Tetrahedron 66 (2010) 2331–2339

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of novel fused azecine ring systems through application of the *tert*-amino effect

Petra Dunkel [a], György Túrós [a], Attila Bényei [b], Krisztina Ludányi [c], Péter Mátyus [a,*]

[a] Department of Organic Chemistry, Semmelweis University, Hőgyes Endre u. 7., H-1092 Budapest, Hungary
[b] Institute of Physical Chemistry, University of Debrecen, Egyetem tér 1., H-4010 Debrecen, Hungary
[c] Department of Pharmacy, Semmelweis University, Hőgyes Endre u. 7., H-1092 Budapest, Hungary

ARTICLE INFO

Article history:
Received 25 August 2009
Received in revised form
28 December 2009
Accepted 1 February 2010
Available online 4 February 2010

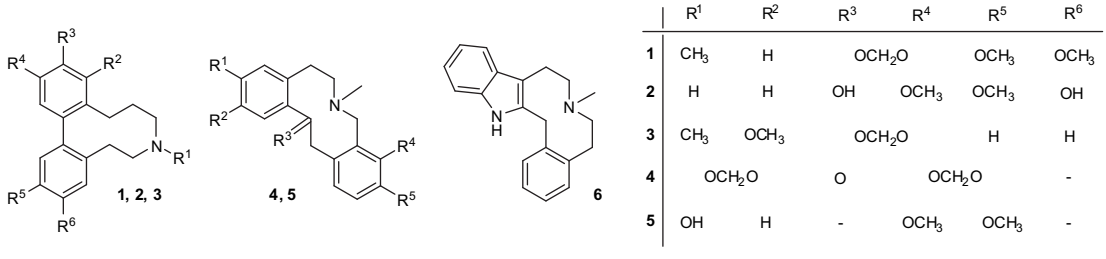
Keywords:
tert-Amino effect
Regioselective Suzuki coupling
Microwave
Fused azecine ring systems

ABSTRACT

Novel fused azecine ring systems were synthesized via the microwave-assisted thermal isomerization of terphenyl or biphenyl-pyridazine compounds possessing a vinyl and a *tert*-amino group, through application of a new extension of the *tert*-amino effect. Substrates for the ring closure were prepared from *ortho*-dihalobenzene or pyridazinone by consecutive Suzuki couplings with *ortho*-*sec*-amino- and formylphenylboronic acids, followed by Knoevenagel condensation of the aldehydes obtained.

1. Introduction

Fused ring systems containing the benzazecine skeleton may be of considerable chemical and biological value. Although the number of such compounds reported in the literature is limited, some members of the class have interesting biological functions. Dysazecine (**1**), the first alkaloid containing a dibenz[*d*,*f*]azecine skeleton to be isolated from plants, was suggested to be a biosynthetic intermediate to homoerythrina alkaloids.[1] Dibenz[*d*,*f*]azecine **2** could possibly be a biogenetic precursor of *Schelhammera* and *Cephalotaxus* alkaloids,[2–4] such as cephalotaxine, the esters of which exhibit antitumour activity.[5] Dyshomoerythrine derivative **3** was prepared as an insecticide,[6] the benzazecine alkaloid protopine (**4**) as a potential antimalarial lead compound.[7a] Furthermore, other interesting pharmacological properties of protopine alkaloids have also been reported (e.g., neuroprotective,[7b] anti-inflammatory[7c] effects). Compound **5** was prepared as an analgetic[8] while LE300 (**6**) and its derivatives are novel types of nanomolar dopamine receptor antagonists (Fig. 1).[9a,b]



	R^1	R^2	R^3	R^4	R^5	R^6
1	CH_3	H	OCH_2O		OCH_3	OCH_3
2	H	H	OH	OCH_3	OCH_3	OH
3	CH_3	OCH_3	OCH_2O		H	H
4	OCH_2O		O	OCH_2O		-
5	OH	H	-	OCH_3	OCH_3	-

Figure 1. Some representatives of fused azecine ring systems with interesting biological effects.

The pathway reported in this communication, involving the '*tert*-amino effect', could serve as a simple, straightforward synthesis of tribenzo[*b*,*d*,*f*]- or pyridazino[*d*]dibenzo[*b*,*f*]azecines.

The term *tert*-amino effect was first used by Meth-Cohn and Suschitzky in 1972 to describe unusual cyclizations of *ortho*-

* Corresponding author. Tel./fax: +36 1 2170851.
E-mail address: peter.matyus@szerves.sote.hu (P. Mátyus).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.02.014

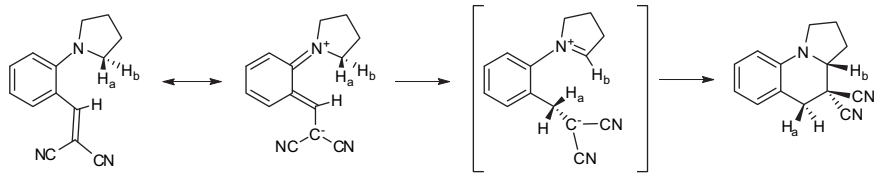


Figure 2. *tert*-Amino effect type 2 ring closure.

substituted *tert*-anilines.[10] Of the seven types of *tert*-amino effect described so far,[11] which differ in the size of the ring formed and the mode of its formation, in a special version of type 2 reactions, a new C–C bond is formed between the α carbon of a *tert*-aniline group and the β atom of an *ortho*-vinyl substituent, resulting in the formation of a tetrahydropyridine ring (Fig. 2).[12] Type 2 ring closures have been widely used for the synthesis of fused ring systems,[13] but only rarely for the synthesis of medium-sized rings or macrocycles.

As part of our ongoing researches on this topic, our present goal was to study possible extensions of the *tert*-amino effect to biaryl[14] (Fig. 3) or triaryl systems in which the *ortho*-positioned *tert*-amino and vinyl groups are situated on aryl rings that are connected directly or linked by a third aryl ring, and to fused systems[15] having the interacting groups in *peri* positions. Such possible extensions were expected to lead to fused medium-sized or macrocyclic aza ring systems that are otherwise difficult to access. We describe here the synthesis of 2-[(2-vinylphenyl)phenyl]-*tert*-anilines and their pyridazinone analogues and our studies on their thermal isomerizations.

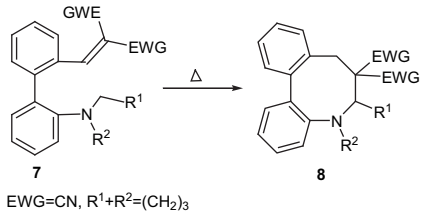
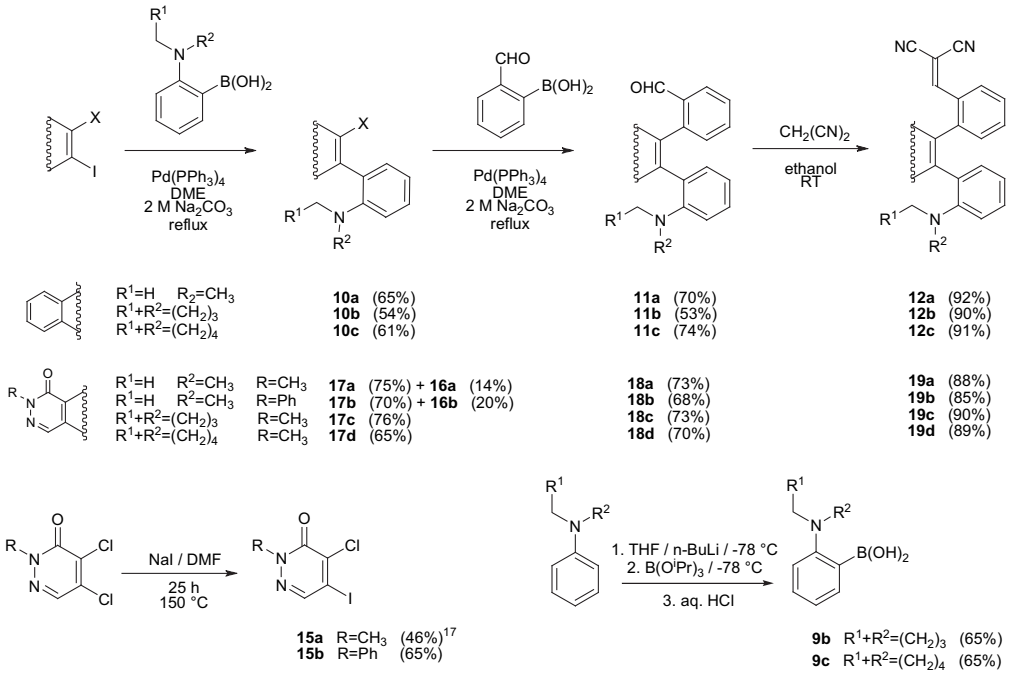


Figure 3. Extension of the *tert*-amino effect to biaryl systems.

2. Results and discussion

For this study of the *tert*-amino effect thermal isomerization, two series of *ortho*-vinyl *tert*-aniline compounds were synthesized (Scheme 1). A benzene (**12a–c**) and a pyridazinone (**19a–d**) series were prepared, via two consecutive Suzuki reactions: firstly reaction with boronic acids having an *ortho-sec*-amino substituent (**9a–c**) (leading to **10a**[16a,b]**–c** and **17a–d**), followed by coupling with 2-formylphenylboronic acid (leading to **11a–c** and **18a–d**). The synthesis of the benzene series (**12a–c**) started from 2-bromoiodobenzene; for the pyridazinone series (**19a–d**), 4-chloro-5-iodo-2-methyl- (**15a**)[17a] and 4-chloro-5-iodo-2-phenylpyridazin-3(2*H*)-one (**15b**) were selected as starting materials to carry out regioselective Suzuki couplings. 5(4)-Chloro-4(5)-iodopyridazin-3(2*H*)-ones have been rarely used for such applications (coupling reactions with 5-chloro-4-iodo isomers have been described by Haider and Wobus,[18] Stevenson et al.;[19] whereas couplings with 4-chloro-5-iodo isomers are reported herein), although such compounds are easily accessible via chloro displacement reactions of 4,5-dichloropyridazin-3(2*H*)-one[17a] or its mucochoric acid precursor.[17b]

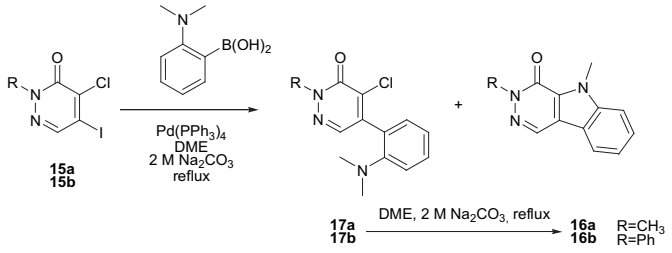
Of the boronic acids used for the first series of Suzuki couplings, 2-dimethylaminophenylboronic acid (**9a**) was prepared by a literature procedure,[20] while boronic acids **9b** and **9c** were obtained in good yields from the corresponding *ortho*-haloarylamines by *ortho*-lithiation and reaction with triisopropyl borate in THF (in a method analogous to that used for the synthesis of 2-(4-methylpiperazin-1-yl)-[21] and 4-pyrrolidinophenylboronic[22] acids) (Scheme 1). For the preparation of the *ortho*-haloarylamines needed, the method described by Verboom et al. was used.[23]



Scheme 1. Synthesis of *ortho*-vinyl-terphenyl and pyridazine-biphenyl-*tert*-anilines.

