazone substrates by a suitable choice of previously reported conditions for Pd-catalyzed CH-oxidative C,N-ring closing processes. The generality of these cyclization, isomerization, and aromatization reactions, for which detailed mechanisms are proposed, provides a systematic access to wide ranges of 3,4,6-trisubstituted 6-methyl-1,4-dihydropyridazines and 6-methylpyridazines, and their 3,4,5-trisubstituted 5-vinylpyrazole isomers.

1. Introduction

Aromatic *N*-heterocycles are planar rigid units that are key to biochemical recognition processes.[1] Due to the H-bond acceptor ability of the nitrogen atom, beside porphyrins (hemoglobin, cytochromes), vitamin B12, and a few α-aminoacids (tryptophan, histidine), nucleobases are essential diaza-aromatics (under representative tautomeric forms), which all contain a pyrimidine six-membered ring. These nucleobases, either monocyclic (cytosine, uracil, thymine), or bicyclic with an annelated imidazole five-membered ring in purines (adenine, guanine), are thus based on N···C···N amidine units. Adenine is also constitutive of redox coenzymes, which active motif in the oxidized form is an aromatic heterocycle: the pyridine ring of nicotinamide in NAD, the pteridine bicycle of riboflavine in FAD. Noteworthy, pteridine also contain a pyrimidine ring, annelated with a pyrazine diaza-aromatic ring based on the N···C···C···N diimine unit. In contrast to the N···C_x···N units x=1, 2, N···N hydrazine/diimide/azo units (x=0) have been considered for comparative purpose in five-membered pyrazoles (vs imidazoles),[2] and six-membered pyridazines (vs pyrimidines).[3] Although pyrazole[4] and pyridazine[5] rings are found in marketed artificial biologically active compounds (many pyrazoles[6] and a few pyridazines in herbicides such as credazine,[7] pyridafol,[8] pyridate,[9] and drugs such as cefozopran,[10] cadralazine,[11] minaprine,[12] hydralazine,[13] cilazapril[14]), their occurrence among natural products, like that of any N_2 motif, is very limited. According to Kumar, in 2013 only 18 natural products containing a pyrazole ring had been identified.[15] Even more strikingly, discarding a few natural hydropyridazine derivatives (like monoamycin extracted from a *Spectromyces* species),[16] the aromatic pyridazine ring itself is extremely rare in Nature, just found in pyridazomycin[17] and amazerone, both extracted from *Streptomyces* bacteria as well.[18]

From a more fundamental standpoint, basic properties such as planarity, rigidity, stability and reactivity of π-conjugated *N*-heterocycles can be compared on the basis of their relative aromatic characters.[19] Although *N*-heterocycles are more compact than parent carbocycles (because of shorter endocyclic bonds), the first *N*-monocycles (with a single N atom and without any π-conjugating substituent) are slightly less aromatic (by ca. 1–2%) than their parent annulenic carbocycles: this is illustrated for pyridine versus benzene, and for pyrrole and pyrrolide anion versus the cyclopentadienide anion (Scheme 1), on the basis of the Aihara or Trinajstic's topological resonance energy,[20] the scale of 'exact' energetic aromaticity, which recently received a direct chemical interpretation.[21] Likewise, anchoring a π-conjugated substituent at a six-π-electron annulenic ring results in a ca. 10% decrease of the TRE (e.g., 0.249 for styrene vs 0.273 for benzene),[20a] and this trend also applies to heterocycles, e.g., to 2-vinylpyrrole versus pyrrole (Scheme 1). Nevertheless further endocyclic 'α-azalogation' (i.e., substitution of a methyne unit adjacent to a first nitrogen atom by a second nitrogen atom, giving a N···N unit)

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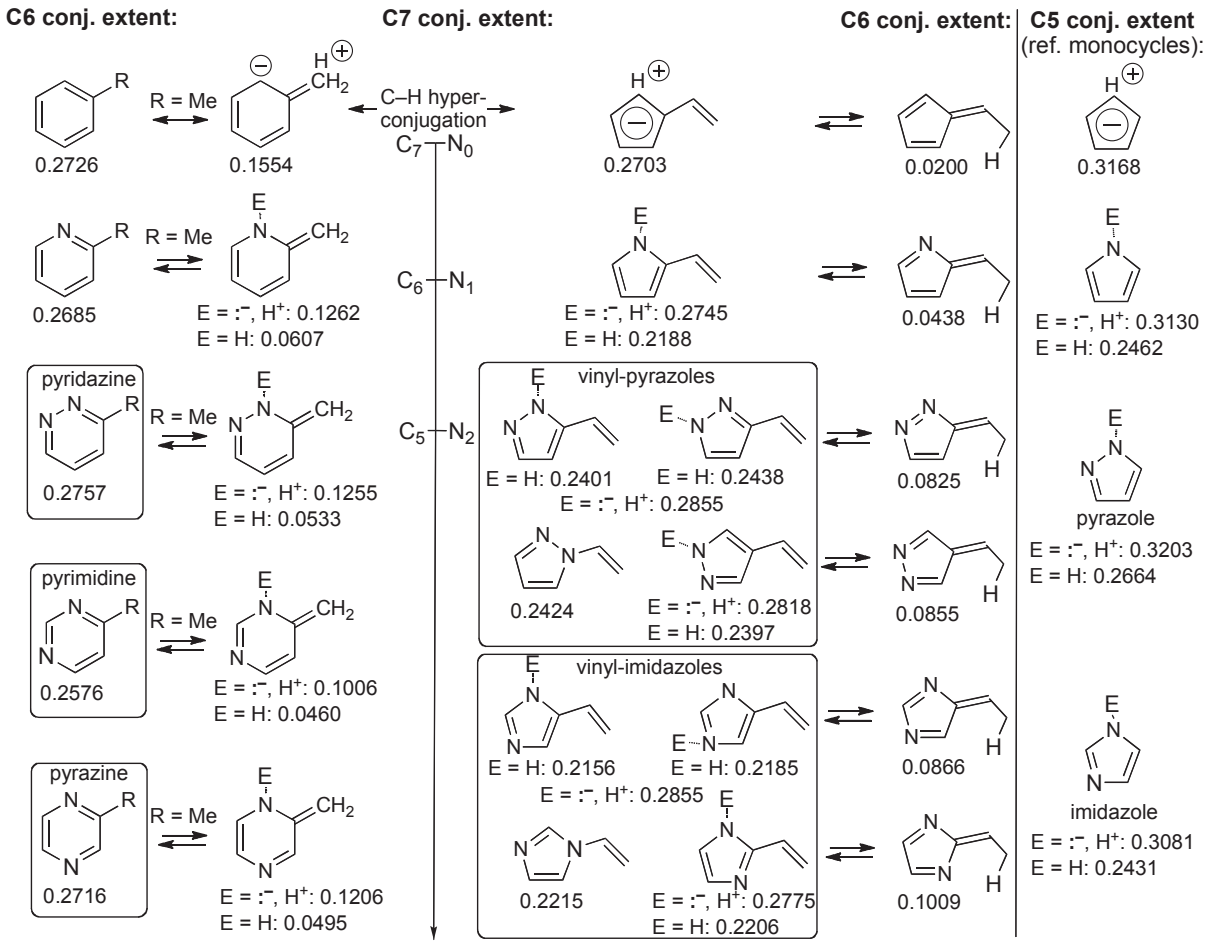
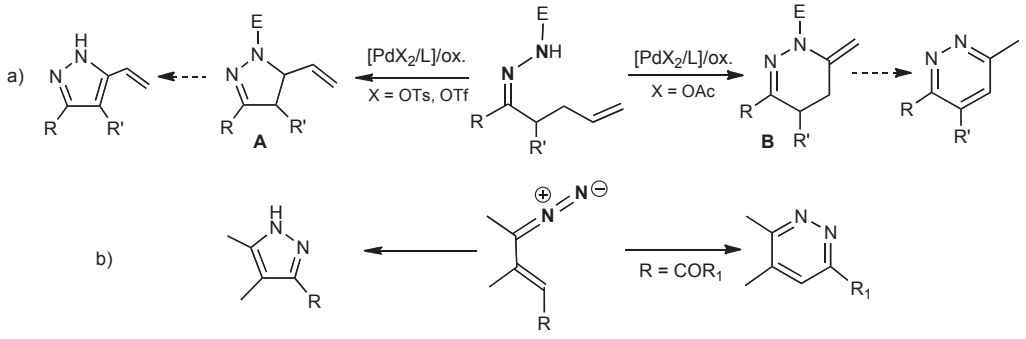


Scheme 1. Topological resonance energy of $C_5H_6N_2$-isomeric diaza-cycles (including tautomeric forms), parent monoaza-cycles, and carbocyclic analogues calculated with the Van-Catledge Hückel parameters for sp^2 and sp^3 N atoms.[23] Values in resonance integral β units.[24]

restores aromaticity:[22] pyridazine, pyrazole, and 5-vinylpyrazoles are thus more aromatic than pyridine (+3%), pyrrole (+10%), and 5-vinylpyrrole (+8%), respectively (Scheme 1). The same pyridazine, pyrazole, and vinylpyrazole are also more aromatic than diaza isomers resulting from β-azalogation (giving a N···C···N unit), i.e., than pyrimidine (+7%), imidazole (+10%), and vinylimidazole (ca. +11%). As a general trend (see details in Scheme 1), diimido compounds (pyrazole and pyridazine derivatives) thus appear more aromatic than simple imido counterparts (imidazole, pyrimidine, and pyrazine derivatives).

Considering the above-mentioned intriguing biological and structural properties of the diimido heterocycles, compelling comparative studies first call for a systematic access to such compounds. The comparison is hereafter addressed for $C_5H_6N_2$-isomeric 6-methylpyridazine and 5-vinylpyrazole derivatives. Functional layout precursors of such isomers have indeed recently been made available from a single substrate for Pd-catalyzed cyclization reactions. Among other transition metal-catalyzed methods used for the preparation of *N*-heterocycles,[25] Pd-catalyzed C—H oxidative C,N-cyclization of *N*-sulfonyl,*C*-homoallyl-hydrazones was indeed shown to follow two distinct routes depending on the electrophilicity of the Pd(II) catalytic center.[26] If the Pd(II) center is associated to non-coordinating anions such as tosylates or triflates, 5-vinylpyrazolines of type **A** are produced through a 5-*exo*-*trig* process from a π-allyl complex intermediate (Scheme 2a). In contrast, if the anionic ligands of the Pd(II) center



Scheme 2. (a) Envisaged preparation of pyrazoles and pyridazines from pyrazolines **A**, and 1,4,5,6-tetrahydropyridazines **B**, respectively, obtained by Pd-cyclization of *N*-sulfonyl,*C*-homoallyl-hydrazones.[26] (b) Preparation of pyrazoles and pyridazines from vinyl-diazo precursors.[30]

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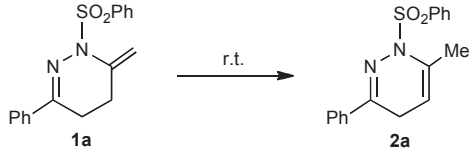
are O,O-chelating acetates, 6-methylidene-1,4,5,6-tetrahydropyridazines of type **B** are formed, possibly through a 6-*endo-trig* process from the assumed same π-allyl complex (if, as previously assumed, [recall Ref. 26a] no π-allyl complex was involved, a 6-*exo-trig* process in the strict sense should be invoked). This fine control of the Baldwin rules[27] for the formation of the allowed products of types **A** and **B** thus opens a possible access to isomeric 5-vinylpyrazole and 6-methylpyridazine, respectively. In line with other systematic routes to pyrazoles[28] and pyridazines,[29] e.g., from a common vinyl-diazo precursor (Scheme 2b),[30] suitable procedures for the aromatization of isomeric precursors **A** and **B** are hereafter described.

2. Results and discussion

2.1. Context

The reactivity of the exocyclic double bond of the 6-methylidene-1,4,5,6-tetrahydropyridazine **1a** was recently evidenced by a quantitative conversion to the 1,4-dihydropyridazine isomer **2a** upon dissolution of **1a** in chloroform at room temperature (Scheme 3).[26] This observation suggests that the *exo*→*endo* migration of the C=C bond is catalyzed by traces of acid in the $CHCl_3$ solvent used. In support of this, using $CHCl_3$ stored over 4 Å molecular sieves (MS), no isomerization was observed and the 1,4,5,6-tetrahydropyridazine **1a** was found stable under such conditions. Related tautomerization processes have been evidenced in general heterocyclic chemistry,[31] in particular for the preparation of pyrazole and pyrazoline derivatives.[32]



Scheme 3. The *exocyclic*→*endocyclic* migration of the C=C bond of the *N*-sulfonyl-6-methylidene-1,4,5,6-tetrahydropyridazine **1a** to the isomeric 1,4-dihydropyridazine **2a**.