With these boronic acids in hand, Suzuki reactions could be carried out smoothly in the presence of $Pd(PPh_3)_4$ as catalyst, in a DME/2 M aq Na_2CO_3 system, affording **10a–c**, **17a–d**, **11a–c** and **18a–d** as products in good yields (Scheme 1).

In the Suzuki coupling of **15a**,**b** with **9a**, formation of an indole derivative (**16a**,**b**) as by-product was observed, presumably via intramolecular substitution of the coupled product. When **17a**,**b** were subjected to Suzuki coupling conditions (for 48 h reflux in DME/2 M aq Na_2CO_3), the 2-substituent of the pyridazinone ring greatly influenced the formation of **16a**,**b**. The presence of a 2-CH_3 group led to a starting material/product ratio of 3.5:1 (as compared with 5:1 in the Suzuki reaction), while a 2-phenyl group resulted in a ratio of 1.56:1 (3.5:1 in the Suzuki reaction) (Scheme 2).



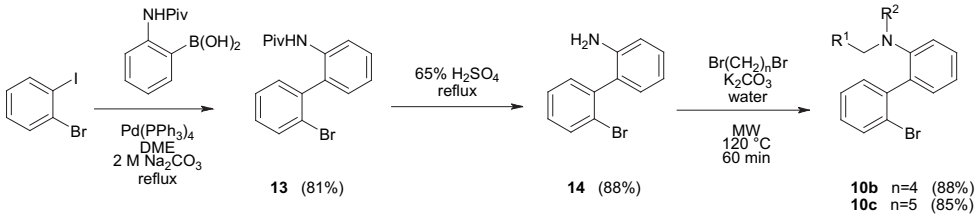
Scheme 2. Formation of indole by-products **16a**,**b**.

An alternative route for the synthesis of biaryl amines **10b**,**c** uses Suzuki coupling first with 2-pivaloylaminophenylboronic acid, followed by deprotection in aq H_2SO_4 (Scheme 3). Primary amine **14** could be converted in high yields to *N*-heterocyclic derivatives via the microwave-assisted N-heterocyclization described by Ju and Varma[24] with dihaloalkanes in alkaline aqueous medium.

representing a novel type of the *tert*-amino effect. Kaval et al. described microwave-assisted *tert*-amino effect cyclizations.[25,26] Use of this methodology seemed feasible with regard to the rate enhancements and yields observed. On irradiation of **12a** under solvent-free microwave (MW) conditions (160 °C, 45 min), 66% of azecine product **20a** was obtained, while 21% of the starting material was recovered. Longer reaction times or higher temperatures resulted in an increased rate of decomposition, and hence a lower isolated yield of the azecine product (Scheme 4).

Using the same procedure led to high rates of decomposition of **12b** and **19a**; further isomerizations were therefore carried out in the solution phase (DMSO). When **12a–c** and **19a–d** were heated in DMSO solution, the desired azecine-fused products **20a–c** and **21a–d** were obtained, the pyridazine analogues behaving similarly to their benzene counterparts. From the *N*,*N*-dimethylamino derivatives (**12a** and **19a**,**b**), the desired fused products (**20a** and **21a**,**b**) were obtained in good yields. For irradiation of the pyrrolidino and piperidino derivatives (**12b**,**c** and **19c**,**d**), a compromise between the conversion of the starting material (as monitored by HPLC) and decomposition (leading to a drop in the isolated yield) was difficult to find, even at relatively low reaction temperatures (Table 1).

The structures of **18a**, **12a**, **20a**, **19a** and **21c** were confirmed by X-ray diffraction.[27] Investigation of the geometric arrangement of the *ortho*, *ortho*′ functionalities in the biphenyl series[14] by X-ray analysis revealed that in the biaryl analogue of compound **12a**, the *tert*-amino and vinyl groups were located on the same face of the biaryl system (compound **7**), their distance from each other (2.878 Å for the *tert*-amino nitrogen–α-vinylic carbon) indicating a weak interaction between them. For triphenylvinyl derivative **12a**, two conformers were found in the asymmetric unit, the corresponding distances between the *tert*-amino nitrogen and the α-vinylic carbon (located on opposite faces of the triaryl system)

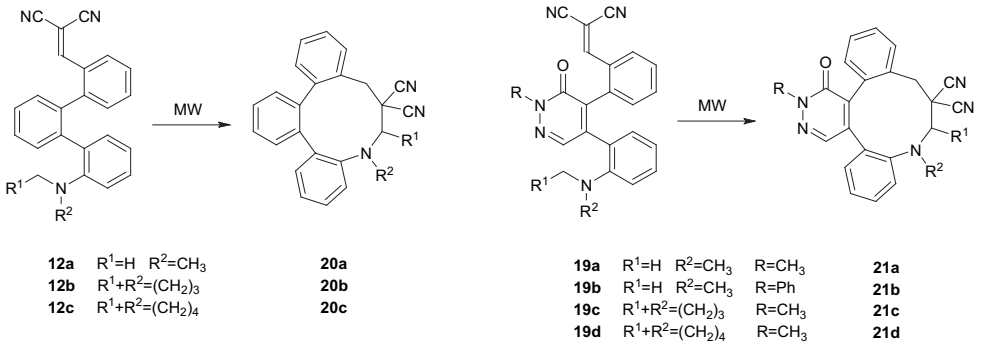


Scheme 3. Synthesis of **10b**,**c** via aqueous N-heterocyclization of **14**.

Aldehydes **11a–c** and **18a–d**, obtained in the Suzuki reactions of amines **10a–c** and **17a–d** with 2-formylphenylboronic acid, were subjected to Knoevenagel condensation (Scheme 1). Vinyl products **12a–c** and **19a–d** could be obtained under mild conditions (ethanol at room temperature in the presence of piperidine), with malononitrile as the active methylene agent.

In the following series of experiments, the thermal isomerizations of vinyl compounds **12a–c** and **19a–d** were studied, being significantly longer, 4.25 and 3.98 Å, respectively. (Fig. 4) Interestingly, two conformers were also found in the asymmetric unit of azecine **21c**.

In the azecine-fused products, the NMR signals of the methylene hydrogens adjacent to the nitrogen and the carbon bearing the electron-withdrawing groups are characteristic of the ring closure. Their appearance in the NMR spectra is accompanied by the disappearance of the signal broadening or signal duplication



Scheme 4. Microwave-assisted isomerization of vinyl compounds.

Table 1
Synthesis of azecine-fused systems. Solution-phase (DMSO) reactions

Compound	Temp (°C)/time (min)[a]	Product (yield)[c]
12a	200/150	**20a** (85%)
12b	100/30	**20b** (19%), **12b** (50%)
	100/90	**20b** (11%), **12b** (6%)
	150/2	**20b** (11%), **12b** (2%)
12c	150/5	**20c** (32%), **12c** (20%)
	150/10	**20c** (13%), **12c** (2%)
	175/2	**20c** (34%), **12c** (3%)
19a	200/150	**21a** (83%)
19b	200/150	**21b** (80%)
19c	100/180	**21c** (20%), **19c** (11%)
	125/10	**21c** (16%), **19c** (24%)
	150/1	**21c** (14%), **19c** (21%)
19d	150/5	**21d** (24%), **19d** (30%)
	175/5	**21d** (44%), **19d** (2%)
	175/10	**21d** (18%), **19d** (7%)
	200/1[b]	**21d** (51%), **19d** (6%)

[a] Hold time for MW-assisted experiments; reactions were carried out in open vessels (if not indicated otherwise) on a 0.25 mmol scale, at a maximum power level of 200 W.
[b] Reaction was carried out in a 10 mL sealed MW process vial.
[c] Isolated yields.

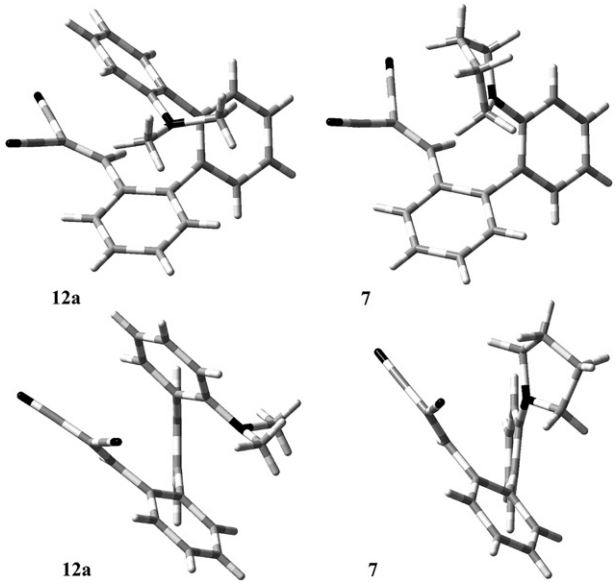
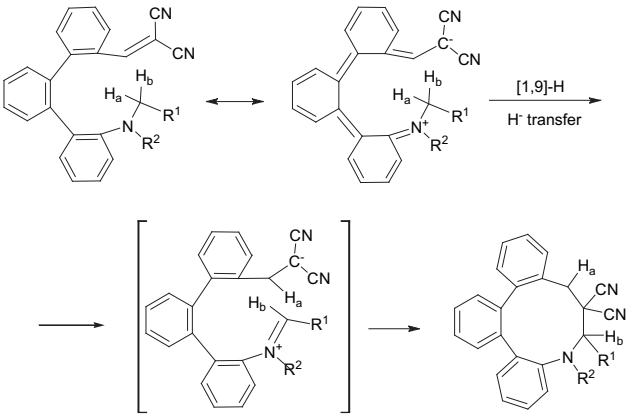


Figure 4. X-ray structures of compounds **12a** and **7**; geometric arrangement of the interacting functionalities.

phenomena observed for the vinyl (and aldehyde) compounds, due to hindered rotation. As exemplified with vinyl compound **12a** and **7** and their cyclic azecine (**20a**) and azocine (**8**) counterparts, the characteristic NMR data[14] (in ppm, $CDCl_3$/DMSO-d_6 for **12a**) of the corresponding atoms are (i) $-CH{=}C(CN)_2$ (vinyl compounds)—^{1}H: 7.31 (**12a**)/7.58 (**7**), ^{13}C: 160.4 (**12a**)/162.4 (**7**), (ii) $-CH_2-C(CN)_2-CHR_1-$ (cyclic products)—^{1}H: 3.40 and 3.52 (**20a**)/3.38 and 3.64 (**8**); ^{13}C: 35.9 (**20a**)/40.1 (**8**).

The formation of the azecine ring could be explained in terms of a two-step mechanism, the first, rate-limiting step involving either a [1,9]-hydrogen migration or, more likely, direct hydride donation[28] between the interacting groups, resulting in a dipolar intermediate, the next step comprising bond formation between the oppositely charged carbons (Scheme 5).



Scheme 5. Proposed mechanism of the isomerization.

3. Conclusion

This study of the extension of the *tert*-amino effect to *ortho, ortho*′-functionalized triaryl compounds and their pyridazinone analogues demonstrates that this novel type of isomerization offers a straightforward synthetic pathway for the synthesis of fused azecine ring systems.

4. Experimental

4.1. Materials and methods

All reagents and solvents were purchased from commercial sources and were utilized without further purification. Melting points were determined on a Büchi-540 capillary melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin–Elmer 1600 FTIR instrument in KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature, if not indicated otherwise, in the solvent indicated, with a Varian Mercury Plus spectrometer at a frequency of 400/600 or 100/150 MHz or a with a Bruker 400 MHz spectrometer, at a frequency of 400 or 100 MHz, and are reported in parts per million. Spectra were recorded at 400 MHz (^{1}H) or 100 MHz (^{13}C), if not indicated otherwise. Chemical shifts are given on the δ-scale relative to tetramethylsilane or the residual solvent signal as an internal reference. For structure elucidation, one-dimensional ^{1}H, ^{13}C, DEPT, two-dimensional ^{1}H, ^{1}H-COSY, ^{1}H, ^{13}C-HSQC, ^{1}H, ^{13}C-HMBC measurements were run. Mass spectra utilizing fast atom bombardment ionization were recorded on a VG-ZAB-2SEQ spectrometer. Elemental analyses were performed on a Carlo Erba 1012 apparatus. MW irradiation experiments were carried out in a monomode CEM-Discover MW reactor, using the standard configuration as delivered, including proprietary software. The experiments were executed either in 10 mL MW process vials or in open-vessel mode, with control of the temperature by infrared detection. After completion of the reaction, the vial/flask was cooled to 50 °C by air jet cooling. For flash column chromatography purification, Kieselgel 60 (Merck, 0.040–0.063 mm) was used; for TLC analysis, Silica gel 60 F_{254} (Merck) plates were applied. Solvent mixtures used for chromatography are always given in a vol/vol ratio. The structures of all compounds were consistent with their analytical and spectroscopic data. Compounds **9a**,[20] **10a**[16a,b] and **15a**[17a] were prepared according to the literature procedures cited. Compounds **9a**,[20] **10a**,[16a,b] **15a**,[17a] **16a**,[29a,b] **16b**[30] and **14**[31a,b] had melting points and spectral data identical with the published values. Spectroscopic data are provided for compounds described previously but not characterized spectroscopically.

4.2. Synthesis of boronic acids 9b,c

A four-neck, round-bottom flask was charged with 1-(2-bromophenyl)pyrrolidine[23] (4.97 g, 22.00 mmol; for **9b**) or 1-(2-bromophenyl)piperidine[23] (5.28 g, 22.00 mmol; for **9c**) and anhydrous THF (75 mL) under argon. *n*-BuLi (2.5 M solution in hexane, 9.90 mL, 24.75 mmol) was added to the solution dropwise (over 20 min) at −78 °C. The reaction mixture was stirred for 75 min at −78 °C, after which time $B(O^iPr)_3$ (10.15 mL, 44.00 mmol) was added dropwise (over 20 min) to the suspension, followed by a further 1 h of stirring at −78 °C. Subsequently, the reaction mixture was allowed to warm up to room temperature and stirred overnight. The following day, the reaction mixture was cooled to −70 °C and 1 M HCl solution (44 mL) was added slowly (over 15 min). The mixture was next allowed to warm up to 0 °C and stirred for 30 min. H_2O (100 mL) and EtOAc (100 mL) were added, the phases were separated and the organic layer was extracted with H_2O (3×100 mL). The pH of the combined aqueous layers was adjusted to 8 with 2 M NaOH. The aqueous phase was extracted with EtOAc (3×100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product obtained was used without further purification.

*4.2.1. 2-(Pyrrolidin-1-yl)phenylboronic acid (**9b**).* Crude product: white crystals (3.03 g, ~85% pure according to ^1H NMR), R_f=0.40 (toluene/EtOH 2:1). ^1H NMR (DMSO-d_6) δ (ppm): 8.10 (br s, 2H), 7.22–7.11 (m, 2H), 6.71–6.67 (m, 2H), 3.23–3.17 (m, 4H), 1.92–1.85 (m, 4H). ^{13}C NMR (CD_3OD): 148.3, 135.2, 125.6, 123.6, 117.7, 56.0, 25.7 (*C*–$B(OH)_2$ was not observed).

*4.2.2. 2-(Piperidine-1-yl)phenylboronic acid (**9c**).* Crude product: white crystals (3.83 g, ~70% pure according to ^1H NMR), R_f=0.37 (toluene/EtOH 2:1). ^1H NMR ($CDCl_3$) δ (ppm): 9.34 (br s, 2H), 7.93 (dm, *J*=7.6 Hz, 1H), 7.45 (tm, *J*=7.6 Hz, 1H), 7.31 (dm, *J*=7.6 Hz, 1H), 7.24 (tm, *J*=7.6 Hz, 1H), 2.95–2.87 (m, 4H), 1.84–1.76 (m, 4H), 1.67–1.55 (br m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 160.4, 136.5, 132.4, 126.2, 121.7, 56.1, 27.3, 24.3 (*C*–$B(OH)_2$ was not observed).

4.3. Synthesis of 4-chloro-5-iodo-2-phenylpyridazin-3(2*H*)-one (15b) via halogen replacement

Compound **15b** was prepared by applying the procedure cited for **15a**.[17a] To a solution of 4,5-dichloro-2-phenylpyridazin-3(2*H*)-one (3.62 g, 15.00 mmol) in DMF (30 mL), NaI (4.50 g, 30.00 mmol) was added, and the mixture was then heated at reflux for 1 h. Following this, further NaI (2.25 g, 15.00 mmol) was added to the mixture and it was heated at reflux again for 1 h. The latter procedure was repeated once more, and the mixture was heated at reflux for 25 h. Then the DMF was removed in vacuo. An aqueous solution (10%) of $Na_2S_2O_3$ was added to the residue until the colour of the iodine had disappeared. The solution was extracted with $CHCl_3$ (4×70 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. Analytically pure **9b** could be obtained by recrystallization from MeOH. White crystals (3.24 g, 65%), mp 152–153 °C, R_f=0.21 (toluene). ^1H NMR ($CDCl_3$) δ (ppm): 8.11 (s, 1H), 7.59–7.54 (m, 2H), 7.50–7.45 (m, 2H), 7.44–7.39 (m, 1H). ^{13}C NMR ($CDCl_3$) δ (ppm): 155.6, 144.3, 142.8, 141.5, 129.6, 129.5, 125.8, 105.2. IR (KBr) ν_{max}: 3054, 1654, 1552, 1126, 896, 754, 688 cm^{-1}. HRMS: calcd for ($C_{10}H_6ClIN_2O+H^+$): 332.9292. Found: 332.9284.

4.4. General procedure for Suzuki cross-coupling reactions (syntheses of 10a[16a]–c, 11a–c, 13, 17a–d and 18a–d)

To a solution of the appropriate halo compound (10.00 mmol, for **10a–c**,**13**: 1-bromo-2-iodobenzene (1.25 mL), for **11a**: **10a** (2.76 g), for **11b**: **10b** (3.02 g), for **11c**: **10c** (3.16 g), for **17a**,**c**,**d**: **15a** (2.70 g), for **17b**: **15b** (3.33 g), for **18a**: **17a** (2.64 g), for **18b**: **17b** (3.26 g), for **18c**: **17c** (2.90 g), for **18d**: **17d** (3.04 g)) in DME (50 mL), $Pd(PPh_3)_4$ (578 mg, 0.50 mmol) was added at room temperature under an argon flow. After stirring at room temperature for 10 min, the appropriate boronic acid (12.00 mmol, for **10a**,**17a**,**b**: **9a**[20] (1.98 g), for **10b**,**17c**: **9b** (2.29 g), for **10c**,**17d**: **9c** (2.46 g), for **13**: 2-pivalamidophenylboronic acid[32,33] (2.65 g), for **11a–c**,**18a–d**: 2-formylphenylboronic acid (1.80 g)) and aq 2 M Na_2CO_3 solution (10 mL) were added, and the reaction mixture was heated at reflux at 110 °C (oil temperature) until the starting material had been consumed (24–48 h, monitored by TLC). The cooled reaction mixture was poured into H_2O (50 mL). After separation of the phases, the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product obtained was purified by flash column chromatography on silica gel with the eluents indicated below.

4.4.1. Biphenyl compounds and their pyridazine analogues

*4.4.1.1. 2′-Bromo-N,N-dimethylbiphenyl-2-amine (**10a**)[16a,b].* The work-up and purification accorded to the literature procedure cited. White crystals (1.80 g, 65%), mp 55–57 °C (lit. mp 55–57 °C)[16b], R_f=0.64 (toluene). ^1H NMR ($CDCl_3$) δ (ppm): 7.66 (dm, *J*=8.0 Hz, 1H), 7.37–7.29 (m, 3H), 7.19–7.11 (m, 2H), 7.06 (dm, *J*=8.0 Hz, 1H), 7.00 (tm, *J*=7.6 Hz, 1H), 2.53 (s, 6H). ^{13}C NMR ($CDCl_3$) δ (ppm): 151.2, 143.2, 134.4, 133.6, 132.5, 132.5, 129.4, 128.8, 127.8, 124.6, 121.5, 118.6, 43.9. IR (KBr) ν_{max}: 2964, 2834, 1452, 1262, 1022, 802, 744 cm^{-1}. Anal. Calcd for $C_{14}H_{14}BrN$ (276.17): C, 60.89; H, 5.11; N, 5.07. Found: C, 60.85; H, 5.00; N, 5.06.