2.2. Six-membered (N_2)-heterocycles

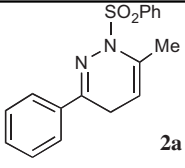
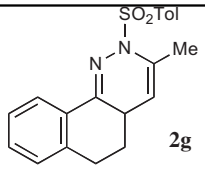
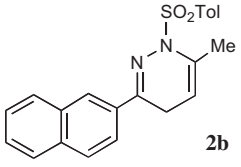
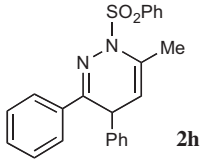
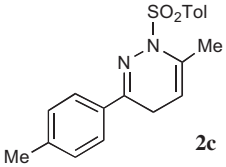
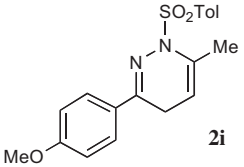
A complete set of *N*-arylsulfonyl-6-methylidene-1,4,5,6-tetrahydropyridazine substrates prepared by Pd-catalyzed C–H oxidative cyclization of *N*-sulfonyl,*C*-homoallyl-hydrazones[26] **1b**–**k** was then considered (Table 1).

As shown in Table 1, the migration of the C=C double bond observed from **1a** was also found to take place from a wide range of *N*-arylsulfonyl-6-methylidene-1,4,5,6-tetrahydropyridazines. In all cases, the corresponding 1,4-dihydropyridazines **2a**–**k** were obtained upon dissolution of the 1,4,5,6-tetrahydropyridazine precursors **1a**–**k** in 'technical' $CHCl_3$ at room temperature. As previously observed for **1a**, pyridazines **1b**–**k** were shown to be stable in $CHCl_3$ stored over 4 Å MS. 1,4-Dihydropyridazines **2a**–**k** were fully characterized by spectroscopic methods in solution, and the structures of **2a** and **2e** were confirmed by X-ray diffraction analysis of single crystals (Fig. 1).[33]

In ^1H and ^{13}C NMR spectra, the main difference between the pyridazine isomers **1** and **2** consists in the exclusive presence of a methyl substituent ($\delta_{CH_3} \approx 2.20$ ppm; $\delta_{CH_3} \approx 20.0$ ppm) in the 1,4-dihydropyridazine series **2**. In the solid state, whereas the 1,4-dihydropyridazines **2a** and **2e** adopt a boat-shaped conformation, which prow is occupied by the sulfonyl-*N* atom and stern by the methylene group (Fig. 1), the 1,4,5,6-tetrahydropyridazines **1** were found to adopt rather a half-chair-type conformation.[26] The steric and electronic factors of the substituents exert a negligible or weak effect on the acid-catalyzed isomerization of 1,4,5,6-tetrahydropyridazines **1**, and in all cases the most stable isomers featuring an endocyclic C=C bond, namely the 1,4-dihydropyridazines of type **2**, were obtained. The isomerization **1**→**2** can be attributed not only to the exocyclic kinetic exposure of the C=C bond in **1**, but also to the trisubstitution thermodynamic stabilization of the C=C bond in **2**.

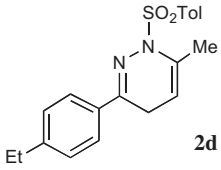
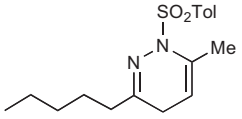
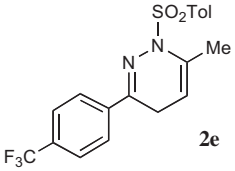
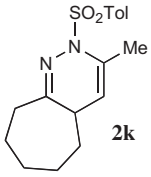
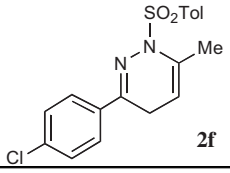
Whereas cyclohexadienes undergo oxidative aromatization to benzene derivatives (e.g., by treatment with DDQ), the 1,4-dihydropyridazines **2** are a priori prone to convert to the aromatic pyridazines by formal elimination of aryl sulfinic acid ($ArSO_2H$). The feasibility of the reaction was first investigated from the reference 1,4-dihydropyridazine **2a** using various bases, and preliminary experiments in THF at 65 °C evidenced the formation of

Table 1
Exocyclic→*endocyclic* isomerization of *N*-sulfonyl-6-methylidene-1,4,5,6-tetrahydropyridazines **1b**–**k** and of the reference substrate **1a** (Scheme 3)[a]

Entry	Substrate	Product[b]	Entry	Substrate	Product[b]
1	**1a**	 **2a**	7	**1g**	 **2g**
2	**1b**	 **2b**	8	**1h**	 **2h**
3	**1c**	 **2c**	9	**1i**	 **2i**

(*continued on next page*)

Table 1 (*continued*)

Entry	Substrate	Product[b]	Entry	Substrate	Product[b]
4	**1d**	 **2d**	10	**1j**	 **2j**
5	**1e**	 **2e**	11	**1k**	 **2k**
6	**1f**	 **2f**			

[a] Reaction conditions: $CHCl_3$, rt, 2 h.
[b] The 1,4-dihydropyridazines **2a**–**k** were obtained in quantitative yields and fully characterized without requirement of any purification techniques.

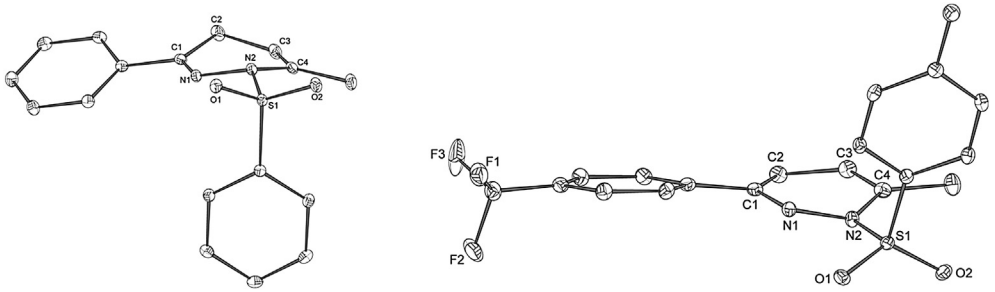
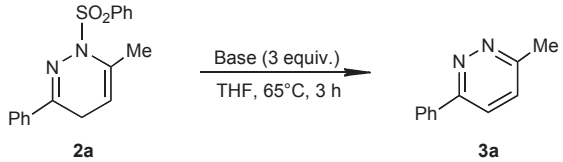


Fig. 1. Molecular views of the X-ray crystal structures of the 1,4-dihydropyridazines **2a** (*left*), and **2e** (*right*), with thermal ellipsoids drawn at the 30% probability level (for clarity, the H atoms are omitted). For more details on **2a**, **2e**, see Experimental section. Selected bond distances [Å] and angles [°]. Compound **2a**: C1–C2 1.5034(12), C1–N1 1.2837(11), N1–N2 1.4083(9), C1–C2–C3 108.73(8), C2–C1–N1 123.94(8), N1–N2–C4 119.05(7). Compound **2e**: C1–C2 1.504(2), C1–N1 1.285(2), N1–N2 1.3879(18), C1–C2–C3 109.63(13), C2–C1–N1 124.57(14), N1–N2–C4 120.44(12).

the pyridazine **3a** (Scheme 4). The yield of the transformation was, however, found to be highly dependent on the nature of the base: high yields with either NaOAc or NaOH (90–92%), lower yield with NaH (61%), and no conversion with Et_3N.



Base	NaOAc	NaOH	NaH	Et_3N
yield (%)	92	90	61	0

Scheme 4. Performances of bases in promoting aromatization of the 1,4-dihydropyridazine reference substrate **2a**.

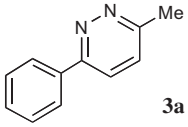
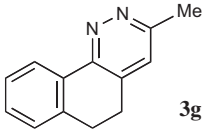
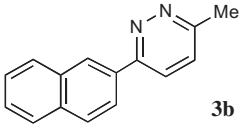
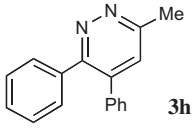
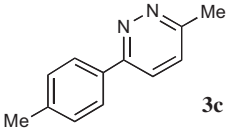
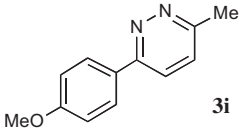
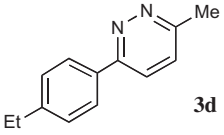
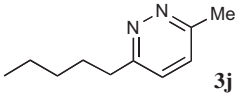
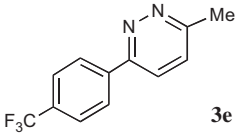
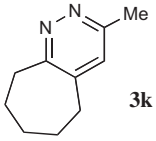
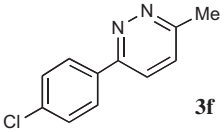
The scope of the reaction was then investigated over the set of substrates **2b**–**k** (Scheme 4, Table 2). The above conditions were found to be efficient over a wide range of *p*-substituted 1,4-dihydropyridazines, involving more or less electro-active groups (Table 2, entries 2–6 and 9; 40–96% yield). From the hindered substrates **2g** and **2h**, the corresponding pyridazines were, however, produced in 54 and 46% yields only (Table 2, entries 7 and 8). The alkyl representatives **2j** and **2k** were also found to undergo aromatization in moderate yields (Table 2, entries 10 and 11).

The structure of the pyridazine products was determined by spectroscopic methods in solution, and confirmed by X-ray diffraction analysis in the crystal state for the representatives **3a**, **3b**, **3c**, **3g**, **3h**, **3i** (Fig. 2).[31] In contrast to the 1,4-dihydropyridazines **2**, and as expected, the six-membered N_2-heterocycle of **3** adopts a planar geometry in the solid state. As a reference, geometrical data of the related pyridazinium salt **3a′** in the solid state are also given (Table 3).[33]

Endocyclic bond lengths and angle values of the six-membered ring of the pyridazine derivatives **2a**, **3a**, and **3a′** are in agreement with the aromatic character of **3a** and, to a lesser extent, to that of **3a′** (Table 3).

The formation of pyridazines **3** from **2** corresponds to a base-mediated elimination of aryl sulfinic acid (Scheme 5, route a). This transformation involves a carbanionic intermediate from which a sulfinate anion is expelled.[34] Alternatively, 1,2-elimination of aryl sulfinic acid might occur from a 1,6-dihydropyridazine tautomer **2′**, which could however not be detected, possibly

Table 2
Aromatization of *N*-sulfonyl-1,4-dihydropyridazine substrates **2b**–**k**, and the reference substrate **2a** (Scheme 4)[a]

Entry	Substrate	Product	Yield[b] (%)	Entry	Substrate	Product	Yield[b] (%)
1	**2a**	 **3a**	92	7	**2g**	 **3g**	54
2	**2b**	 **3b**	96	8	**2h**	 **3h**	46
3	**2c**	 **3c**	64	9	**2i**	 **3i**	40
4	**2d**	 **3d**	64	10	**2j**	 **3j**	71
5	**2e**	 **3e**	90	11	**2k**	 **3k**	43
6	**2f**	 **3f**	59				

[a] Reaction conditions: NaOAc (3 equiv), THF, 65 °C.
[b] Yield of isolated product.