*4.4.1.2. 1-(2′-Bromobiphenyl-2-yl)pyrrolidine (**10b**).* Column chromatography: *n*-hexane/EtOAc 9:1. Colourless oil (1.63 g, 54%), R_f=0.67 (hexane/EtOAc 9:1). ^1H NMR ($CDCl_3$) δ (ppm): 7.64 (dm, *J*=8.0 Hz, 1H), 7.37 (dm, *J*=7.6 Hz, 1H), 7.33–7.26 (m, 2H), 7.16 (ddd, *J*=7.2, 1.8, 0.8 Hz, 1H), 7.08 (dm, *J*=7.6 Hz, 1H), 6.86–6.79 (m, 2H), 2.99–2.85 (m, 4H), 1.80–1.72 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 148.1, 144.7, 133.1, 133.0, 132.9, 129.1, 128.7, 128.5, 127.4, 125.3, 117.4, 114.7, 50.8, 26.4. IR (KBr) ν_{max}: 2922, 1596, 1498, 1464, 1336, 1154, 1024, 746 cm^{-1}. HRMS: calcd for ($C_{16}H_{16}BrN+H^+$): 302.0544. Found: 302.0535.

*4.4.1.3. 1-(2′-Bromobiphenyl-2-yl)piperidine (**10c**).* Column chromatography: *n*-hexane. Colourless oil (1.93 g, 61%), R_f=0.8 (*n*-hexane/EtOAc 9:1). ^1H NMR ($CDCl_3$) δ (ppm): 7.64 (dm, *J*=8.0 Hz, 1H), 7.38 (dm, *J*=7.6 Hz, 1H), 7.34–7.29 (m, 2H), 7.18–7.11 (m, 2H), 7.08–7.01 (m, 2H), 2.82–2.70 (m, 4H), 1.42–1.23 (m, 6H). ^{13}C NMR ($CDCl_3$) δ (ppm): 152.8, 142.7, 136.2, 133.4, 132.7, 131.9, 129.5, 128.7, 127.5, 124.7, 122.5, 119.8, 53.4, 26.8, 24.9. IR (KBr) ν_{max}: 2932, 2794, 1462, 1228, 1026, 924, 748 cm^{-1}. Anal. Calcd for $C_{17}H_{18}BrN$ (316.24): C, 64.57; H, 5.74; N, 4.43. Found: C, 64.88; H, 5.83; N, 4.54.

*4.4.1.4. N-(2′-Bromobiphenyl-2-yl)-2,2-dimethylpropanamide (**13**).* Column chromatography: toluene/EtOAc 16:1. Colourless oil (2.69 g, 81%), R_f=0.47 (toluene/EtOAc 16:1). ^1H NMR ($CDCl_3$) δ (ppm): 8.27 (dm, *J*=8.0 Hz, 1H), 7.73 (dm, *J*=8.0 Hz, 1H), 7.46–7.39 (m, 2H), 7.33–7.28 (m, 2H), 7.21–7.14 (m, 2H), 7.11 (br s, 1H), 1.05 (s, 9H). ^{13}C NMR ($CDCl_3$) δ (ppm): 177.0, 139.5, 135.9, 133.7, 132.5, 132.4, 130.6, 130.0, 129.8, 128.7, 124.7, 124.7, 122.0, 40.3, 28.0. IR (KBr) ν_{max}: 3438, 2960, 1688, 1518, 1442, 1304, 1160, 758 cm^{-1}. Anal. Calcd for $C_{17}H_{18}BrNO$ (332.23): C, 61.46; H, 5.46; N, 4.22. Found: C, 61.26; H, 5.42; N, 4.33.

*4.4.1.5. 4-Chloro-5-[2-(dimethylamino)phenyl]-2-methylpyridazin-3(2H)-one (**17a**).* Column chromatography: *n*-hexane/EtOAc 2:1. Yellow crystals (1.98 g, 75%), mp 104–105 °C, R_f=0.36

(*n*-hexane/EtOAc 2:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.74 (s, 1H), 7.40 (ddd, *J*=8.2, 7.5, 1.7 Hz, 1H), 7.27 (dm, *J*=7.5 Hz, 1H), 7.13 (dm, *J*=8.2 Hz, 1H), 7.08 (tm, *J*=7.5 Hz, 1H), 3.88 (s, 3H), 2.63 (s, 6H). ^{13}C NMR ($CDCl_3$) δ (ppm): 158.9, 152.3, 143.2, 138.7, 133.6, 131.7, 131.4, 126.5, 122.6, 119.3, 44.4, 41.5. IR (KBr) ν_{max}: 2922, 1652, 1266, 868, 740 cm^{-1}. Anal. Calcd for $C_{13}H_{14}ClN_3O$ (263.72): C, 59.21; H, 5.35; N, 15.93. Found: C, 58.95; H, 5.18; N, 15.64.

*4.4.1.6. 3,5-Dimethyl-3,5-dihydro-4H-pyridazino[4,5-b]indol-4-one (**16a**)*[29a,b]. White crystals (recrystallized from MeOH, 299 mg, 14%), mp 214–215 °C (lit. mp 214–215 °C)[29b], R_f=0.23 (*n*-hexane/EtOAc 2:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.42 (s, 1H), 7.97 (d, *J*=8.0 Hz, 1H), 7.58–7.52 (m, 1H), 7.48 (d, *J*=8.0 Hz, 1H), 7.39–7.35 (m, 1H), 4.32 (s, 3H), 3.91 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 156.7, 141.2, 132.9, 131.3, 127.9, 122.5, 121.7, 120.9, 118.2, 111.2, 39.9, 32.2. IR (KBr) ν_{max}: 3054, 2940, 1644, 1522, 1476, 1340, 952, 740 cm^{-1}. Anal. Calcd for $C_{12}H_{11}N_3O$ (213.23): C, 67.59; H, 5.20; N, 19.71. Found: C, 67.23; H, 5.03; N, 19.56.

*4.4.1.7. 4-Chloro-5-[2-(dimethylamino)phenyl]-2-phenylpyridazin-3(2H)-one (**17b**).* Column chromatography: *n*-hexane/EtOAc 3:1. Yellow crystals (2.28 g, 70%), mp 90–92 °C, R_f=0.33 (*n*-hexane/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.88 (s, 1H), 7.72–7.67 (m, 2H), 7.53–7.47 (m, 2H), 7.46–7.36 (m, 3H), 7.17 (dm, *J*=8.0 Hz, 1H), 7.12 (tm, *J*=7.6 Hz, 1H), 2.68 (s, 6H). ^{13}C NMR ($CDCl_3$) δ (ppm): 158.2, 152.5, 143.0, 142.2, 139.5, 134.7, 131.8, 131.6, 129.5, 129.0, 126.4, 125.9, 122.7, 119.4, 44.6. IR (KBr) ν_{max}: 2930, 2782, 1656, 1486, 1320, 1146, 756 cm^{-1}. Anal. Calcd for $C_{18}H_{16}ClN_3O$ (325.79): C, 66.36; H, 4.95; N, 12.90. Found: C, 65.98; H, 4.83; N, 12.56.

*4.4.1.8. 5-Methyl-3-phenyl-3,5-dihydro-4H-pyridazino[4,5-b]indol-4-one (**16b**)*[30]. White crystals (recrystallized from MeOH, 551 mg, 20%), mp 171–172 °C (lit. mp 169 °C)[30], R_f=0.17 (*n*-hexane/EtOAc 3:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.62 (s, 1H), 8.05 (dm, *J*=8.0 Hz, 1H), 7.67–7.48 (m, 6H), 7.45–7.39 (m, 2H), 4.38 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 142.6, 141.6, 133.9, 131.7, 129.5, 129.2, 128.6, 128.1, 126.9, 122.8, 121.8, 121.0, 118.0, 111.4, 32.4. IR (KBr) ν_{max}: 3054, 2928, 1658, 1530, 1300, 956, 738 cm^{-1}. Anal. Calcd for $C_{17}H_{13}N_3O$ (275.30): C, 74.17; H, 4.76; N, 15.26. Found: C, 73.81; H, 4.50; N, 15.22.

*4.4.1.9. 4-Chloro-2-methyl-5-(2-pyrrolidin-1-ylphenyl)pyridazin-3(2H)-one (**17c**).* Column chromatography: *n*-hexane/EtOAc 4:1. Yellow crystals (2.20 g, 76%), mp 91–92 °C, R_f=0.24 (*n*-hexane/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.75 (s, 1H), 7.31 (ddd, *J*=8.5, 7.2, 1.7 Hz, 1H), 7.14 (dd, *J*=7.7, 1.7 Hz, 1H), 6.91 (dd, *J*=8.5, 1.1 Hz, 1H), 6.86 (ddd, *J*=7.7, 7.2, 1.1 Hz, 1H), 3.87 (s, 3H), 3.04–2.98 (m, 4H), 1.89–1.81 (m, 4H). ^{13}C NMR ($CDCl_3$) δ (ppm): 158.6, 148.4, 144.6, 138.5, 132.9, 131.7, 131.0, 120.3, 118.4, 115.3, 51.7, 41.6, 26.4. IR (KBr) ν_{max}: 2920, 2854, 1656, 1446, 1358, 1022, 868, 746 cm^{-1}. Anal. Calcd for $C_{15}H_{16}ClN_3O$ (289.76): C, 62.18; H, 5.57; N, 14.50. Found: C, 61.91; H, 5.16; N, 14.31.

*4.4.1.10. 4-Chloro-2-methyl-5-(2-piperidin-1-ylphenyl)pyridazin-3(2H)-one (**17d**).* Column chromatography: CH_2Cl_2. Yellow crystals (1.97 g, 65%), mp 96–97 °C, R_f=0.38 (CH_2Cl_2/EtOAc 95:5). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.80 (s, 1H), 7.41 (ddd, *J*=8.4, 7.2, 1.6 Hz, 1H), 7.31 (dm, *J*=7.6 Hz, 1H), 7.15–7.09 (m, 2H), 3.88 (s, 3H), 2.81 (br m, 4H), 1.48 (br m, 6H). ^{13}C NMR ($CDCl_3$) δ (ppm): 159.0, 152.6, 142.9, 139.2, 133.7, 131.6, 131.5, 127.8, 123.3, 120.3, 54.1, 41.5, 26.7, 24.6. IR (KBr) ν_{max}: 2918, 1654, 1448, 1228, 1022, 866, 750 cm^{-1}. Anal. Calcd for $C_{16}H_{18}ClN_3O$ (303.79): C, 63.26; H, 5.97; N, 13.83. Found: C, 62.90; H, 5.62; N, 13.49.

4.4.2. Triphenyl compounds and their pyridazine analogues. At room temperature, in the ^{1}H and ^{13}C NMR spectra of some aldehydes (**11a–c**, **18a–d**) and vinyl (**12a–c**, **19a–d**) compounds, broad signals or two separate signal sets with different population ratios were observed, due to hindered rotation around the C–C bonds connecting the phenyl (and pyridazine) rings. For unambiguous structure elucidation, NMR spectra were also recorded at elevated temperatures (100/120 °C).

*4.4.2.1. 2″-Dimethylamino-1,1′:2′,1″-terphenyl-2-carbaldehyde (**11a**).* Column chromatography: toluene/hexane 1:1. Yellow crystals (2.11 g, 70%), mp 119–120 °C, R_f=0.35 (toluene/hexane 1:1). ^{1}H NMR (DMSO-d_6) δ (ppm) (major rotamer at 25 °C): 9.72 (s, 1H), 7.83 (dm, *J*=7.6 Hz, 1H), 7.57 (td, *J*=7.4, 1.4 Hz, 1H), 7.53–7.38 (m, 2H), 7.35–7.25 (m, 3H), 7.21–7.10 (m, 2H), 7.03 (tm, *J*=7.3 Hz, 1H), 6.70–6.63 (m, 2H), 1.97 (s, 6H). ^{13}C NMR (DMSO-d_6) δ (ppm) (major rotamer at 25 °C): 191.5, 150.3, 145.6, 140.6, 136.9, 134.6, 133.8, 131.6, 131.5, 131.2, 130.6, 130.4, 128.6, 128.5, 126.8, 126.5, 125.0, 122.2, 118.0, 42.6. IR (KBr) ν_{max}: 2940, 2862, 1686, 1594, 1258, 1096, 940, 754 cm^{-1}. Anal. Calcd for $C_{21}H_{19}NO$ (301.38): C, 83.69; H, 6.35; N, 4.65. Found: C, 83.33; H, 6.21; N, 4.54.

*4.4.2.2. 2″-Pyrrolidin-1-yl-1,1′:2′,1″-terphenyl-2-carbaldehyde (**11b**).* Column chromatography: toluene. Yellow crystals (1.74 g, 53%), mp 104–105 °C, R_f=0.40 (toluene). ^{1}H NMR (DMSO-d_6, 120 °C) δ (ppm): 9.65 (br s, 1H), 7.64 (br d, *J*=8.0 Hz, 1H), 7.56–7.48 (m, 2H), 7.47–7.35 (br m, 2H), 7.33–7.27 (m, 2H), 7.09 (br s, 1H), 7.05 (dm, *J*=7.2 Hz, 1H), 7.01 (tm, *J*=7.4 Hz, 1H), 6.73 (t, *J*=7.2 Hz, 1H), 6.50 (dm, *J*=8.0 Hz, 1H), 2.53–2.00 (br m, 4H), 1.54–1.51 (m, 4H). ^{13}C NMR (DMSO-d_6, 120 °C) δ (ppm): 189.6, 147.0, 144.0, 141.5, 136.6, 132.6, 131.5, 131.2, 130.4, 130.4, 129.7, 129.6, 127.6, 127.2, 126.3, 126.0, 125.0, 117.8, 114.2, 49.3, 23.7. IR (KBr) ν_{max}: 2918, 2850, 1692, 1596, 1468, 1334, 754 cm^{-1}. Anal. Calcd for $C_{23}H_{21}NO$ (327.42): C, 84.37; H, 6.46; N, 4.28. Found: C, 84.05; H, 6.24; N, 4.28.

*4.4.2.3. 2″-Piperidin-1-yl-1,1′:2′,1″-terphenyl-2-carbaldehyde (**11c**).* Column chromatography: toluene. White crystals (2.53 g, 74%), mp 131–133 °C, R_f=0.30 (toluene). ^{1}H NMR (DMSO-d_6, 100 °C) δ (ppm): 9.77 (br s, 1H), 7.66 (br d, *J*=7.6 Hz, 1H), 7.56–7.50 (m, 1H), 7.49–7.38 (br m, 3H), 7.35–7.29 (m, 2H), 7.21 (br m, 1H), 7.13 (tm, *J*=7.8 Hz, 1H), 7.09 (dm, *J*=7.8 Hz, 1H), 6.93 (t, *J*=7.6 Hz, 1H), 6.79 (dm, *J*=8.0 Hz, 1H), 2.52–2.38 (br m, 4H), 1.45–1.20 (m, 6H). ^{13}C NMR (DMSO-d_6, 100 °C) δ (ppm): 190.6, 150.9, 144.3, 140.3, 135.9, 134.2, 132.6, 131.6, 131.4, 131.0, 130.3, 129.9, 127.9, 127.6, 126.4, 126.4, 125.3, 121.4, 118.1, 51.8, 24.5, 22.9. IR (KBr) ν_{max}: 2936, 2852, 1690, 1594, 1440, 1196, 756 cm^{-1}. HRMS calcd for ($C_{24}H_{23}NO$+H^+): 342.1858. Found: 342.1845.

*4.4.2.4. 2-{5-[2-(Dimethylamino)phenyl]-2-methyl-3-oxo-2,3-dihydropyridazin-4-yl}benzaldehyde (**18a**).* Column chromatography: toluene/EtOAc 4:1. Yellow crystals (2.43 g, 73%), mp 156–158 °C, R_f=0.26 (toluene/EtOAc 4:1). ^{1}H NMR (DMSO-d_6, 100 °C) δ (ppm): 9.79 (s, 1H), 8.01 (s, 1H), 7.82 (dm, *J*=7.2 Hz, 1H), 7.41–7.33 (m, 2H), 7.20 (tm, *J*=7.2 Hz, 1H), 7.13 (br d, *J*=7.2 Hz, 1H), 6.94 (t, *J*=7.2 Hz, 1H), 6.89 (br d, *J*=7.2 Hz, 1H), 6.84 (dm, *J*=8.0 Hz, 1H), 3.77 (s, 3H), 2.34 (s, 6H). ^{13}C NMR (DMSO-d_6, 100 °C) δ (ppm): 190.4, 159.0, 150.5, 141.3, 137.6, 135.9, 134.6, 134.5, 131.9, 130.1, 129.4, 129.3, 127.6, 126.9, 126.6, 121.1, 118.0, 42.6, 39.3. IR (KBr) ν_{max}: 2920, 2850, 1696, 1642, 1594, 1494, 1268, 736 cm^{-1}. Anal. Calcd for $C_{20}H_{19}N_3O_2$ (333.38): C, 72.05; H, 5.74; N, 12.60. Found: C, 72.15; H, 5.72; N, 12.64.

*4.4.2.5. 2-{5-[2-(Dimethylamino)phenyl]-2-phenyl-3-oxo-2,3-dihydropyridazin-4-yl}benzaldehyde (**18b**).* Column chromatography: toluene/EtOAc 3:1. Yellow crystals (2.69 g, 68%), mp 191–192 °C, R_f=0.51 (toluene/EtOAc 3:1). ^{1}H NMR (DMSO-d_6, 100 °C) δ (ppm): 9.92 (s, 1H), 8.18 (s, 1H), 7.86 (dm, *J*=7.2 Hz, 1H), 7.72–7.68 (m, 2H),

7.55–7.49 (m, 2H), 7.45–7.37 (m, 3H), 7.24 (tm, *J*=7.8 Hz, 1H), 7.19 (br d, *J*=7.2 Hz, 1H), 7.00–6.93 (m, 2H), 6.89 (dm, *J*=8.0 Hz, 1H), 2.43 (s, 6H). ^{13}C NMR (DMSO-d_6, 100 °C) δ (ppm): 190.5, 158.6, 150.6, 141.4, 140.9, 138.6, 136.1, 135.4, 134.7, 132.0, 130.1, 129.5, 129.3, 127.9, 127.7, 127.4, 127.2, 126.6, 124.8, 121.0, 118.0, 42.7. IR (KBr) ν_{max}: 2918, 1702, 1646, 1492, 1302, 1140, 764 cm^{-1}. Anal. Calcd for $C_{25}H_{21}N_3O_2$ (395.45): C, 75.93; H, 5.35; N, 10.63. Found: C, 75.73; H, 5.11; N, 10.56.

*4.4.2.6. 2-[2-Methyl-3-oxo-5-(2-pyrrolidin-1-ylphenyl)-2,3-dihydropyridazin-4-yl]benzaldehyde (**18c**).* Column chromatography: *n*-hexane/EtOAc 1:1. Yellow crystals (2.62 g, 73%), mp 185–187 °C, R_f=0.37 (*n*-hexane/EtOAc 1:1). ^{1}H NMR (DMSO-d_6, 100 °C) δ (ppm): 9.78 (s, 1H), 8.01 (s, 1H), 7.79–7.75 (m, 1H), 7.42–7.37 (m, 2H), 7.10 (tm, *J*=7.8 Hz, 1H), 7.03–6.95 (br m, 2H), 6.73 (br t, *J*=7.8 Hz, 1H), 6.66 (dm, *J*=8.0 Hz, 1H), 3.76 (s, 3H), 3.00–2.80 (br m, 4H), 1.85–1.70 (br m, 4H). ^{13}C NMR (DMSO-d_6, 100 °C) δ (ppm): 190.3, 158.8, 147.1, 142.5, 137.6, 135.3, 134.2, 134.1, 132.0, 130.3, 129.6, 128.9, 127.6, 127.0, 122.7, 118.0, 114.9, 50.0, 39.2, 24.1. IR (KBr) ν_{max}: 2960, 1690, 1640, 1592, 1442, 1324, 760 cm^{-1}. Anal. Calcd for $C_{22}H_{21}N_3O_2$ (359.42): C, 73.52; H, 5.89; N, 11.69. Found: C, 73.17; H, 5.77; N, 11.29.

*4.4.2.7. 2-[2-Methyl-3-oxo-5-(2-piperidine-1-ylphenyl)-2,3-dihydropyridazin-4-yl]benzaldehyde (**18d**).* Column chromatography: toluene/EtOAc 1:1. Yellow crystals (2.61 g, 70%), mp 171–172 °C, R_f=0.57 (toluene/EtOAc 1:1). ^{1}H NMR (DMSO-d_6, 100 °C) δ (ppm): 9.92 (s, 1H), 8.02 (s, 1H), 7.87–7.82 (m, 1H), 7.47–7.40 (m, 2H), 7.23 (tm, *J*=7.8 Hz, 1H), 7.05–7.00 (m, 2H), 6.97 (dm, *J*=7.2 Hz, 1H), 6.89 (t, *J*=7.2 Hz, 1H), 3.76 (s, 3H), 2.90–2.60 (br m, 4H), 1.60–1.40 (m, 6H). ^{13}C NMR (DMSO-d_6, 100 °C) δ (ppm): 190.7, 159.1, 151.0, 140.9, 137.9, 135.1, 134.7, 134.3, 132.2, 130.4, 129.6, 129.4, 128.0, 127.8, 127.7, 121.8, 119.3, 52.3, 39.1, 24.8, 22.9. IR (KBr) ν_{max}: 2942, 1692, 1640, 1592, 1442, 1226, 764 cm^{-1}. Anal. Calcd for $C_{23}H_{23}N_3O_2$ (373.45): C, 73.97; H, 6.21; N, 11.25. Found: C, 73.59; H, 5.82; N, 11.15.