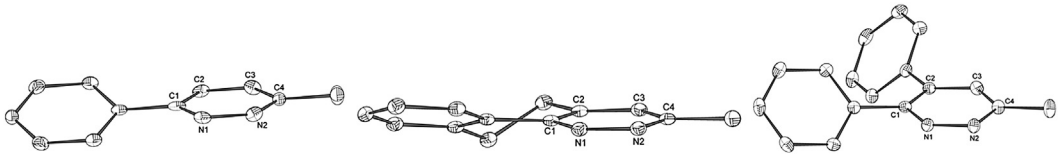


Fig. 2. Molecular views of the X-ray crystal structures of the pyridazines **3a** (*left*), **3g** (*middle*), and **3h** (*right*), with thermal ellipsoids drawn at the 30% probability level (for clarity, the H atoms are omitted). For more details on **3a**, **g**, **h** and data for **3b**, **c**, **i**, see Experimental section. Selected bond distances [Å] and angles [°]. Compound **3a**: see Table 3. Compound **3g**: C1–C2 1.4136(15), C1–N1 1.3337(13), N1–N2 1.3518(12), C1–C2–C3 116.44(9), C2–C1–N1 122.74(10), N1–N2–C4 119.67(9). Compound **3h**: C1–C2 1.4151(13), C1–N1 1.3387(12), N1–N2 1.3404(11), C1–C2–C3 116.05(8), C2–C1–N1 121.75(8), N1–N2–C4 119.78(8).

because it undergoes aromatization to **3** by a concerted *E*2 elimination, thus more readily than **2** (which requires a two-step *E*1cb mechanism). The present result provides definitive experimental support for a previous claim about the transient formation of 1,4-dihydopyridazines in the preparation of pyridazines from 1,4,5,6-tetrahydropyridazine precursors.[35]

In the absence of a base, formation of the pyridazinium salt **3a**′ was observed after **2a** was kept in technical CH_2Cl_2 under air for a few days (Scheme 5, route b). This result might indicate an oxidative aromatization process after hydrolysis of the N–SO_2Ar bond of **2** to the 1,4-dihydropyridazine intermediate **2**″. The latter would thus act as a hydride donor, just as the 1,4-dihydropyridine ring of NADH, NADPH or Hantzsch esters does.

From **2a**, the formation of phenyl sulfinic acid was evidenced by IR and mass spectroscopic methods (ESI$^-$: *m*/*z* 141.0), thus confirming the proposed eliminative-type mechanism (Scheme 5, route a).

2.3. Five-membered (N_2)-heterocycles

The preparation of aromatic five-membered isomers of methylpyridazines, namely vinylpyrazoles, was then envisaged from vinylpyrazolines. Conditions similar to those used in the pyridazine series were thus applied to the 5-vinylpyrazoline reference substrate **4a** (Scheme 6). In presence of 3 equiv of NaOH pellets in THF at 65 °C, the pyrazoline **4a** was found to undergo deprotonation over 3 h, affording the pyrazole **5a** in 68% yield.

The scope of the reaction was then investigated over a set of *N*-arylsulfonyl-5-vinylpyrazolines **4b**–**i** (Scheme 6).[26] As indicated in Table 4, the aromatization occurred from a wide range of substrates.

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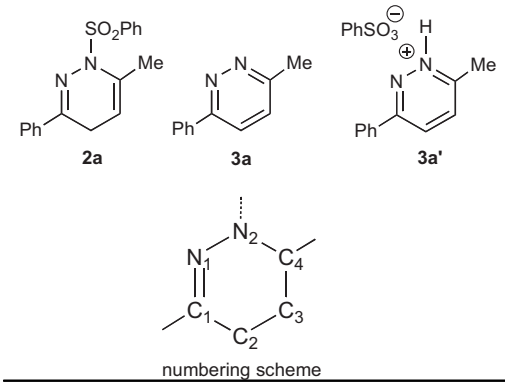
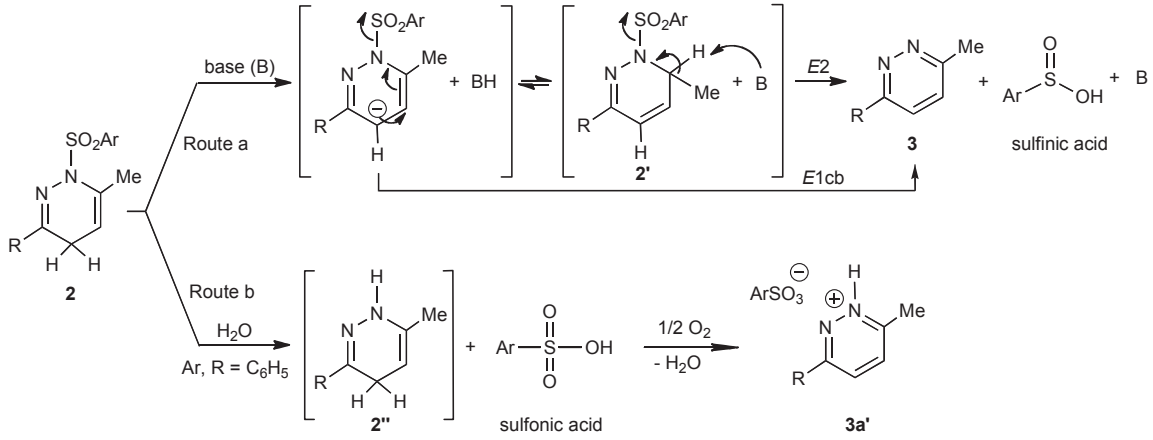
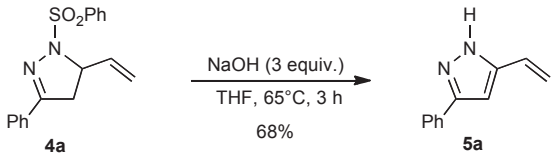
Table 3
Selected bond lengths (Å) and angles (°) from X-ray diffraction analyses of single crystals of the six-membered heterocycles **2a**, **3a**, and **3a′**

Lewis structures		**2a**	**3a**[a]	**3a′**
	C_1-C_2	1.5034(12)	1.356(5)	1.4182(16)
	C_2-C_3	1.4917(13)	1.348(6)	1.3680(19)
	C_3-C_4	1.3300(13)	1.356(5)	1.4084(17)
	C_1-N_1	1.2837(11)	1.356(5)	1.3302(15)
	C_4-N_2	1.4396(10)	1.356(5)	1.3259(15)
	N_1-N_2	1.4083(9)	1.348(6)	1.3345(16)
	$C_1-N_1-N_2$	118.08(7)	117.8(4)	117.10(10)
	$C_1-C_2-C_3$	108.73(8)	117.8(4)	119.36(11)

[a] The asymmetric unit contains half a molecule. Two positions have been assigned respectively, to C(3)/N(2) and C(2)/N(1) with half occupancy. A C_2 symmetry axis generates the full molecule. For molecular views, see Figs. 1 and 2.



Scheme 5. Proposed mechanisms for the formation of pyridazine derivatives **3** from 1,4-dihydropyridazines **2**: (a) following a base-induced eliminative aromatization process; (b) through an oxidative aromatization process.



Scheme 6. Aromatization of the *N*-sulfonyl-5-vinylpyrazoline reference **4a** in presence of NaOH.

Pyrazolines with electro-active substituents at the *para*-position of the phenyl ring (Table 4, entries 2–6 and 9) and hindered pyrazolines (Table 4, entries 7 and 8) can be indeed converted to the corresponding pyrazoles in moderate to high yields (42–95%). The pyrazole products **5a**–**i** were fully characterized by spectroscopic methods, and also by X-ray diffraction analysis of a single crystal of **5h** (Fig. 3).[33]

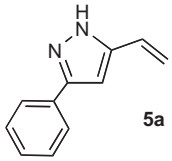
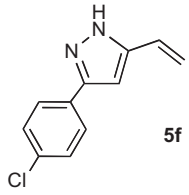
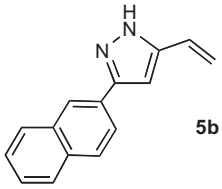
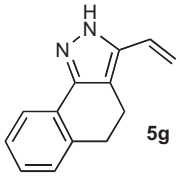
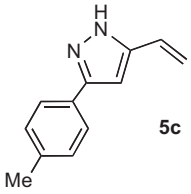
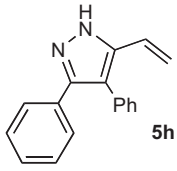
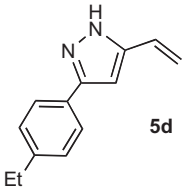
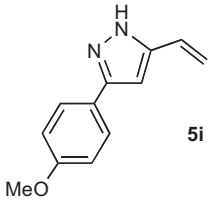
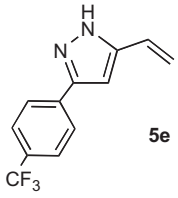
The formation of 5-vinylpyrazoles was evidenced by ^1H and ^{13}C NMR spectroscopy through the disappearance of the CH_2 group signals of the pyrazoline precursors, and by the appearance of alkene-type CH signals. As observed for pyridazines **3**, the N_2-heterocycle of **5h** adopts a planar geometry in the solid state. A protic H atom shifts between the two adjacent N atoms of the pyrazole ring (approximately 60% on N-2, 40% on N-1), resulting in quasi-similar endocyclic C–C [1.4030(16) and 1.4043(16) Å] and C–N [1.3438(15) and 1.3487(15) Å] bond lengths.

Noteworthy, no intermediate isomers resulting from a stepwise migration of the terminal allylic C=C bond was detected upon dissolution of **4** in 'technical' $CHCl_3$. In spite of the a priori stabilizing trisubstituted character of the C=C bond in the putative intermediate **4′**, the strained exocyclic environment of the former destabilizes **4′**,[36] thus preventing the formation of the *N*-sulfonyl-5-ethylpyrazole **4″** (Scheme 7). As previously suggested in the pyridazine series, the formation of the pyrazoles **5** should proceed via a base-induced eliminative aromatization process through either E1cb (routes a and b) or E2 (route c) mechanisms. It is noteworthy that re-protonation of the π-allylic carbanionic intermediate of route b would afford **4′**, and thus **4″**, which are not observed. The routes a and c are therefore likely preferred: in both cases, after elimination of the sulfinate anion, aromaticity-driven prototropy leads to the observed pyrazoles **5** (Scheme 7).

3. Conclusion

Aromatization of 6-methylidene-1,4,5,6-tetrahydropyridazines and 5-vinylpyrazolines to 6-methylpyridazines and 5-vinylpyrazoles generated from the same *C*-homoallyl-hydrazones, respectively, has been shown to proceed under acidic and/or basic

Table 4
Aromatization from various types of *N*-sulfonyl-vinylpyrazolines **4b**–**i**, and the reference substrate **4a** (Scheme 6)[a]

Entry	Substrate	Product	Yield[b] (%)	Entry	Substrate	Product	Yield[b] (%)
1	**4a**	 **5a**	68	7	**4f**	 **5f**	95
2	**4b**	 **5b**	42	8	**4g**	 **5g**	79
3	**4c**	 **5c**	62	9	**4h**	 **5h**	42
4	**4d**	 **5d**	86	10	**4i**	 **5i**	94
5	**4e**	 **5e**	42				

[a] Reaction conditions: NaOH (3 equiv), THF, 65 °C.
[b] Yield of isolated product.

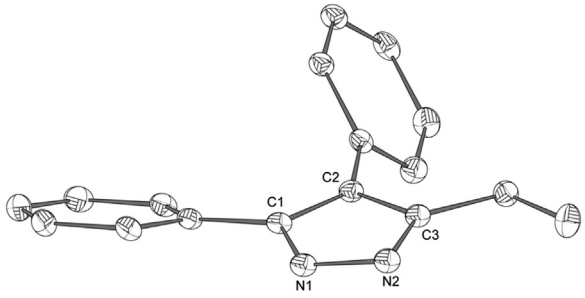


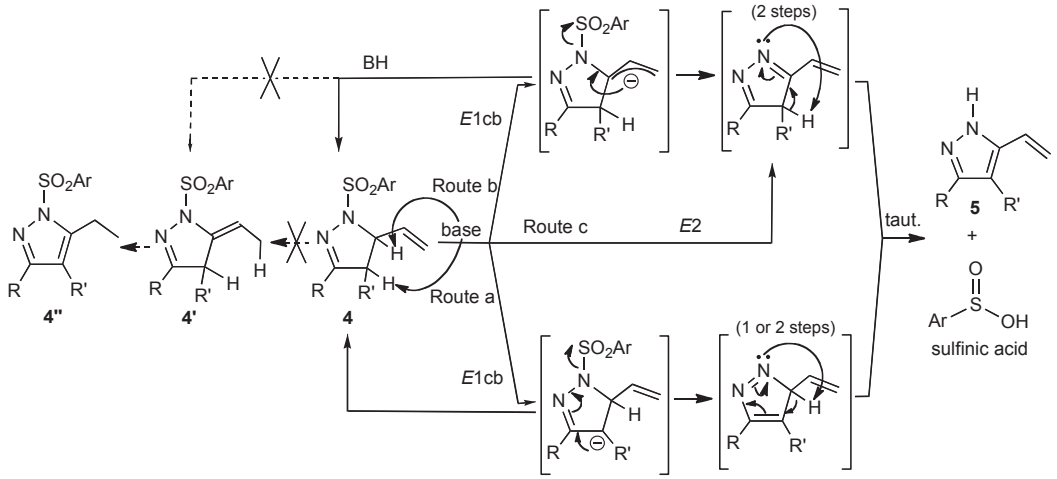
Fig. 3. Molecular view of the X-ray crystal structure of the pyrazole **5h**, with thermal ellipsoids drawn at the 30% probability level (for clarity, the H atoms are omitted). Selected bond distances [Å] and angles [°]: C1–C2 1.4030(16), C2–C3 1.4043(16), C1–N1 1.3487(15), C3–N2 1.3438(15), N1–N2 1.3494(15), C2–C1–N1 107.85(10), C1–N1–N2 109.63(9), N1–N2–C3 108.59(9).

eliminative conditions. Toward the strongly aromatic pyridazine targets (TRE≈0.28β vs 0.27β for benzenic derivatives: see Scheme 1), a stepwise mechanism is evidenced through 6-methyl-1,4-dihydropyridazine intermediates generated under acidic treatment (*exocyclic*→*endocyclic* migration of the C=C bond). In contrast, 5-vinylpyrazolines were found to be stable under acidic conditions, and no intermediate could be isolated in the base-induced eliminative aromatization to the corresponding 5-vinylpyrazoles, which are less aromatic than their six-membered isomers (TRE≈0.24β vs 0.28β: see Scheme 1). Although no correlation can be a priori claimed, it happens that the aromatization sequence proceeds in higher yield in the pyridazine series than in the vinylpyrazole series. The disclosed systematic approach provides alternative routes to methylpyridazine and vinylpyrazole isomers, and unveils new horizons in the chemistry of the valuable (N_2)-heterocycles.

4. Experimental section

4.1. General remarks

THF was dried and distilled over sodium/benzophenone. All other reagents were used as commercially available. Column chromatography was carried out on silica gel (60 Å, CC 70–200 μm). The following analytical instruments were used. ^{1}H and ^{13}C NMR: Bruker DPX 300, and Avance 400. NMR chemical shifts δ are given in parts per million (ppm), with positive values to high frequency



Scheme 7. Proposed mechanisms for the formation of pyrazoles **5** from 5-vinylpyrazolines **4** through a base-induced eliminative aromatization process.

relative to the tetramethylsilane reference for ^{1}H and ^{13}C; coupling constants *J* are given in hertz (Hz). Mass spectra were obtained on a Perkin Elmer Sciex spectrometer (MS/MS API-365). 6-Methylidene-1,4,5,6-tetrahydropyridazines and 5-vinylpyrazolines were prepared according to the literature.[26]

4.2. Typical procedure for the preparation of the 1,4-dihydropyridazines 2a–k (example of 2a)

In a round flask (5 mL), 1,4,5,6-tetrahydropyridazine **1a** was dissolved in $CHCl_3$. The mixture was then stirred at room temperature for 2 h. The solvent was finally evaporated under reduced pressure to give **2a** as a white solid, which was fully characterized without the need of any purification.

4.3. Characterization of the 1,4-dihydropyridazine products 2a–k

4.3.1. 1-(Benzenesulfonyl)-6-methyl-3-phenyl-1,4-dihydropyridazine ***2a***. White solid. Mp 115–117 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=2.25 (s, 3H, CH_3), 3.08 (br s, 2H, CH_2), 4.87 (br s, 1H, CH), 7.39–7.43 (m, 3H, CH_{ar}), 7.55 (t, *J*=7.6 Hz, 2H, CH_{ar}), 7.61 (t, *J*=6.8 Hz, 1H, CH_{ar}), 7.72 (d, *J*=8.0 Hz, 2H, CH_{ar}), 8.07 (d, *J*=7.6 Hz, 2H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=19.80 (CH_3), 24.02 (CH_2), 102.33 (CH), 126.36 (CH_{ar}), 128.10 (CH_{ar}), 128.43 (CH_{ar}), 128.91 (CH_{ar}), 130.09 (CH_{ar}), 133.10 (CH_{ar}), 134.48 (C_{ar}), 135.34 (C_{ar}), 138.99 (CN), 149.06 (CN). MS (DCI-CH_4): *m*/*z*: 313.10 [MH^+]. HRMS (ES^+): calcd for $C_{17}H_{16}N_2O_2S$ 312.0939; found 312.0937.

4.3.2. 6-Methyl-1-[(4-methylbenzene)sulfonyl]-3-(naphthalen-2-yl)-1,4-dihydropyridazine ***2b***. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=2.28 (br s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.21 (br s, 2H, CH_2), 4.91 (br s, 1H, CH), 7.34 (d, *J*=8.0 Hz, 2H, CH_{ar}), 7.52–7.55 (m, 2H, CH_{ar}), 7.85–7.88 (m, 3H, CH_{ar}), 7.98 (d, *J*=8.4 Hz, 3H, CH_{ar}), 8.05 (dd, *J*=1.6 and 7.8 Hz, 1H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=19.95 (CH_3), 21.63 (CH_3), 23.78 (CH_2), 102.31 (CH), 123.61 (CH_{ar}), 126.29 (CH_{ar}), 126.48 (CH_{ar}), 127.08 (CH_{ar}), 127.72 (CH_{ar}), 128.16 (CH_{ar}), 128.18 (CH_{ar}), 128.60 (CH_{ar}), 129.56 (CH_{ar}), 132.87 (C_{ar}), 132.91 (C_{ar}), 134.08 (C_{ar}), 134.43 (C_{ar}), 135.99 (C_{ar}), 144.06 (CN), 148.39 (CN). MS (DCI-CH_4): *m*/*z*: 377.13 [MH^+]. HRMS (ES^+): calcd for $C_{22}H_{21}N_2O_2S$ 377.1324; found 377.1336.

4.3.3. 6-Methyl-1-[(4-methylbenzene)sulfonyl]-3-(4-methylphenyl)-1,4-dihydropyridazine ***2c***. Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.24 (d, *J*=1.2 Hz, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 3.03 (br s, 2H, CH_2), 4.84 (br s, 1H, CH), 7.20 (d, *J*=8.4 Hz, 2H, CH_{ar}), 7.31 (d, *J*=8.4 Hz, 2H, CH_{ar}), 7.62 (d, *J*=8.1 Hz, 2H, CH_{ar}), 7.94 (d, *J*=8.1 Hz, 2H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=19.85 (CH_3), 21.38 (CH_3), 21.61 (CH_3), 23.97 (CH_2), 102.28 (CH), 126.30 (CH_{ar}), 128.14 (CH_{ar}), 129.12 (CH_{ar}), 129.49 (CH_{ar}), 132.64 (C_{ar}), 134.51 (C_{ar}), 136.03 (C_{ar}), 140.24 (C_{ar}), 143.93 (CN), 148.94 (CN). MS (DCI-CH_4): *m*/*z*: 341.13 [MH^+]. HRMS (ES^+): calcd for $C_{19}H_{21}N_2O_2S$ 341.1324; found 341.1322.

4.3.4. 3-(4-Ethylphenyl)-6-methyl-1-[(4-methylbenzene)sulfonyl]-1,4-dihydropyridazine ***2d***. Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.25 (t, *J*=7.6 Hz, 3H, CH_3), 2.24 (d, *J*=1.2 Hz, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.68 (q, *J*=7.6 Hz, 2H, CH_2), 3.04 (br s, 2H, CH_2), 4.84 (br s, 1H, CH), 7.23 (d, *J*=8.1 Hz, 2H, CH_{ar}), 7.32 (d, *J*=8.1 Hz, 2H, CH_{ar}), 7.65 (d, *J*=8.4 Hz, 2H, CH_{ar}), 7.94 (d, *J*=8.4 Hz, 2H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=15.42 (CH_3), 19.86 (CH_3), 21.62 (CH_3), 24.01 (CH_2), 28.74 (CH_2), 102.27 (CH), 126.41 (CH_{ar}), 127.94 (CH_{ar}), 128.14 (CH_{ar}), 129.50 (CH_{ar}), 132.88 (C_{ar}), 134.51 (C_{ar}), 136.01 (C_{ar}), 143.94 (C_{ar}), 146.56 (CN), 148.96 (CN). MS (DCI-CH_4): *m*/*z*: 355.15 [MH^+]. HRMS (ES^+): calcd for $C_{20}H_{23}N_2O_2S$ 355.1480; found 355.1497.

4.3.5. 6-Methyl-1-[(4-methylbenzene)sulfonyl]-3-[4-(trifluoromethyl)phenyl]-1,4-dihydropyridazine ***2e***. White solid. Mp 131–133 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=2.26 (d, *J*=1.2 Hz, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.10 (br s, 2H, CH_2), 4.85 (br s, 1H, CH), 7.34 (d, *J*=8.0 Hz, 2H, CH_{ar}), 7.66 (d, *J*=8.0 Hz, 2H, CH_{ar}), 7.82 (d, *J*=8.4 Hz, 2H, CH_{ar}), 7.93 (d, *J*=8.4 Hz, 2H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=19.80 (CH_3), 21.64 (CH_3), 23.84 (CH_2), 101.66 (CH), 125.42 (q, *J*=3.8 Hz, CH_{ar}), 126.55 (CH_{ar}), 128.14 (CH_{ar}), 129.62 (CH_{ar}), 131.45 (q, *J*=32.5 Hz, CCF_3), 134.55 (C_{ar}), 135.83 (C_{ar}), 138.80 (C_{ar}), 144.28 (CN), 146.75 (CN). MS (DCI-CH_4): *m*/*z*: 395.11 [MH^+]. HRMS (ES^+): calcd for $C_{19}H_{18}F_3N_2O_2S$ 395.1041; found 395.1053.

4.3.6. 3-(4-Chlorophenyl)-6-methyl-1-[(4-methylbenzene)sulfonyl]-1,4-dihydropyridazine ***2f***. White solid. Mp 102–104 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.24 (d, *J*=1.2 Hz, 3H, CH_3), 2.44 (s, 3H, CH_3), 3.05 (br s, 2H, CH_2), 4.84 (br s, 1H, CH), 7.32–7.39 (m, 4H, CH_{ar}), 7.65 (d, *J*=8.7 Hz, 2H, CH_{ar}), 7.91 (d, *J*=8.1 Hz, 2H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=19.82 (CH_3), 21.63 (CH_3), 23.81 (CH_2), 101.87 (CH), 127.58 (CH_{ar}), 128.11 (CH_{ar}), 128.64 (CH_{ar}), 129.57 (CH_{ar}), 133.91 (C_{ar}), 134.49 (C_{ar}), 135.89 (C_{ar}), 136.07 (C_{ar}), 144.15 (CN), 147.38 (CN). MS (DCI-CH_4): *m*/*z*: 361.08 [MH^+]. HRMS (ES^+): calcd for $C_{18}H_{18}N_2O_2SCl$ 361.0778; found 361.0786.

4.3.7. 3-Methyl-2-[(4-methylbenzene)sulfonyl]-2H,4aH,5H,6H-benzo[h]cinnoline ***2g***. Brown solid. Mp 136–138 °C. ^{1}H NMR ($CDCl_3$,

400 MHz): δ=1.63–1.74 (m, 1H, CH_2), 2.12–2.17 (m, 1H, CH_2), 2.23 (br s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.74–2.83 (m, 2H, CH_2), 2.89–2.98 (m, 1H, CH), 4.62 (t, J=1.6 Hz, 1H, CH), 7.14 (d, J=7.6 Hz, 1H, CH_{ar}), 7.25–7.34 (m, 4H, CH_{ar}), 7.98 (d, J=8.0 Hz, 2H, CH_{ar}), 8.12 (dd, J=7.6 Hz and 1.2 Hz, 1H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=19.22 (CH_3), 21.62 (CH_3), 27.99 (CH_2), 28.94 (CH_2), 33.34 (CH), 107.47 (CH), 125.89 (CH_{ar}), 126.60 (CH_{ar}), 128.21 (CH_{ar}), 128.72 (CH_{ar}), 129.50 (CH_{ar}), 129.98 (CH_{ar}), 130.04 (C_{ar}), 135.26 (C_{ar}), 136.17 (C_{ar}), 139.99 (C_{ar}), 143.95 (CN), 149.06 (CN). MS (DCI-CH_4): *m/z*: 352.13 [MH^+]. HRMS (ES^+): calcd for $C_{20}H_{20}N_2O_2S$ 352.1245; found 352.1256.