4.5. 2′-Bromobiphenyl-2-amine (14)[31a,b]

H_2SO_4 (65% aq, 30 mL) was added to **13** (1.99 g, 5.98 mmol) and the reaction mixture was heated at reflux for 15 h. After cooling to room temperature, the mixture was poured into H_2O (30 mL). The pH was adjusted to 8 with concentrated aq NH_3 and the aqueous phase was extracted with CH_2Cl_2 (4×30 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to dryness. To the oil obtained, *n*-hexane was added to afford white crystals, which were filtered off and washed with *n*-hexane. White crystals (1.31 g, 88%), mp 48–50 °C (lit. mp 46–50 °C),[31b] R_f=0.63 (toluene/EtOAc 5:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.69 (dm, *J*=8.0, 1H), 7.38 (tm, *J*=7.6 Hz, 1H), 7.32 (dm, *J*=7.6 Hz, 1H), 7.27–7.20 (m, 2H), 7.03 (dm, *J*=7.6 Hz, 1H), 6.84 (tm, *J*=7.2 Hz, 1H), 6.79 (dm, *J*=8.0 Hz, 1H), 3.53 (br s, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 144.2, 140.6, 133.8, 132.4, 130.9, 129.9, 129.8, 128.5, 127.8, 125.0, 119.0, 116.2. IR (KBr) ν_{max}: 3374, 2920, 1616, 1466, 1254, 1026, 752 cm^{-1}. Anal. Calcd for $C_{12}H_{10}BrN$ (248.12): C, 58.09; H, 4.06; N, 5.65. Found: C, 58.28; H, 3.78; N, 5.60.

4.6. Synthesis of 10b,c via aqueous N-heterocyclization[24] of 14

A 10 mL MW process vial was charged with **14** (248 mg, 1.00 mmol), dihaloalkane (1.10 mmol) (for **10b**: 1,4-dibromobutane (0.13 mL), for **10c**: 1,5-dibromopentane (0.15 mL)), K_2CO_3 (162 mg, 1.10 mmol) and water (2 mL). The mixture was irradiated in a closed vessel with pressure control at 120 °C for 60 min (hold time) at 70 W maximum power. After completion of the reaction, the mixture was extracted with EtOAc (4×5 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to dryness. The crude product obtained was purified by column chromatography (*n*-hexane/EtOAc 9:1). Compound **10b**: 266 mg, 88%, compound **10c**: 269 mg, 85%.

4.7. General procedure for the synthesis of vinyl compounds 12a–c and 19a–d via Knoevenagel condensation

To a solution of the aldehyde (**11a–c** and **18a–d**) (2.00 mmol) in EtOH (10 mL), malononitrile (132 mg, 2.00 mmol) and a few drops of piperidine were added. The mixture was stirred at room temperature until the starting material had been consumed (monitored by TLC, reaction time: 1–2 h). The mixture was then evaporated to dryness, and EtOH (2 mL) was added to the crude product. The precipitated crystals were filtered off and washed with EtOH to afford the analytically pure product.

*4.7.1. {[2″-(Dimethylamino)-1,1′:2′,1″-terphenyl-2-yl]methylidene}malononitrile (**12a**).* Orange crystals (643 mg, 92%), mp 157–158 °C, R_f=0.57 (toluene). ^{1}H NMR (DMSO-d_6) δ (ppm) (major rotamer at 25 °C): 7.74 (tm, *J*=7.2 Hz, 1H), 7.69–7.64 (m, 1H), 7.60 (td, *J*=7.6, 1.2 Hz, 1H), 7.56–7.47 (m, 3H), 7.45–7.28 (m, 3H), 7.25–7.19 (m, 2H), 7.03 (tm, *J*=7.6 Hz, 1H), 6.57 (dd, *J*=7.7, 1.3 Hz, 1H), 1.95 (s, 6H). ^{13}C NMR (DMSO-d_6) δ (ppm) (major rotamer at 25 °C): 160.4, 149.4, 144.4, 141.5, 136.6, 133.0, 132.9, 131.4, 131.0, 130.9, 130.0, 129.6, 129.3, 127.5, 127.2, 127.1, 126.0, 122.0, 117.2, 114.4, 112.6, 79.8, 41.1. IR (KBr) ν_{max}: 2772, 2224, 1582, 1494, 1430, 1336, 948, 758 cm^{-1}. Anal. Calcd for $C_{24}H_{19}N_3$ (349.43): C, 82.49; H, 5.48; N, 12.03. Found: C, 82.48; H, 5.30; N, 11.91.

*4.7.2. {[2″-(Pyrrolidin-1-yl)-1,1′:2′,1″-terphenyl-2-yl]methylidene}malononitrile (**12b**).* Red crystals (676 mg, 90%), mp 152–153 °C, R_f=0.52 (toluene). ^{1}H NMR (DMSO-d_6) δ (ppm) (major rotamer at 25 °C): 7.73–7.66 (m, 2H), 7.60–7.46 (m, 4H), 7.44 (tm, *J*=7.8 Hz, 1H), 7.33 (dm, *J*=7.6 Hz, 1H), 7.20–7.14 (m, 2H), 7.11 (tm, *J*=7.6 Hz, 1H), 6.86 (tm, *J*=7.6 Hz, 1H), 6.40 (dm, *J*=8.0 Hz, 1H), 2.65–2.55 (m, 2H), 2.10–2.00 (m, 2H), 1.70–1.60 (m, 2H), 1.50–1.35 (m, 2H). ^{13}C NMR (DMSO-d_6) δ (ppm) (major rotamer at 25 °C): 159.4, 146.9, 143.6, 142.5, 137.1, 133.1, 133.0, 131.5, 130.4, 129.8, 129.3, 128.9, 127.7, 127.6, 127.5, 126.9, 125.7, 119.1, 114.6, 113.8, 112.8, 79.6, 49.5, 24.8. IR (KBr) ν_{max}: 2920, 2226, 1640, 1440, 1342, 1160, 954, 752 cm^{-1}. Anal. Calcd for $C_{26}H_{21}N_3$ (375.47): C, 83.17; H, 5.64; N, 11.19. Found: C, 82.80; H, 5.47; N, 11.02.

*4.7.3. {[2″-(Piperidin-1-yl)-1,1′:2′,1″-terphenyl-2-yl]methylidene}malononitrile (**12c**).* Orange crystals (709 mg, 91%), mp 156–158 °C, R_f=0.54 (toluene). ^{1}H NMR (DMSO-d_6) δ (ppm) (major rotamer at 25 °C): 7.73–7.66 (m, 2H), 7.65–7.57 (m, 2H), 7.54–7.36 (m, 5H), 7.28–7.17 (m, 2H), 7.06 (tm, *J*=7.6 Hz, 1H), 6.71 (dm, *J*=8.0 Hz, 1H), 2.55–2.45 (br m, 2H), 2.05–1.95 (br m, 2H), 1.37–1.11 (br m, 6H). ^{13}C NMR (DMSO-d_6) δ (ppm) (major rotamer at 25 °C): 160.7, 150.7, 144.2, 141.2, 136.9, 133.3, 133.2, 133.1, 132.9, 131.0, 130.5, 129.5, 129.4, 128.0, 127.5, 127.4, 126.2, 122.8, 118.2, 114.4, 112.7, 80.5, 51.6, 24.8, 23.6. IR (KBr) ν_{max}: 2930, 2222, 1656, 1580, 1438, 1272, 1026, 752 cm^{-1}. HRMS: calcd for ($C_{27}H_{23}N_3$+H$^+$): 390.1970. Found: 390.1958.

*4.7.4. (2-{5-[2-(Dimethylamino)phenyl]-2-methyl-3-oxo-2,3-dihydropyridazin-4-yl}benzylidene)malononitrile (**19a**).* Orange crystals (671 mg, 88%), mp 161–162 °C, R_f=0.33 (*n*-hexane/EtOAc 1:1). ^{1}H NMR (DMSO-d_6, 100 °C) δ (ppm): 8.02 (s, 1H), 7.97–7.90 (m, 2H), 7.53–7.40 (m, 2H), 7.28–7.15 (m, 3H), 6.98 (tm, *J*=7.8 Hz, 1H), 6.81 (dm, *J*=8.0 Hz, 1H), 3.79 (s, 3H), 2.32 (s, 6H). ^{13}C NMR (DMSO-d_6, 100 °C) δ (ppm): 159.7, 158.5, 150.1, 142.4, 137.5, 136.3, 132.6, 131.6, 130.5, 130.4, 129.8, 129.4, 127.8, 126.2, 125.8, 121.0, 117.7, 113.4, 112.1, 81.6, 42.3, 39.5. IR (KBr) ν_{max}: 2920, 2232, 1750, 1634, 1380, 1170,

732 cm^{-1}. Anal. Calcd for $C_{23}H_{19}N_5O$ (381.43): C, 72.42; H, 5.02; N, 18.36. Found: C, 72.03; H, 4.78; N, 18.23.

*4.7.5. (2-{5-[2-(Dimethylamino)phenyl]-3-oxo-2-phenyl-2,3-dihydropyridazin-4-yl}benzylidene)malononitrile (**19b**).* Orange crystals (754 mg, 85%), mp 145–147 °C, R_f=0.70 (*n*-hexane/EtOAc 1:1). ^{1}H NMR (DMSO-d_6, 100 °C) δ (ppm): 8.22 (s, 1H), 8.09 (s, 1H), 7.95 (dm, *J*=7.6 Hz, 1H), 7.76–7.70 (m, 2H), 7.57–7.40 (m, 5H), 7.35–7.20 (m, 3H), 7.00 (t, *J*=7.2 Hz, 1H), 6.85 (dm, *J*=7.6 Hz, 1H), 2.40 (s, 6H). ^{13}C NMR (DMSO-d_6, 100 °C) δ (ppm): 159.8, 158.2, 150.2, 142.2, 141.4, 138.5, 136.1, 133.9, 131.6, 130.5, 130.4, 129.9, 129.4, 127.8, 127.8, 127.2, 126.2, 125.4, 124.8, 121.0, 117.7, 113.4, 112.1, 81.8, 42.3. IR (KBr) ν_{max}: 2918, 2228, 1646, 1496, 1142, 756 cm^{-1}. Anal. Calcd for $C_{28}H_{21}N_5O$ (443.50): C, 75.83; H, 4.77; N, 15.79. Found: C, 75.59; H, 4.56; N, 15.74.

*4.7.6. (2-{2-Methyl-3-oxo-5-[2-(pyrrolidin-1-yl)phenyl]-2,3-dihydropyridazin-4-yl}benzylidene)malononitrile (**19c**).* Orange crystals (733 mg, 90%), mp 112–115 °C (dec), R_f=0.60 (toluene/EtOAc 1:1). ^{1}H NMR (DMSO-d_6) δ (ppm) (major rotamer at 25 °C): 8.12 (s, 1H), 7.87 (s, 1H), 7.73 (dm, *J*=8.0 Hz, 1H), 7.64 (tm, *J*=7.6 Hz, 1H), 7.57 (dm, *J*=7.6 Hz, 1H), 7.45 (tm, *J*=7.6 Hz, 1H), 7.19–7.11 (m, 2H), 6.84 (tm, *J*=7.6 Hz, 1H), 6.49 (dm, *J*=8.4 Hz, 1H), 3.75 (s, 3H), 2.95–2.88 (m, 2H), 2.24–2.18 (m, 2H), 1.85–1.75 (br m, 2H), 1.58–1.50 (m, 2H). ^{13}C NMR (DMSO-d_6) δ (ppm) (major rotamer at 25 °C): 159.6, 158.9, 146.9, 144.1, 137.9, 136.1, 132.2, 131.4, 131.3, 131.2, 130.2, 128.7, 128.6, 126.3, 120.1, 118.5, 114.3, 114.0, 112.8, 80.9, 50.2, 40.3, 25.1. IR (KBr) ν_{max}: 2952, 2226, 1636, 1442, 1352, 1014, 752 cm^{-1}. Anal. Calcd for $C_{25}H_{21}N_5O$ (407.47): C, 73.69; H, 5.19; N, 17.19. Found: C, 73.35; H, 4.88; N, 16.91.

*4.7.7. (2-{2-Methyl-3-oxo-5-[2-(piperidin-1-yl)phenyl]-2,3-dihydropyridazin-4-yl}benzylidene)malononitrile (**19d**).* Yellow crystals (750 mg, 89%), mp 186–187 °C, R_f=0.76 (toluene/EtOAc 1:1). ^{1}H NMR (DMSO-d_6, 100 °C) δ (ppm): 8.08 (s, 1H), 8.04 (s, 1H), 7.95 (dm, *J*=7.6 Hz, 1H), 7.52–7.42 (m, 2H), 7.30–7.24 (m, 2H), 7.03–6.91 (m, 3H), 3.78 (s, 3H), 2.74–2.65 (br m, 4H), 1.66–1.43 (m, 6H). ^{13}C NMR (DMSO-d_6, 100 °C) δ (ppm): 160.1, 158.6, 150.8, 142.2, 137.8, 135.8, 132.8, 131.7, 130.9, 130.5, 129.9, 129.8, 127.9, 127.3, 126.5, 121.8, 119.1, 113.2, 112.0, 82.3, 52.2, 39.3, 24.7, 22.9. IR (KBr) ν_{max}: 2934, 2230, 1640, 1586, 1442, 1228, 1016, 762 cm^{-1}. Anal. Calcd for $C_{26}H_{23}N_5O$ (421.49): C, 74.09; H, 5.50; N, 16.62. Found: C, 73.73; H, 5.19; N, 16.29.

4.8. MW-assisted isomerization of vinyl compounds in DMSO (synthesis of 20a–c and 21a–d)

A solution of the vinyl precursor (**12a–c** and **19a–d**) (0.25 mmol) in 1 mL dry DMSO was irradiated in an open vessel or in a 10 mL MW process vial at the temperature and for the reaction time shown in Table 1. The reaction mixture was subsequently cooled to ambient temperature and poured into CH_2Cl_2 (15 mL). The organic layer was washed with H_2O (3×15 mL), dried ($MgSO_4$), filtered and evaporated to dryness. The residue obtained was purified by flash column chromatography on silica gel with the eluents indicated below.

*4.8.1. 5-Methyl-5,8-dihydrotribenzo[b,d,f]azecine-7,7(6H)-dicarbonitrile (**20a**).* Column chromatography: *n*-hexane/EtOAc 97:3. White crystals, mp 149–152 °C, R_f=0.36 (*n*-hexane/EtOAc 9:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.65 (dm, *J*=8.0 Hz, 1H), 7.51–7.46 (m, 1H), 7.42–7.38 (m, 2H), 7.35–7.31 (m, 1H), 7.19–7.09 (m, 4H), 6.96 (tm, *J*=7.6 Hz, 1H), 6.73–6.67 (m, 2H), 3.55 (d, *J*=13.1 Hz, 1H), 3.52 (d, *J*=13.8 Hz, 1H), 3.40 (d, *J*=13.8 Hz, 1H), 2.85 (d, *J*=13.1 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 153.0, 144.1, 141.6, 140.4, 139.2, 132.5, 131.1, 131.0, 130.2, 130.0, 129.6, 129.1, 128.6, 128.0, 127.6, 127.5, 126.1, 123.0, 117.6, 116.7, 59.0, 44.2, 38.5, 35.9. IR (KBr) ν_{max}: 2952, 2858, 2244, 1444, 1258, 1072, 954, 756 cm^{-1}. Anal. Calcd for $C_{24}H_{19}N_3$ (349.43): C, 82.49; H, 5.48; N, 12.03. Found: C, 82.65; H, 5.69; N, 11.96.

*4.8.2. 6,7,8,8a-Tetrahydrotribenzo[e,g,i]pyrrolo[1,2-a]azecine-9,9(10H)-dicarbonitrile (**20b**).* Column chromatography: *n*-hexane/EtOAc 7:1. White crystals, mp 137–140 °C, R_f=0.43 (*n*-hexane/EtOAc 7:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.65 (dm, *J*=8.0 Hz, 1H), 7.50–7.45 (m, 1H), 7.42–7.36 (m, 2H), 7.29–7.25 (m, 1H), 7.16–7.05 (m, 4H), 6.93 (tm, *J*=7.6 Hz, 1H), 6.66 (dd, *J*=7.6, 1.4 Hz, 1H), 6.49 (dm, *J*=7.6 Hz, 1H), 3.55 (d, *J*=14.0 Hz, 1H), 3.47 (dd, *J*=8.4, 2.0 Hz, 1H), 3.35 (d, *J*=14.0 Hz, 1H), 3.08–2.99 (m, 1H), 2.69–2.61 (m, 1H), 2.52–2.41 (m, 1H), 2.32–2.23 (m, 1H), 2.11–1.94 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 152.7, 144.1, 141.5, 141.5, 140.2, 132.1, 131.8, 131.1, 129.8, 129.4, 129.3, 128.7, 128.5, 127.9, 127.4, 127.4, 125.9, 122.7, 117.6, 117.3, 70.1, 56.2, 45.0, 37.1, 31.3, 24.2. IR (KBr) ν_{max}: 2954, 2242, 1690, 1640, 1440, 1264, 1092, 756 cm^{-1}. HRMS: calcd for ($C_{26}H_{21}N_3$+H^+): 376.1814. Found: 376.1804.

*4.8.3. 7,8,9,9a-Tetrahydro-6H-tribenzo[e,g,i]pyrido[1,2-a]azecine-10,10(11H)-dicarbonitrile (**20c**).* Column chromatography: toluene. White crystals, mp 141–143 °C, R_f=0.61 (toluene). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.72 (dm, *J*=8.0 Hz, 1H), 7.51–7.36 (m, 3H), 7.28–7.23 (m, 1H), 7.16–7.03 (m, 4H), 6.91 (tm, *J*=7.6 Hz, 1H), 6.81–6.76 (m, 1H), 6.62 (dd, *J*=8.0, 1.3 Hz, 1H), 3.46 (d, *J*=13.6 Hz, 1H), 3.37 (d, *J*=13.6 Hz, 1H), 3.23–3.19 (m, 1H), 2.86–2.77 (m, 1H), 2.64–2.57 (m, 1H), 2.38–2.15 (m, 3H), 1.84–1.75 (m, 1H), 1.47–1.34 (m, 1H), 1.24–1.16 (m, 1H). ^{13}C NMR ($CDCl_3$): 151.4, 143.9, 141.4, 141.2, 138.8, 132.1, 131.7, 131.4, 130.0, 129.6, 128.7, 128.7, 128.5, 127.8, 127.5, 127.2, 124.8, 123.2, 118.7, 118.1, 59.4, 48.7, 43.4, 37.8, 25.3, 19.8, 19.8. IR (KBr) ν_{max}: 2928, 2244, 1634, 1442, 1228, 1054, 754 cm^{-1}. Anal. Calcd for $C_{27}H_{23}N_3$ (389.49): C, 83.26; H, 5.95; N, 10.79. Found: C, 82.95; H, 5.68; N, 10.58.

*4.8.4. 5,14-Dimethyl-13-oxo-5,8,13,14-tetrahydrodibenzo[b,f]pyridazino[4,5-d]azecine-7,7(6H)-dicarbonitrile (**21a**).* Column chromatography: *n*-hexane/EtOAc 4:1. White crystals, mp 289–294 °C (dec), R_f=0.39 (*n*-hexane/EtOAc 1:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.86 (s, 1H), 7.66 (dm, *J*=7.8 Hz, 1H), 7.31–7.20 (m, 4H), 7.05 (tm, *J*=7.8 Hz, 1H), 6.85 (dm, *J*=8.0 Hz, 1H), 6.63 (dm, *J*=7.8 Hz, 1H), 3.93 (s, 3H), 3.58 (d, *J*=13.8 Hz, 2H), 3.24 (d, *J*=13.8 Hz, 1H), 2.79 (d, *J*=13.2 Hz, 1H), 2.62 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 160.4, 152.8, 142.1, 140.6, 137.4, 135.9, 133.1, 132.6, 131.5, 131.0, 129.6, 129.3, 129.3, 128.9, 126.8, 124.4, 117.3, 116.2, 59.2, 45.4, 41.4, 38.1, 36.9. IR (KBr) ν_{max}: 2920, 2242, 1644, 1448, 1260, 1014, 764 cm^{-1}. Anal. Calcd for $C_{23}H_{19}N_5O$ (381.43): C, 72.42; H, 5.02; N, 18.36. Found: C, 72.22; H, 4.84; N, 18.22.