4.3.8. 6-Methyl-1-[(4-methylbenzene)sulfonyl]-3,4-diphenyl-1,4-dihydropyridazine ***2h***. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=2.29 (s, 3H, CH_3), 4.62 (d, J=6.0 Hz, 1H, CH), 5.09 (d, J=6.0 Hz, 1H, CH), 7.05 (d, J=6.8 Hz, 2H, CH_{ar}), 7.19–7.25 (m, 4H, CH_{ar}), 7.33 (t, J=7.2 Hz, 3H, CH_{ar}), 7.58 (t, J=7.2 Hz, 2H, CH_{ar}), 7.72 (d, J=6.8 Hz, 2H, CH_{ar}), 8.11 (d, J=7.2 Hz, 2H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=20.23 (CH_3), 40.15 (CH), 107.46 (CH), 126.92 (CH_{ar}), 127.13 (CH_{ar}), 127.16 (CH_{ar}), 128.20 (CH_{ar}), 128.36 (CH_{ar}), 129.06 (CH_{ar}), 129.14 (CH_{ar}), 129.77 (CH_{ar}), 132.34 (C_{ar}), 133.31 (CH_{ar}), 135.11 (C_{ar}), 138.84 (C_{ar}), 141.70 (CN), 148.61 (CN). MS (DCI-CH_4): *m/z*: 389.13 [MH^+]. HRMS (ES^+): calcd for $C_{23}H_{21}N_2O_2S$ 389.1324; found 389.1335.

4.3.9. 3-(4-Methoxyphenyl)-6-methyl-1-[(4-methylbenzene)sulfonyl]-1,4-dihydropyridazine ***2i***. Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.23 (d, J=1.6 Hz, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.02 (br s, 2H, CH_2), 3.85 (s, 3H, CH_3), 4.84 (br s, 1H, CH), 6.91 (d, J=9.0 Hz, 2H, CH_{ar}), 7.31 (d, J=8.4 Hz, 2H, CH_{ar}), 7.68 (d, J=9.0 Hz, 2H, CH_{ar}), 7.93 (d, J=8.4 Hz, 2H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=19.87 (CH_3), 21.61 (CH_3), 23.95 (CH_2), 55.37 (CH_3), 102.29 (CH), 113.73 (CH_{ar}), 127.88 (CH_{ar}), 128.11 (CH_{ar}), 129.48 (CH_{ar}), 134.51 (C_{ar}), 136.03 (C_{ar}), 143.91 (C_{ar}), 148.73 (CN), 157.49 (CN), 161.16 (C_{ar}). MS (DCI-CH_4): *m/z*: 357.13 [MH^+]. HRMS (ES^+): calcd for $C_{19}H_{21}N_2O_3S$ 357.1273; found 357.1281.

4.3.10. 6-Methyl-1-[(4-methylbenzene)sulfonyl]-3-pentyl-1,4-dihydropyridazine ***2j***. Brown solid. Mp 186–189 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=0.84–0.92 (m, 3H, CH_3), 1.22–1.32 (m, 4H, CH_2), 1.48–1.55 (m, 2H, CH_2), 2.16 (s, 3H, CH_3), 2.26 (t, J=7.2 Hz, 2H, CH_2), 2.43 (s, 3H, CH_3), 2.51 (d, J=0.8 Hz, 2H, CH_2), 4.71 (s, 1H, CH), 7.29 (d, J=8.4 Hz, 2H, CH_{ar}), 7.86 (d, J=8.0 Hz, 2H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 75.6 MHz): δ=13.90 (CH_3), 20.66 (CH_3), 21.64 (CH_3), 22.34 (CH_2), 25.25 (CH_2), 27.90 (CH_2), 31.24 (CH_2), 34.66 (CH_2), 103.42 (CH), 126.06 (CH_{ar}), 128.32 (CH_{ar}), 128.78 (CH_{ar}), 129.81 (CH_{ar}), 140.11 (C_{ar}), 144.79 (C_{ar}), 158.62 (CN), 162.74 (CN). MS (DCI-CH_4): *m/z*: 320.15 [MH^+]. HRMS (ES^+): calcd for $C_{17}H_{24}N_2O_2S$ 320.1559; found 320.1545.

4.3.11. 3-Methyl-2-[(4-methylbenzene)sulfonyl]-2H,4aH,5H,6H,7H,8H,9H-cyclohepta[c]pyridazine ***2k***. Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=1.32–1.43 (m, 4H, CH_2), 1.60–1.70 (m, 6H, CH_2), 2.14 (d, J=1.6 Hz, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.55 (m, 1H, CH), 4.61 (br s, 1H, CH), 7.29 (d, J=8.4 Hz, 2H, CH_{ar}), 7.88 (d, J=8.4 Hz, 2H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=19.17 (CH_3), 21.59 (CH_3), 26.53 (CH_2), 28.19 (CH_2), 29.20 (CH_2), 32.46 (CH_2), 35.14 (CH_2), 37.27 (CH), 108.68 (CH), 128.01 (CH_{ar}), 129.35 (CH_{ar}), 134.73 (C_{ar}), 136.27 (C_{ar}), 143.69 (CN), 160.72 (CN). MS (DCI-CH_4): *m/z*: 319.15 [MH^+]. HRMS (ES^+): calcd for $C_{17}H_{23}N_2O_2S$ 319.1480; found 319.1487.

4.4. Typical procedure for the preparation of pyridazines 3a–k (example of 3a)

In an around flask (5 mL), were added successively 1,4-dihydropyridazine **2a** (0.064 mmol, 1 equiv), NaOAc (0.192 mmol, 3 equiv), a Teflon stirring bar, and THF (4 mL). The reaction mixture was then stirred at 65 °C for 3 h. The solution was then allowed to cool down to room temperature, and water (3 mL) was added. The aqueous layer was extracted with EtOAc (3×4 mL), and the combined organic layers were washed with brine (3×4 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel (pentane/EtOAc) to give **3a** as a white solid (92%).

4.5. Characterization of the pyridazine products 3a–k

4.5.1. 3-Methyl-6-phenylpyridazine ***3a***. Yield 92%. White solid. Mp 106–108 °C.[37] ^{1}H NMR ($CDCl_3$, 400 MHz): δ=2.76 (s, 3H, CH_3), 7.38 (d, J=8.8 Hz, 1H, CH_{ar}), 7.48–7.54 (m, 3H, CH_{ar}), 7.75 (d, J=8.8 Hz, 1H, CH_{ar}), 8.07 (d, J=7.6 Hz, 2H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=22.08 (CH_3), 123.86 (CH_{ar}), 126.89 (CH_{ar}), 127.23 (CH_{ar}), 128.95 (CH_{ar}), 129.73 (CH_{ar}), 136.50 (C_{ar}), 157.21 (CN), 158.53 (CN). MS (DCI-CH_4): *m/z*: 171.09 [MH^+]. HRMS (ES^+): calcd for $C_{11}H_{11}N_2$ 171.0922; found 171.0920. IR (ATR): 3061, 2916, 1587, 1496, 1450, 1415, 1168, 1113, 1034, 1012, 850, 770, 739, 689 cm^{-1}.

4.5.2. 3-Methyl-6-(naphthalen-2-yl)pyridazine ***3b***. Yield 96%. Brown solid. Mp 179–182 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=2.76 (s, 3H, CH_3), 7.35 (d, J=8.8 Hz, 1H, CH_{ar}), 7.52–7.54 (m, 2H, CH_{ar}), 7.84–7.89 (m, 2H, CH_{ar}), 7.93–7.98 (m, 2H, CH_{ar}), 8.24 (d, J=8.4 Hz, 1H, CH_{ar}), 8.50 (s, 1H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=22.09 (CH_3), 124.03 (CH_{ar}), 124.20 (CH_{ar}), 126.52 (CH_{ar}), 126.53 (CH_{ar}), 126.96 (CH_{ar}), 127.29 (CH_{ar}), 127.75 (CH_{ar}), 128.76 (CH_{ar}), 133.38 (C_{ar}), 133.75 (C_{ar}), 133.96 (C_{ar}), 157.07 (CN), 158.54 (CN). MS (DCI-CH_4): *m/z*: 221.11 [MH^+]. HRMS (ES^+): calcd for $C_{15}H_{13}N_2$ 221.1079; found 221.1083. IR (ATR): 3057, 2920, 2851, 1961, 1825, 1682, 1587, 1552, 1500, 1472, 1438, 1415, 1359, 1276, 1241, 1128, 1104, 1028, 959, 943, 915, 859, 868, 844, 810, 824, 763, 746, 654 cm^{-1}.

4.5.3. 3-Methyl-6-(4-methylphenyl)pyridazine ***3c***. Yield 64%. Brown solid. Mp 118–121 °C.[38] ^{1}H NMR ($CDCl_3$, 400 MHz): δ=2.44 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 7.32–7.38 (m, 3H, CH_{ar}), 7.73 (d, J=8.8 Hz, 1H, CH_{ar}), 7.98 (d, J=8.0 Hz, 2H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=21.34 (CH_3), 22.06 (CH_3), 123.59 (CH_{ar}), 126.75 (CH_{ar}), 127.15 (CH_{ar}), 129.68 (CH_{ar}), 133.68 (C_{ar}), 139.87 (C_{ar}), 157.15 (CN), 158.24 (CN). MS (DCI-CH_4): *m/z*: 185.10 [MH^+]. HRMS (ES^+): calcd for $C_{12}H_{13}N_2$ 185.1079; found 185.1087. IR (ATR): 2922, 2853, 1733, 1456, 812, 743 cm^{-1}.

4.5.4. 3-(4-Ethylphenyl)-6-methylpyridazine ***3d***. Yield 64%. Brown solid. Mp 73–75 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=1.30 (t, J=8.0 Hz, 3H, CH_3), 2.74 (q, J=8.0 Hz, 2H, CH_2), 2.77 (s, 3H, CH_3), 7.35–7.38 (m, 3H, CH_{ar}), 7.74 (d, J=8.4 Hz, 1H, CH_{ar}), 8.01 (d, J=7.2 Hz, 2H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=15.48 (CH_3), 22.08 (CH_3), 28.73 (CH_2), 123.63 (CH_{ar}), 126.86 (CH_{ar}), 127.15 (CH_{ar}), 128.51 (CH_{ar}), 133.92 (C_{ar}), 146.19 (C_{ar}), 157.19 (CN), 158.24 (CN). MS (DCI-CH_4): *m/z*: 199.12 [MH^+]. HRMS (ES^+): calcd for $C_{13}H_{15}N_2$ 199.1235; found 199.1237. IR (ATR): 3055, 2963, 2910, 1588, 1429, 1407, 1162, 1007, 826, 754 cm^{-1}.

4.5.5. 3-Methyl-6-[4-(trifluoromethyl)phenyl]pyridazine ***3e***. Yield 90%. White solid. Mp 180–182 °C.[38] ^{1}H NMR ($CDCl_3$, 400 MHz): δ=2.80 (s, 3H, CH_3), 7.44 (d, J=8.8 Hz, 1H, CH_{ar}), 7.80 (t, J=8.0 Hz, 3H, CH_{ar}), 8.20 (d, J=8.4 Hz, 2H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=22.12 (CH_3), 123.99 (CH_{ar}), 124.04 (q, J=272.2 Hz, CF_3), 125.91 (q, J=3.8 Hz, CH_{ar}), 127.19 (CH_{ar}), 127.37 (CH_{ar}), 131.45 (q, J=32.6 Hz, CCF_3), 139.84 (C_{ar}), 155.93 (CN), 159.33 (CN). MS (DCI-CH_4): *m/z*: 238.07 [MH^+]. HRMS (ES^+): calcd for $C_{12}H_9F_3N_2$ 238.0718; found 238.0719. IR (ATR): 3069, 2928, 1552, 1428, 1322, 1158, 1110, 1067, 1010, 830, 711 cm^{-1}.

4.5.6. 3-(4-Chlorophenyl)-6-methylpyridazine ***3f***. Yield 59%. White solid. Mp 146–149 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=2.75 (s, 3H,

CH_3), 7.38 (d, J=8.8 Hz, 1H, CH_{ar}), 7.47 (d, J=8.0 Hz, 2H, CH_{ar}), 7.71 (d, J=8.8 Hz, 1H, CH_{ar}), 8.00 (d, J=8.4 Hz, 2H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=22.08 (CH_3), 123.57 (CH_{ar}), 127.29 (CH_{ar}), 128.11 (CH_{ar}), 129.17 (CH_{ar}), 134.90 (C_{ar}), 136.01 (C_{ar}), 156.10 (CN), 158.77 (CN). MS (DCI-CH_4): m/z: 205.05 [MH^+]. HRMS (ES^+): calcd for $C_{11}H_{10}ClN_2$ 205.0533; found 205.0530. IR (ATR): 3057, 2922, 2853, 1595, 1489, 1422, 1399, 1333, 1092, 1008, 818, 759 cm^{-1}.

4.5.7. 3-Methyl-5H,6H-benzo[h]cinnoline ***3g***. Yield 54%. Brown solid. Mp 108–110 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=2.71 (s, 3H, CH_3), 2.91–2.98 (m, 4H, CH_2), 7.14 (s, 1H, CH_{ar}), 7.26 (t, J=7.2 Hz, 1H, CH_{ar}), 7.36–7.44 (m, 2H, CH_{ar}), 8.57 (d, J=7.6 Hz, 1H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=22.11 (CH_3), 27.16 (CH_2), 27.42 (CH_2), 125.14 (CH_{ar}), 125.44 (CH_{ar}), 127.53 (CH_{ar}), 128.01 (CH_{ar}), 129.96 (CH_{ar}), 131.79 (C_{ar}), 136.23 (C_{ar}), 137.79 (C_{ar}), 153.51 (CN), 158.43 (CN). MS (DCI-CH_4): m/z: 197.11 [MH^+]. HRMS (ES^+): calcd for $C_{13}H_{12}N_2$ 197.1079; found 197.1082. IR (ATR): 2955, 2920, 2847, 1606, 1487, 1410, 1285, 1107, 1012, 890, 794, 753, 695 cm^{-1}.

4.5.8. 6-Methyl-3,4-diphenylpyridazine ***3h***. Yield 46%. Brown solid. Mp 117–119 °C.[39] ^{1}H NMR ($CDCl_3$, 400 MHz): δ=2.81 (s, 3H, CH_3), 7.19 (d, J=7.6 Hz, 2H, CH_{ar}), 7.28–7.34 (m, 7H, CH_{ar}), 7.43 (d, J=7.2 Hz, 2H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=22.00 (CH_3), 127.68 (CH_{ar}), 128.09 (CH_{ar}), 128.51 (CH_{ar}), 128.57 (CH_{ar}), 128.63 (CH_{ar}), 129.06 (CH_{ar}), 129.99 (CH_{ar}), 136.97 (C_{ar}), 137.01 (C_{ar}), 138.97 (C_{ar}), 157.78 (CN), 158.60 (CN). MS (DCI-CH_4): m/z: 247.12 [MH^+]. HRMS (ES^+): calcd for $C_{17}H_{15}N_2$ 247.1235; found 247.1225. IR (ATR): 3026, 2958, 1571, 1494, 1400, 1036, 1011, 889, 795, 752, 696 cm^{-1}.

4.5.9. 3-(4-Methoxyphenyl)-6-methylpyridazine ***3i***. Yield 40%. White solid. Mp 136–138 °C.[38] ^{1}H NMR ($CDCl_3$, 400 MHz): δ=2.76 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 7.04 (d, J=8.4 Hz, 2H, CH_{ar}), 7.34 (d, J=8.8 Hz, 1H, CH_{ar}), 7.70 (d, J=8.8 Hz, 1H, CH_{ar}), 8.05 (d, J=8.4 Hz, 2H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=22.02 (CH_3), 55.40 (CH_3), 114.37 (CH_{ar}), 123.21 (CH_{ar}), 127.15 (CH_{ar}), 128.19 (CH_{ar}), 128.98 (C_{ar}), 156.76 (CN), 157.88 (CN), 161.07 (C_{ar}). MS (DCI-CH_4): m/z: 201.10 [MH^+]. HRMS (ES^+): calcd for $C_{12}H_{13}N_2O$ 201.1028; found 201.1025. IR (ATR): 3046, 2957, 2925, 2839, 2046, 1912, 1605, 1508, 1427, 1283, 1249, 1172, 1114, 1034, 832, 814, 671 cm^{-1}.

4.5.10. 3-Methyl-6-(4-pentylphenyl)pyridazine ***3j***. Yield 62%. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=0.90 (t, J=6.4 Hz, 3H, CH_3), 1.35 (m, 4H, CH_2), 1.72–1.80 (m, 2H, CH_2), 2.68 (s, 3H, CH_3), 2.93 (t, J=8.0 Hz, 2H, CH_2), 7.22 (br s, 2H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=13.97 (CH_3), 21.98 (CH_3), 22.46 (CH_2), 29.38 (CH_2), 31.41 (CH_2), 35.87 (CH_2), 126.19 (CH_{ar}), 126.85 (CH_{ar}), 157.74 (CN), 161.49 (CN). MS (DCI-CH_4): m/z: 165.1 [MH^+]. HRMS (ES^+): calcd for $C_{10}H_{17}N_2$ 165.1392; found 165.1395. IR (ATR): 2925, 2856, 1551, 1436, 1165, 1080, 815, 680, 642, 525, 520 cm^{-1}.

4.5.11. 3-Methyl-6-{6,7,8,9-tetrahydro-5H-benzo[7]annulen-2-yl} pyridazine ***3k***. Yield 43%. Brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=1.69–1.76 (m, 4H, CH_2), 1.87–1.91 (m, 2H, CH_2), 2.63 (s, 3H, CH_3), 2.74 (br s, 2H, CH_2), 3.21 (br s, 2H, CH_2), 7.02 (s, 1H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=26.59 (CH_3), 27.51 (CH_2), 29.71 (CH_2), 32.19 (CH_2), 34.84 (CH_2), 36.41 (CH_2), 126.59 (CH_{ar}), 142.60 (C_{ar}), 158.24 (CN), 163.14 (CN). MS (DCI-CH_4): m/z: 162.12 [MH^+]. HRMS (ES^+): calcd for $C_{10}H_{15}N_2$ 163.1235; found 163.1248. IR (ATR): 2926, 2853, 1607, 1509, 1430, 1285, 1252, 1174, 1035, 913, 813, 794, 672 cm^{-1}.

4.6. Typical procedure for the preparation of pyrazoles 5a–i (example of 5a)

In a round flask (5 mL), were added successively pyrazoline **4a** (0.346 mmol, 1 equiv), NaOH (1.038 mmol, 3 equiv), a Teflon stirring bar, and THF (4 mL). The mixture was then stirred at 65 °C for 3 h. The solution was then allowed to cool down to room temperature, and water (3 mL) was added. The aqueous layer was extracted with EtOAc (3×4 mL), and the combined organic layers were washed with brine (3×4 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel (pentane/EtOAc) to give **5a** as a white solid (68%).

4.7. Characterization of the pyrazole products 5a–i

4.7.1. 5-Ethenyl-3-phenyl-1H-pyrazole ***5a***. Yield 68%. White solid. Mp 96–98 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=5.34 (d, J=11.2 Hz, 1H, CH_2), 5.76 (d, J=17.6 Hz, 1H, CH_2), 6.66 (s, 1H, CH), 6.68 (t, J=11.2 Hz, 1H, CH), 7.34 (t, J=7.2 Hz, 1H, CH_{ar}), 7.40 (t, J=7.2 Hz, 2H, CH_{ar}), 7.70 (d, J=8.0 Hz, 2H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=100.08 (CH), 116.05 (CH_2), 125.69 (CH_{ar}), 126.25 (CH_{ar}), 128.20 (CH_{ar}), 128.82 (CH_{ar}), 131.43 (C_{ar}), 146.99 (CN), 148.86 (CN). MS (DCI-CH_4): m/z: 171.09 [MH^+]. HRMS (ES^+): calcd for $C_{11}H_{11}N_2$ 171.0922; found 171.0920. IR (ATR): 2917, 2870, 1560, 1461, 1274, 1204, 1168, 1075, 1000, 964, 912, 806, 758, 687, 507 cm^{-1}.

4.7.2. 5-Ethenyl-3-(naphthalen-2-yl)-1H-pyrazole amine ***5b***. Yield 42%. Yellow solid. Mp 99–102 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=5.40 (d, J=11.2 Hz, 1H, CH_2), 5.80 (d, J=17.6 Hz, 1H, CH_2), 6.70–6.77 (m, 1H, CH), 6.81 (s, 1H, CH), 7.49 (br s, 2H, CH_{ar}), 7.85 (br s, 2H, CH_{ar}), 7.87 (s, 2H, CH_{ar}), 8.18 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=100.46 (CH), 116.14 (CH_2), 123.79 (CH_{ar}), 124.34 (CH_{ar}), 126.00 (CH_{ar}), 126.18 (CH_{ar}), 126.45 (CH_{ar}), 127.75 (CH_{ar}), 128.18 (CH_{ar}), 128.58 (CH_{ar}), 129.00 (C_{ar}), 133.15 (C_{ar}), 133.47 (C_{ar}), 146.80 (br s, CN), 149.50 (br s, CN). MS (DCI-CH_4): m/z: 221.10 [MH^+]. HRMS (ES^+): calcd for $C_{15}H_{13}N_2$, 221.1079; found 221.1075. IR (ATR): 3121, 2918, 1559, 1428, 1270, 1164, 979, 895, 858, 802, 747, 681, 627, 582, 527 cm^{-1}.

4.7.3. 5-Ethenyl-3-(4-methylphenyl)-1H-pyrazole amine ***5c***. Yield 62%. White solid. Mp 112–114 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=2.40 (s, 3H, CH_3), 5.35 (dd, J=1.0 Hz and 10.8 Hz, 1H, CH_2), 5.76 (dd, J=1.0 Hz and 18.0 Hz, 1H, CH_2), 6.64 (s, 1H, CH), 6.66–6.73 (m, 1H, CH), 7.22 (d, J=8.0 Hz, 2H, CH_{ar}), 7.59 (d, J=7.4 Hz, 2H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=21.29 (CH_3), 99.75 (CH), 115.83 (CH_2), 125.55 (CH_{ar}), 126.62 (CH_{ar}), 128.48 (C_{ar}), 129.53 (CH_{ar}), 138.12 (C_{ar}), 147.48 (CN), 148.57 (CN). MS (DCI-CH_4): m/z: 185.10 [MH^+]. HRMS (ES^+): calcd for $C_{12}H_{13}N_2$ 185.1079; found 185.1077. IR (ATR): 3069, 2919, 1509, 1453, 1376, 1166, 1047, 991, 965, 901, 820, 788, 689, 570, 523 cm^{-1}.

4.7.4. 5-Ethenyl-3-(4-ethylphenyl)-1H-pyrazole amine ***5d***. Yield 86%. Brown solid. Mp 72–75 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=1.28 (t, J=7.2 Hz, 3H, CH_3), 2.68 (q, J=7.2 Hz, 2H, CH_2), 5.36 (d, J=11.2 Hz, 1H, CH_2), 5.75 (d, J=17.6 Hz, 1H, CH_2), 6.64 (s, 1H, CH), 6.66–6.74 (m, 1H, CH), 7.25 (d, J=7.6 Hz, 2H, CH_{ar}), 7.61 (d, J=7.6 Hz, 2H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=15.51 (CH_3), 28.67 (CH_2), 99.82 (CH), 115.86 (CH_2), 125.62 (CH_{ar}), 126.61 (CH_{ar}), 128.36 (CH_{ar}), 128.67 (C_{ar}), 144.52 (C_{ar}), 147.42 (CN), 148.46 (CN). MS (DCI-CH_4): m/z: 199.12 [MH^+]. HRMS (ES^+): calcd for $C_{13}H_{15}N_2$ 199.1235; found 199.1232. IR (ATR): 3133, 2920, 1716, 1508, 1431, 1258, 1258, 1161, 1113, 985, 909, 810, 723, 560, 521, 506 cm^{-1}.