*4.8.5. 5-Methyl-13-oxo-14-phenyl-5,8,13,14-tetrahydrodibenzo[b,f]pyridazino[4,5-d]azecine-7,7(6H)-dicarbonitrile (**21b**).* Column chromatography: *n*-hexane/EtOAc 4:1. White crystals, mp 195–198 °C, R_f=0.70 (*n*-hexane/EtOAc 1:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.03 (s, 1H), 7.82–7.75 (m, 2H), 7.67 (dm, *J*=7.8 Hz, 1H), 7.52–7.48 (m, 2H), 7.43–7.39 (m, 1H), 7.38 (dm, *J*=7.2 Hz, 1H), 7.32–7.22 (m, 3H), 7.08 (tm, *J*=7.8 Hz, 1H), 6.89 (dm, *J*=7.8 Hz, 1H), 6.72 (dm, *J*=7.8 Hz, 1H), 3.61 (d, *J*=13.8 Hz, 1H), 3.58 (d, *J*=13.8 Hz, 1H), 3.31 (d, *J*=13.8 Hz, 1H), 2.80 (d, *J*=13.8 Hz, 1H), 2.69 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 159.9, 152.9, 142.2, 142.2, 141.9, 138.5, 135.9, 133.0, 132.9, 131.7, 131.0, 129.7, 129.4, 129.3, 129.3, 129.0, 129.0, 126.9, 125.9, 124.5, 117.2, 116.2, 59.3, 45.6, 38.1, 37.0. IR (KBr) ν_{max}: 2922, 2242, 1652, 1490, 1294, 1126, 758 cm^{-1}. Anal. Calcd for $C_{28}H_{21}N_5O$ (443.50): C, 75.83; H, 4.77; N, 15.79. Found: C, 75.62; H, 4.54; N, 15.41.

*4.8.6. 3-Methyl-4-oxo-3,9,10a,11,12,13-hexahydrodibenzo[e,i]pyridazino[4,5-g]pyrrolo[1,2-a]azecine-10,10(4H)-dicarbonitrile (**21c**).* Column chromatography: *n*-hexane/EtOAc 1:1. White

crystals, mp 184–188 °C, R_f=0.35 (*n*-hexane/EtOAc 1:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.87 (s, 1H), 7.68 (dm, *J*=7.8 Hz, 1H), 7.26–7.18 (m, 4H), 7.02 (tm, *J*=7.2 Hz, 1H), 6.64–6.58 (m, 2H), 3.94 (s, 3H), 3.56 (d, *J*=14.4 Hz, 1H), 3.42–3.35 (m, 2H), 3.27 (d, *J*=14.4 Hz, 1H), 2.75–2.68 (m, 1H), 2.55–2.48 (m, 1H), 2.38–2.30 (m, 1H), 2.22–2.15 (m, 1H), 2.12–2.04 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 160.6, 152.5, 143.5, 140.5, 137.3, 136.0, 134.2, 132.8, 131.3, 130.6, 129.4, 129.3, 129.1, 128.8, 126.7, 124.4, 117.1, 117.0, 70.7, 56.9, 44.8, 41.7, 37.9, 31.2, 24.3. IR (KBr) ν_{max}: 2918, 2246, 1644, 1444, 1266, 1016, 758 cm^{-1}. HRMS: calcd for ($C_{25}H_{21}N_5O$+H^+): 408.1824. Found: 408.1811.

*4.8.7. 3-Methyl-4-oxo-3,9,11,12,13,14-hexahydro-4H-dibenzo[e,i]pyridazino[4,5-g]pyrido[1,2-a]azecine-10,10(10aH)-dicarbonitrile (**21d**).* Column chromatography: toluene/EtOAc 2:1. Yellow crystals, mp 140–144 °C, R_f=0.38 (toluene/EtOAc 2:1). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.16 (s, 1H), 7.59 (dm, *J*=8.0 Hz, 1H), 7.33 (dd, *J*=7.2, 1.8 Hz, 1H), 7.22 (tm, *J*=8.0 Hz, 1H), 7.19–7.10 (m, 2H), 7.06 (dm, *J*=8.0 Hz, 1H), 7.00 (tm, *J*=8.0 Hz, 1H), 6.62 (dm, *J*=7.6 Hz, 1H), 3.79 (s, 3H), 3.72 (d, *J*=14.0 Hz, 1H), 3.14 (dm, *J*=13.6 Hz, 1H), 3.04 (tm, *J*=14.5 Hz, 1H), 3.01 (d, *J*=14.0 Hz, 1H), 2.56 (dm, *J*=14.5 Hz, 1H), 2.41–2.31 (m, 1H), 2.28–2.15 (m, 1H), 2.00–1.94 (m, 1H), 1.80–1.73 (m, 1H), 1.35–1.22 (m, 2H). ^{13}C NMR (DMSO-d_6) δ (ppm): 159.1, 150.0, 142.2, 138.3, 137.2, 135.8, 132.5, 131.7, 130.1, 129.6, 129.5, 129.3, 128.0, 127.6, 124.3, 123.6, 117.9, 117.1, 58.5, 48.8, 42.2, 40.3, 36.2, 23.9, 18.8, 18.7. IR (KBr) ν_{max}: 2932, 2240, 1648, 1444, 1228, 1014, 764 cm^{-1}. Anal. Calcd for $C_{26}H_{23}N_5O$ (421.49): C, 74.09; H, 5.50; N, 16.62. Found: C, 73.77; H, 5.38; N, 16.36.

Acknowledgements

The authors thank the Hungarian Scientific Research Fund for financial support (K73389), Dr. Tamás Gáti for his contribution to the assignment of NMR spectra, and Dr. Péter Tétényi for recording IR spectra.

References and notes

1. Aladesanmi, A. J.; Kelley, C. J.; Leary, J. D. *J. Nat. Prod.* **1983**, *46*, 127–131.
2. McDonald, E.; Suksamrarn, A. *Tetrahedron Lett.* **1975**, *49*, 4425–4428.
3. Marino, J. P.; Samanen, J. M. *J. Org. Chem.* **1976**, *41*, 179–180.
4. McDonald, E.; Suksamrarn, A. *J. Chem. Soc., Perkin Trans. 1* **1978**, *5*, 434–440.
5. Efferth, T.; Sauerbrey, A.; Halatsch, M.-E.; Ross, D. D.; Gebhart, E. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2003**, *367*, 56–67.
6. Hart, J. B.; Mason, J. M.; Gerard, P. J. *Tetrahedron* **2001**, *57*, 10033–10038.
7. (a) Kulkarni, B. K.; Dhar, R. K.; de Souza, N. J. *J. Heterocycl. Chem.* **1990**, *27*, 623–626; (b) Xiao, X.; Liu, J.; Hu, J.; Zhu, X.; Yang, H.; Wang, C.; Zhang, Y. *Eur. J. Pharmacol.* **2008**, *591*, 21–27; (c) Saeed, S. A.; Gilani, A. H.; Majoo, R. U.; Shah, B. H. *Pharmacol. Res.* **1997**, *36*, 1–7.
8. Sawa, Y.; Hirose, K.; Maeda, S.; Hamada, Y. U.S. Patent 3,932,384, 1976; *Chem. Abstr.* **1976**, *80*, 146050.
9. (a) Kassack, M. U.; Höfgen, B.; Decker, M.; Eckstein, N.; Lehmann, J. *Naunyn-Schmiedeberg's Arch. Pharmacol* **2002**, *366*, 543–550; (b) Mohr, P.; Decker, M.; Enzensperger, C.; Lehmann, J. *J. Med. Chem.* **2006**, *49*, 2110–2116.
10. Meth-Cohn, O.; Suschitzky, H. *Adv. Heterocycl. Chem.* **1972**, *14*, 211–278.
11. Quintela, J. M. *Recent Res. Dev. Org. Chem.* **2003**, *7*, 259–278.
12. Verboom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 311–324.
13. Mátyus, P.; Éliás, O.; Tapolcsányi, P.; Polonka-Bálint, Á.; Halász-Dajka, B. *Synthesis* **2006**, *16*, 2625–2639.
14. Polonka-Bálint, Á.; Saraceno, C.; Ludányi, K.; Bényei, A.; Mátyus, P. *Synlett* **2008**, 2846–2850.
15. Földi, Á. A.; Mátyus, P., unpublished results.
16. (a) Buchwald, S. L.; Huang, X.; Zim, D. WO 2004052939; *Chem. Abstr.* **2004**, *141*, 71718; (b) Bonnaventure, I.; Charette, A. B. *J. Org. Chem.* **2008**, *73*, 6330–6340.
17. (a) Krajsovszky, G.; Károlyházy, L.; Riedl, Zs.; Csámpai, A.; Dunkel, P.; Lernyei, Á.; Dajka-Halász, B.; Hajós, Gy.; Mátyus, P. *J. Mol. Struct. (THEOCHEM)* **2005**, *713*, 235–243; (b) Beška, E.; Rapoš, P. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2470–2471.
18. Haider, N.; Wobus, A. *Heterocycles* **2006**, *68*, 2549–2561.
19. Stevenson, T. M.; Crouse, B. A.; Thieu, T. V.; Gebreysus, C.; Finkelstein, B. L.; Sethuraman, M. R.; Dubas-Cordery, C. M.; Piotrowski, D. L. *J. Heterocycl. Chem.* **2005**, *42*, 427–435.
20. Lauer, M.; Wulff, G. *J. Organomet. Chem.* **1983**, *256*, 1–9.
21. Howard, H. R. EP 0957099; *Chem. Abstr.* **1999**, *131*, 351348.
22. Biadatti, T.; Dumais, L.; Soulet, C.; Talano, S.; Daver, S. WO 2006066978; *Chem. Abstr.* **2006**, *145*, 103438.
23. Verboom, W.; Reinhoudt, D. N.; Visser, R.; Harkema, S. *J. Org. Chem.* **1984**, *49*, 269–276.
24. Ju, Y.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 135–141.
25. Kaval, N.; Dehaen, W.; Mátyus, P.; Van der Eycken, E. *Green Chem.* **2004**, *6*, 125–127.
26. Kaval, N.; Halász-Dajka, B.; Vo-Thanh, G.; Dehaen, W.; Van der Eycken, J.; Mátyus, P.; Loupy, A.; Van der Eycken, E. *Tetrahedron* **2005**, *61*, 9052–9057.
27. The X-ray data are available from the Cambridge Crystallographic Data Centre CCDC under the numbers 731714–731718 for **12a**, **18a**, **19a**, **20a** and **21c**, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk. The details of the X-ray structures will be published elsewhere.
28. O'Leary, J.; Formosa, X.; Skranc, W.; Wallis, J. D. *Org. Biomol. Chem.* **2005**, *3*, 3273–3283.
29. (a) Guven, A.; Jones, R. A. *J. Chem. Res., Miniprint* **1993**, *9*, 2411–2428; (b) Mongevega, A.; Palop, J. A.; Martinez, M. T.; Fernandez-Alvarez, E. *An. Quim.* **1979**, *75*, 889.
30. Ali, M. I.; El-Sayed, A. A.; Abdel-Fattah, A. M.; El-Reedy, A. M. *Indian J. Chem. B* **1977**, *15*, 64–66.
31. (a) Gait, S. F.; Peek, M. E.; Rees, C. W.; Storr, R. C. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1248–1260; (b) Mascarelli, G. *Gazz. Chim. Ital.* **1931**, *61*, 782–788.
32. Fuhrer, W.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 1133–1136.
33. Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. *Tetrahedron* **1993**, *49*, 49–64.