4.7.5. 5-Ethenyl-3-[4-(trifluoromethyl)phenyl]-1H-pyrazole ***5e***. Yield 42%. Yellow solid. Mp 138–140 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=5.43 (d, J=11.2 Hz, 1H, CH_2), 5.76 (d, J=17.6 Hz, 1H, CH_2), 6.65–6.72 (m, 1H, CH), 6.73 (s, 1H, CH), 7.68 (d, J=8.0 Hz, 2H, CH_{ar}), 7.89 (d, J=8.0 Hz, 2H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=100.74 (CH), 116.67 (CH_2), 124.01 (q, J=271.8 Hz, CF_3), 125.09 (CH_{ar}), 125.69 (q, J_{CF}=4.0 Hz, CH_{ar}), 125.74 (CH_{ar}), 130.00 (q, J=32.2 Hz, CCF_3), 135.26 (C_{ar}), 145.83 (CN), 148.90 (CN). MS (DCI-CH_4): m/z: 239.08 [MH^+]. HRMS (ES^+): calcd for $C_{12}H_{10}F_3N_2$

239.0796; found 239.0802. IR (ATR): 3242, 2924, 1835, 1618, 1448, 1323, 1163, 1105, 1069, 1016, 986, 960, 915, 844, 804, 755, 708, 658, 594, 533, 501 cm^{-1}

4.7.6. 3-(4-Chlorophenyl)-5-ethenyl-1H-pyrazole ***5f***. Yield 95%. White solid. Mp 108–111 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ=5.38 (d, J=11.2 Hz, 1H, CH_2), 5.75 (d, J=17.6 Hz, 1H, CH_2), 6.62–6.69 (m, 2H, CH), 7.38 (d, J=7.2 Hz, 2H, CH_{ar}), 7.67 (d, J=7.6 Hz, 2H, CH_{ar}), 10.57 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=100.31 (CH), 116.36 (CH_2), 125.22 (CH_{ar}), 126.90 (CH_{ar}), 128.97 (CH_{ar}), 131.03 (C_{ar}), 133.94 (C_{ar}), 146.14 (CN) 149.48 (CN). MS (DCI-CH_4): m/z: 205.05 [MH^+]. HRMS (ES^+): calcd for $C_{11}H_{10}N_2Cl$ 205.0533; found 205.0533. IR (ATR): 3088, 2917, 1491, 1443, 1283, 1163, 1093, 1003, 964, 911, 830, 792, 697, 667, 539, 501 cm^{-1}.

4.7.7. 3-Ethenyl-2H,4H,5H-benzo[g]indazole ***5g***. Yield 79%. Yellow oil. ^1H NMR ($CDCl_3$, 400 MHz): δ=2.82 (t, J=7.2 Hz, 2H, CH_2), 2.97 (t, J=7.2 Hz, 2H, CH_2), 5.33 (d, J=11.6 Hz, 1H, CH_2), 5.63 (d, J=18.0 Hz, 1H, CH_2), 6.61–6.68 (m, 1H, CH), 7.19–7.28 (m, 3H, CH_{ar}), 7.73 (t, J=4.0 Hz, 1H, CH_{ar}), 10.56 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=19.24 (CH_2), 29.48 (CH_2), 115.56 (CH_2), 122.07 (CH), 124.92 (CH_{ar}), 126.81 (CH_{ar}), 127.60 (CH_{ar}), 128.29 (CH_{ar}), 133.21 (C_{ar}), 136.42 (C_{ar}), 139.34 (C_{ar}), 146.89 (CN), 155.78 (CN). MS (DCI-CH_4): m/z: 197.10 [MH^+]. HRMS (ES^+): calcd for $C_{13}H_{13}N_2$ 197.1079; found 197.1077. IR (ATR): 3103, 2926, 1634, 1474, 1436, 1308, 1155, 1081, 985, 906, 753, 734, 553, 514, 502 cm^{-1}.

4.7.8. 5-Ethenyl-3,4-Diphenyl-1H-pyrazole ***5h***. Yield 42%. White solid. Mp 189–192 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ=5.26 (d, J=11.2 Hz, 1H, CH_2), 5.72 (d, J=18.0 Hz, 1H, CH_2), 6.52–6.60 (m, 1H, CH), 7.24–7.28 (m, 5H, CH_{ar}), 7.35–7.40 (m, 5H, CH_{ar}), 11.44 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=115.82 (CH_2), 118.43 (C_{ar}), 125.02 (CH), 126.98 (CH_{ar}), 127.84 (CH_{ar}), 128.40 (CH_{ar}), 128.48 (CH_{ar}), 130.48 (CH_{ar}), 131.71 (C_{ar}), 132.92 (C_{ar}), 142.96 (CN), 146.79 (CN). MS (DCI-CH_4): m/z: 247.12 [MH^+]. HRMS (ES^+): calcd for $C_{17}H_{15}N_2$ 247.1235; found 247.1242. IR (ATR): 3139, 2921, 1602, 1443, 1263, 1179, 1113, 1071, 969, 914, 770, 752, 694, 613, 502 cm^{-1}.

4.7.9. 5-Ethenyl-3-(4-methoxyphenyl)-1H-pyrazole amine ***5i***. Yield 94%. White solid. Mp 114–116 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ=3.86 (s, 3H, CH_3), 5.36 (d, J=11.2 Hz, 1H, CH_2), 5.76 (d, J=18.0 Hz, 1H, CH_2), 6.60 (s, 1H, CH), 6.66–6.73 (m, 1H, CH), 6.96 (d, J=7.6 Hz, 2H, CH_{ar}), 7.63 (d, J=7.6 Hz, 2H, CH_{ar}). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ=55.36 (CH_3), 99.52 (CH), 114.28 (CH_{ar}), 115.89 (CH_2), 124.07 (C_{ar}), 126.48 (CH_{ar}), 126.94 (CH_{ar}), 147.25 (CN), 148.51 (CN), 159.73 (C_{ar}). MS (DCI-CH_4): m/z: 201.10 [MH^+]. HRMS (ES^+): calcd for $C_{12}H_{13}N_2O$ 201.1028; found 201.1017. IR (ATR): 3076, 2918, 1888, 1612, 1506, 1431, 1252, 1180, 1030, 982, 913, 832, 794, 686, 598, 523, 508 cm^{-1}.

4.8. Crystal structure determination of compounds 2a, 2e, 3a, 3a′, 3b, 3c, 3g, 3h, 3i, and 5h

X-ray diffraction data for the crystals were collected at 100 K on an Oxford Diffraction Gemini diffractometer using Cu Kα radiation source (**2e**, **3a**, **3g**, **3h**, **3i**, **5h**, λ=1.54180 Å) or Mo Kα radiation source (**2a**, **3a′**, **3b**, **3c**, λ=0.71073 Å). Multiscan absorption corrections were applied. The structures were solved by direct methods using SIR92[40] or SUPERFLIP,[41] and refined by means of least-square procedures using the PC version of CRYSTALS.[42] Atomic scattering factors were taken from the International Tables for X-ray Crystallography.[43] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined with riding constraints.

4.8.1. Crystal data for ***2a***. $C_{17}H_{16}N_2O_2S_1$, M=312.39 g mol^{-1}, monoclinic, a=9.90996(16), b=9.6596(2), c=15.4753(3) Å, β=91.243(2)°, V=1481.04(4) $Å^3$, T=100 K, space group: $P2_1/n$, Z=4, μ(Mo Kα)=0.227 mm^{-1}, 31,270 reflections measured, 3771 unique (R_{int}=0.020), 199 parameters, refinement on F, 3426 reflections used in the calculations [$I>3\sigma(I)$], $R1$=0.0292, $wR2$=0.0367.

4.8.2. Crystal data for ***2e***. $C_{19}H_{17}F_3N_2O_2S$, M=394.42 g mol^{-1}, monoclinic, a=14.1633(5), b=8.3742(2), c=15.1505(5) Å, β=105.975(3), V=1727.56(10) $Å^3$, T=100 K, space group $P2_1/n$, Z=4, μ(Cu Kα)=2.116 mm^{-1}, 20,565 reflections measured, 2613 unique (R_{int}=0.030), 244 parameters, refinement on F, 2449 reflections used in the calculations [$I>2\sigma(I)$], $R1$=0.0322, $wR2$=0.0439.

4.8.3. Crystal data for ***3a***. $C_{11}H_{10}N_2$, M=170.21 g mol^{-1}, monoclinic, a=5.7269(3), b=22.9224(11), c=7.1956(4) Å, β=112.312(6), V=873.87(8) $Å^3$, T=100 K, space group $C2/c$, Z=4, μ(Cu Kα)=0.614 mm^{-1}, 2852 reflections measured, 658 unique (R_{int}=0.012), 66 parameters, refinement on F, 647 reflections used in the calculations [$I>3\sigma(I)$], $R1$=0.0991, $wR2$=0.0926. The asymmetric unit contains half a molecule. Two positions have been assigned, respectively, to C(3)/N(2) and C(2)/N(1) with half occupancy. A two-fold symmetry axis generates the full molecule.

4.8.4. Crystal data for ***3a′***. $C_{17}H_{16}N_2O_3S$, M=328.39 g mol^{-1}, orthorhombic, a=18.1395(10), b=7.2588(4), c=11.8611(7) Å, V=1561.76(15) $Å^3$, T=100 K, space group $Pna21$, Z=4, μ(Mo Kα)=0.224 mm^{-1}, 27,660 reflections measured, 5152 unique (R_{int}=0.027), 209 parameters, refinement on F, 4559 reflections used in the calculations [$I>3\sigma(I)$], $R1$=0.0294, $wR2$=0.0333.

4.8.5. Crystal data for ***3b***. $C_{19}H_{17}F_3N_2O_2S$, M=394.42 g mol^{-1}, monoclinic, a=11.49986(18), b=9.08278(12), c=10.79807(17) Å, β=100.3163(15), V=1109.63(3) $Å^3$, T=100 K, space group $P2_1/c$, Z=4, μ(Mo Kα)=0.079 mm^{-1}, 23,837 reflections measured, 2842 unique (R_{int}=0.024), 154 parameters, refinement on F, 2336 reflections used in the calculations [$I>3\sigma(I)$], $R1$=0.0379, $wR2$=0.0464.

4.8.6. Crystal data for ***3c***. $C_{12}H_{12}N_2$, M=184.24 g mol^{-1}, monoclinic, a=6.13072(10), b=13.2919(2), c=11.8273(2) Å, β=90.5889(15), V=963.74(3) $Å^3$, T=100 K, space group $P2_1/c$, Z=4, μ(Mo Kα)=0.077 mm^{-1}, 16,085 reflections measured, 2342 unique (R_{int}=0.019), 127 parameters, refinement on F, 1894 reflections used in the calculations [$I>3\sigma(I)$], $R1$=0.0395, $wR2$=0.0524.

4.8.7. Crystal data for ***3g***. $C_{13}H_{12}N_2$, M=196.25 g mol^{-1}, monoclinic, a=7.54824(18), b=11.6750(4), c=11.3748(4) Å, β=99.212(3), V=989.48(5) $Å^3$, T=100 K, space group $P2_1/n$, Z=4, μ(Cu Kα)=0.615 mm^{-1}, 6153 reflections measured, 1513 unique (R_{int}=0.017), 136 parameters, refinement on F, 1411 reflections used in the calculations [$I>3\sigma(I)$], $R1$=0.0303, $wR2$=0.0371.

4.8.8. Crystal data for ***3h***. $C_{17}H_{14}N_2$, M=394.42 g mol^{-1}, monoclinic, a=10.77108(12), b=9.80238(13), c=25.0180(3) Å, β=92.1531(10), V=2639.59(5) $Å^3$, T=100 K, space group $P2_1/c$, Z=8, μ(Cu Kα)=0.571 mm^{-1}, 38,640 reflections measured, 3983 unique (R_{int}=0.022), 344 parameters, refinement on F, 3730 reflections used in the calculations [$I>3\sigma(I)$], $R1$=0.0277, $wR2$=0.0357.

4.8.9. Crystal data for ***3i***. $C_{12}H_{12}N_2O$, M=200.24 g mol^{-1}, monoclinic, a=20.7510(14), b=5.8173(3), c=18.3779(12) Å, β=115.374(8), V=2004.5(2) $Å^3$, T=100 K, space group $C2/c$, Z=8, μ(Cu Kα)=0.693 mm^{-1}, 6465 reflections measured, 1875 unique (R_{int}=0.018), 136 parameters, refinement on F, 1694 reflections used in the calculations [$I>3\sigma(I)$], $R1$=0.0449, $wR2$=0.0550.

4.8.10. Crystal data for ***5h***. $C_{17}H_{14}N_2$, M=246.31 g mol^{-1}, monoclinic, a=10.59135(18), b=17.5216(3), c=27.9341(5) Å,

β=90.5984(15), V=5183.67(16) Å^3, T=100 K, space group $C2/c$, Z=16, μ(Cu Kα)=0.581 mm^{-1}, 25,473 reflections measured, 4998 unique (R_{int}=0.018), 343 parameters, refinement on F, 4631 reflections used in the calculations [$I>3\sigma(I)$], $R1$=0.0416, $wR2$=0.0556.

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Supplementary data

^{1}H and ^{13}C NMR spectra of all newly described compounds. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.05.005.

References and notes

1. (a) Balaban, A. T.; Oniciu, D. C.; Katritzky, A. R. *Chem. Rev.* **2004**, *104*, 2777; (b) Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society*; Wiley: New York, NY, 1997.
2. (a) Johnson, M.; Younglove, B.; Lee, L.; LeBlanc, R.; Holt, H., Jr.; Hills, P.; Mackay, H.; Brown, T.; Mooberry, S. L.; Lee, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5897; (b) Oezdemir, Z.; Kandilci, B.; Guemuesel, H. B.; Calis, U.; Bilgin, A. A. *Eur. J. Med. Chem.* **2007**, *42*, 373; (c) Spring, D. R. *Chem. Soc. Rev.* **2005**, *34*, 472; (d) Kumar, S.; Bawa, S.; Drabu, S.; Kumar, R.; Gupta, H. *Recent Patents Anti-Infect. Drug Discov.* **2009**, *4*, 154.
3. Lopes, S. M. M.; Brigas, A. F.; Palacios, F.; Lemos, A.; Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2012**, 2152 and cited references therein.
4. (a) Elguero, J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F., Eds.; Pergamon: Oxford, UK, 1996; Vol. 3, p P1; (b) Oliveira, R.; Sanmartin, R.; Dominguez, E. *J. Org. Chem.* **2000**, *65*, 7010; (c) Recnik, S.; Svete, J.; Stanovnik, B. *Heterocycles* **2002**, *57*, 2091.
5. (a) Maes, B. U. W.; Lemière, G. L. F. Pyridazines and their Benzo Derivatives In*Aitken, A., Ed.. Comprehensive Heterocyclic Chemistry III*; Elsevier: Oxford, UK, 2008; Vol. 8, p P1; (b) Alfini, R.; Cecchi, M.; Giomi, D. *Molecules* **2010**, *15*, 1722.
6. Gilchrist, T. L. In *Heterocyclic Chemistry Addison-Wesley Longman: England, 1998*; *Lednicer, D. Strategies for Organic Drugs Synthesis and Design; Wiley & Sons: New York, NY, 1998, Chapters 8 and 9.*
7. Lachut, F. J. U.S. Patent 025,706, 1998.
8. Haas, U. J. U.S. Patent CA2,436,648 A1, 2004.
9. Fenderson, J. M.; Van Loocke, W.; O'Neal, W. B.; Quaghebeur, T.; Schumn, K. C. U. S. Patent 5,905,059 A, 1999.
10. Lizawa, Y.; Okonogi, K.; Hayashi, R.; Iwahi, T.; Yamazaki, T.; Imada, A. *Antimicrob. Agents Chemother.* **1993**, *37*, 100.
11. Hauffe, S. A.; Dubois, J. P.; Imhof, P. R. *Eur. J. Drug Metab. Pharmacokinet.* **1985**, *10*, 217.
12. Bizière, K.; Worms, P.; Kan, J. P.; Mandel, P.; Garattini, S.; Roncucci, R. *Drugs Exp. Clin. Res.* **1985**, *11*, 831.
13. Bourreli, B.; Pinaud, M.; Passuti, N.; Gunst, J. P.; Drouet, J. C.; Remi, J. P. *Can. J. Anesth.* **1988**, *35*, 242.
14. Szucs, T. *Drugs* **1991**, *41*, 18.
15. Kumar, V.; Kaur, K.; Gupta, G. K.; Sharma, A. K. *Eur. J. Med. Chem.* **2013**, *69*, 735.
16. (a) Hassall, C. H.; Ogihara, Y.; Thomas, W. A. *J. Chem. Soc. C* **1971**, 522; (b) Wermuth, C. G. *Med. Chem. Commun.* **2011**, *2*, 935.
17. Bockholt, H.; Beale, J. M.; Rohr, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1648.
18. Winter, J. M.; Jansma, A. L.; Handel, T. M.; Moore, B. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 767.
19. Elguero, J.; Katritzky, A. R.; Denisko, O. *Advances in Heterocyclic Chemistry*; Academic: New York, NY, 2000, Vol. 76, p 2.
20. (a) Aihara, J. *J. Am. Chem. Soc.* **1976**, *98*, 2750; (b) Gutman, I.; Milun, M.; Trinajstic, N. *J. Am. Chem. Soc.* **1977**, *99*, 1692.
21. Chauvin, R.; Lepetit, C. *Phys. Chem. Chem. Phys.* **2013**, *15*, 3855.
22. Aihara, J. *Bull. Chem. Soc. Jpn.* **1988**, *81*, 241.
23. Van-Catledge, F. A. *J. Org. Chem.* **1980**, *45*, 4802.
24. The C–C resonance integral kept uniform for all the sp^2-C–sp^2-C bonds, whatever the substituents. All the sp^2-C atoms are also given the same Hückel coulomb integral α=0, whatever the substituents. TRE values for C6 and C5 reference monocycles (without any π-conjugated substituent) are also given. TRE values were calculated as the enthalpies of the 'twist-rocking' equations ½A®$\bar{A}\rightarrow A$, where A is a given π-cyclic molecular structure, $\bar{A}$ its Möbius-twistomer, and A®$\bar{A}$ the twisted head-to-tail metathesis cyclo-dimer of A,[21] using the freeware HuLiS program: see references: (a) Goudard, N.; Carissan, Y.; Hagebaum-Reignier, D.; Humbel, S. HuLiS 3.0, 2007, JDK 1.6.0_51. http://www.hulis.free.fr/. (b) Carissan, Y.; Hagebaum-Reignier, D.; Goudard, N.; Humbel, S. *J. Phys. Chem. A* **2008**, *112*, 13256.
25. (a) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402; (b) Sadimenko, A. P. *Adv. Heterocycl. Chem.* **2010**, *100*, 175; (c) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084.
26. (a) Mboyi, C. D.; Abdellah, I.; Duhayon, C.; Canac, Y.; Chauvin, R. *ChemCatChem* **2013**, *5*, 3014; (b) Dang, T. T.; Abdellah, I.; Canac, Y.; Chauvin, R. *ChemCatChem* **2011**, *3*, 1491.
27. (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734; (b) David Johnson, C. *Acc. Chem. Res.* **1993**, *26*, 476.
28. Selected examples on pyrazole syntheses: (a) Mallouk, S.; Bougrin, K.; Doua, H.; Benhida, R.; Soufiaoui, M. *Tetrahedron Lett.* **2004**, *45*, 4143; (b) Waldo, J. P.; Mehta, S.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 6666; (c) Alex, K.; Tillack, A.; Schwarz, N.; Beller, M. *Org. Lett.* **2008**, *10*, 2377; (d) Wen, J.; Fu, Y.; Zhang, R. Y.; Zhang, J.; Chen, S. Y.; Yu, X. Q. *Tetrahedron* **2011**, *67*, 9618; (e) Dadiboyena, S.; Nefzi, A. *Eur. J. Med. Chem.* **2011**, *46*, 5258.
29. Selected examples in pyridazine synthesis: (a) South, M. S.; Jakuboski, T. L. *Tetrahedron Lett.* **1995**, *36*, 5703; (b) Attanasi, O. A.; Filippone, P.; Fiorucci, C.; Foresti, E.; Mantellini, F. *J. Org. Chem.* **1998**, *63*, 9880; (c) Helm, M. D.; Moore, J. E.; Plant, A.; Harrity, J. P. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3889; (d) Mann, E.; Moisan, L.; Hou, J. L.; Rebek, J., Jr. *Tetrahedron Lett.* **2008**, *49*, 903; (e) Attanasi, O. A.; Favi, G.; Filippone, P.; Perrulli, F. R.; Santeusanio, S. *Org. Lett.* **2009**, *11*, 309; (f) Bel Abed, H.; Mammoliti, O.; Van Lommen, G.; Herdewijn, P. *Tetrahedron Lett.* **2012**, *53*, 6489; (g) Bel Abed, H.; Mammoliti, O.; Bande, O.; Van Lommen, G.; Herdewijn, P. *J. Org. Chem.* **2013**, *78*, 7845.
30. Supurgibekov, M. B.; Zakharova, V. M.; Sieler, J.; Nikolaev, V. A. *Tetrahedron Lett.* **2011**, *52*, 341.
31. Elguero, J.; Marzin, C.; Katrizky, A. R.; Linda, P. *The Tautomerism of Heterocycles*; Academic: New York, NY, 1976.
32. (a) Guimon, C.; Pfister-Guillouzo, G.; Begtrup, M. *Can. J. Chem.* **1983**, *61*, 1197; (b) Tóth, G.; Lévai, A.; Dinya, Z.; Snatzke, G. *Tetrahedron* **1991**, *47*, 8119; (c) Tóth, G.; Lévai, A.; Duddeck, H. *Magn. Reson. Chem.* **1992**, *30*, 235; (d) Tóth, G.; Lévai, A.; Szóllósy, A.; Duddeck, H. *Tetrahedron* **1993**, *49*, 863; (e) Dardonville, C.; Elguero, J.; Rozas, I.; Fernández-Castaño, C.; Foces-Foces, C.; Sobrados, I. *New J. Chem.* **1998**, 1421; (f) Dawood, K. M.; Fuchigami, T. *J. Org. Chem.* **2005**, *70*, 7537; (g) Sanguinet, L.; Pozzo, J. L.; Rodriguez, V.; Adamietz, F.; Castet, F.; Ducasse, L.; Champagne, B. *J. Phys. Chem. B* **2005**, *109*, 11139; (h) Ben Hadda, T.; Ali, M. A.; Masand, V.; Gharby, S.; Fergoug, T.; Warad, I. *Med. Chem. Res.* **2013**, *22*, 1438; (i) Dadiboyena, S.; Valente, E. J.; Hamme, A. T., II. *Tetrahedron Lett.* **2014**, *55*, 2208.
33. CCDC 971142 (**2a**), CCDC 971143 (**2e**), CCDC 971144 (**3a**), CCDC 971145 (**3a′**), CCDC 971146 (**3b**), CCDC 971147 (**3c**), CCDC 971148 (**3g**), CCDC 971149 (**3h**), CCDC 971150 (**3i**), and CCDC 971151 (**5h**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
34. (a) Kice, J. L.; Campbell, J. D. *J. Org. Chem.* **1971**, *36*, 2291; (b) Wood, J. M.; Hinchliffe, P. S.; Davis, A. M.; Austin, R. P.; Page, M. I. *Chem. Commun.* **2002**, 772.
35. Clarke, S. J.; Gilchrist, T. L. *J. Chem. Res., Synop.* **1985**, 310; *J. Chem. Res., Miniprint* **1985**, 3371.
36. An unsaturated five-membered ring can indeed hardly accommodate endocyclic bond angles much greater than 108°, which would be of ca. 120° at the three sp^2 vertices of a quasi-planar ring in **4′**.
37. Gao, Q.; Zhu, Y.; Lian, M.; Liu, M.; Yuan, J.; Yin, G.; Wu, A. *J. Org. Chem.* **2012**, *77*, 9865.
38. Sengmany, S.; Léonel, E.; Polissaint, F.; Nédelec, J. Y.; Pipelier, M.; Thobie-Gautier, C.; Dubreuil, D. *J. Org. Chem.* **2007**, *72*, 5631.
39. Evans, S.; Schweizer, E. E. *J. Org. Chem.* **1977**, *42*, 2321.
40. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.* **1994**, *27*, 435.
41. Palatinus, L.; Chapuis, G. *J. Appl. Crystallogr.* **2007**, *40*, 786.
42. Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.
43. International Tables for X-ray CrystallographyVol. IV; Kynoch: Birmingham, England, 1974, Vol. IV.