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Intramolecular [4+2] cycloaddition reactions of indolylalkylpyridazines: synthesis of annulated carbazoles

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Dedicated with best wishes to Professor Peter Stanetty on the occasion of his 60th birthday

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Abstract—Mono- and bicyclic 1,2-diazines tethered to indole dienophiles by alkylene chains were found to undergo thermally induced intramolecular Diels–Alder reactions with inverse electron demand, affording tetra- and pentacyclic condensed carbazoles.

1. Introduction

The electron-rich C(2)–C(3) bond of indole has been known to participate as a dienophile in inverse-electron-demand Diels–Alder (IDA) reactions with electron-deficient azines as dienes, such as 1,2,4,5-tetrazines[1–9] and 1,2,4-triazines,[6,9–13] affording pyridazino[4,5-*b*]indoles or carbolines, respectively.[14] In the case of the 1,2,4-triazine ring system, various intramolecular IDA reactions with an indole as the dienophile component have been studied by Snyder,[6,9,11–13] and these reactions lead to bridged carbolines, e.g. 5,6-dihydro-4*H*-pyrido[1,2,3-*lm*]-β-carbolines featuring the skeleton of the canthine alkaloids.[11] Also for indole-tethered 1,2,4,5-tetrazines, some applications of such intramolecular [4+2] cycloaddition processes have been reported.[6,9]

So far, very few examples of pyridazines participating in IDA reactions with indole dienophiles have been described. The highly reactive tetramethyl pyridazine-3,4,5,6-tetracarboxylate was found to react with indole to afford a phenanthridone instead of the expected carbazole,[10] whereas 4,5-dicyanopyridazine on heating with indole or *N*-methylindole gives dicyanocarbazoles along with minor amounts of 3-(4-cyanopyridazin-5-yl)indole derivatives,[15] the latter resulting from nucleophilic substitution of one cyano group by the electron-rich indole C(3). Recently, the intramolecular IDA reaction of cyclophanes containing an indole and a pyridazine unit has been shown to yield pentacyclic compounds featuring a reduced carbazole skeleton very elegantly.[16,17]

In the course of our investigations on the synthesis and antitumour activity of polycyclic hetarenes, especially condensed carbazoles of the ellipticine/olivacine type (Fig. 1),[18–22] we became interested in the intramolecular IDA reaction of indoles with pyridazines as a promising tool for the construction of novel fused carbazoles with an alkylene bridge between the carbazole nitrogen in ring B and the adjacent carbon in ring C. Such compounds would combine some of the structural features of the *b*-fused carbazole antitumour agents like ellipticine as well as of the canthine alkaloids which are also known to possess cytotoxic activity.[23] Here, we report on the concise synthesis of suitable indol-1-ylalkyl-substituted pyridazines and fused pyridazines and on their intramolecular [4+2] cycloaddition reactions, affording annulated carbazoles.

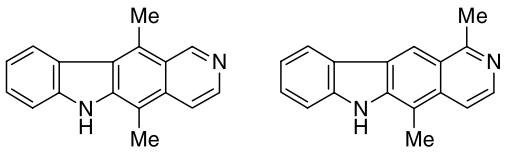

Figure 1.

2. Results and discussion

2.1. Synthesis of tethered cycloaddition educts

For the preparation of the requisite 3-(indol-1-yl)propyl-substituted pyridazines, two alternative pathways were developed. Starting from a *N*-propargylindole of type **1**, Sonogashira coupling with 3-iodopyridazine[24,25] (**2**) or

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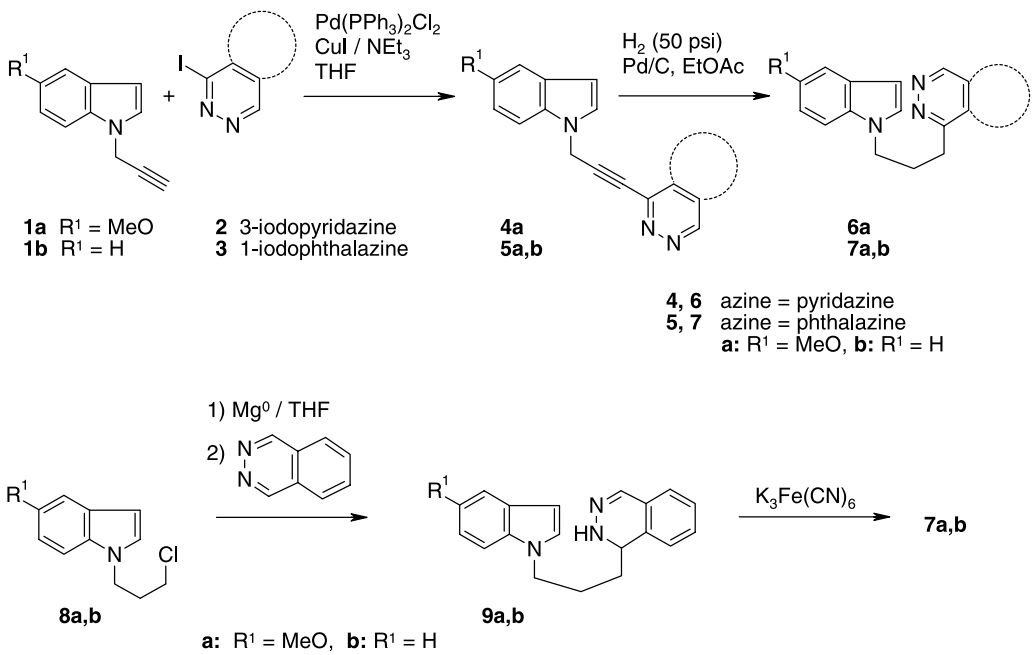
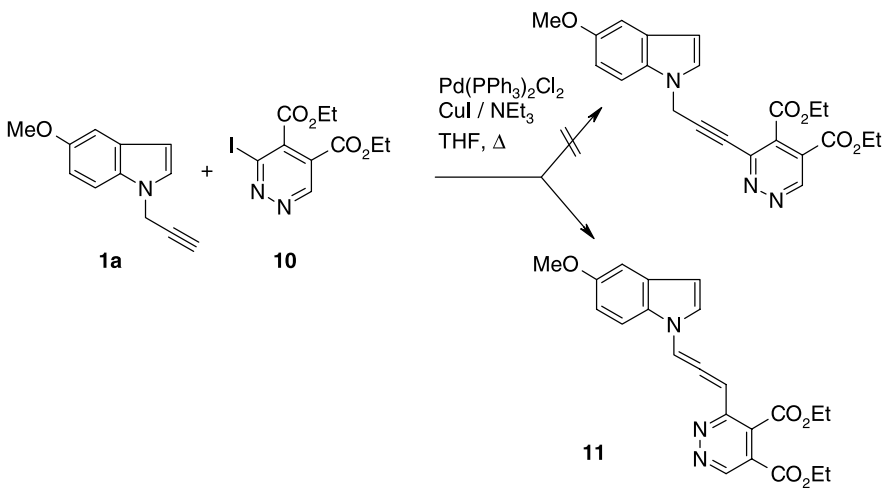


Scheme 1.

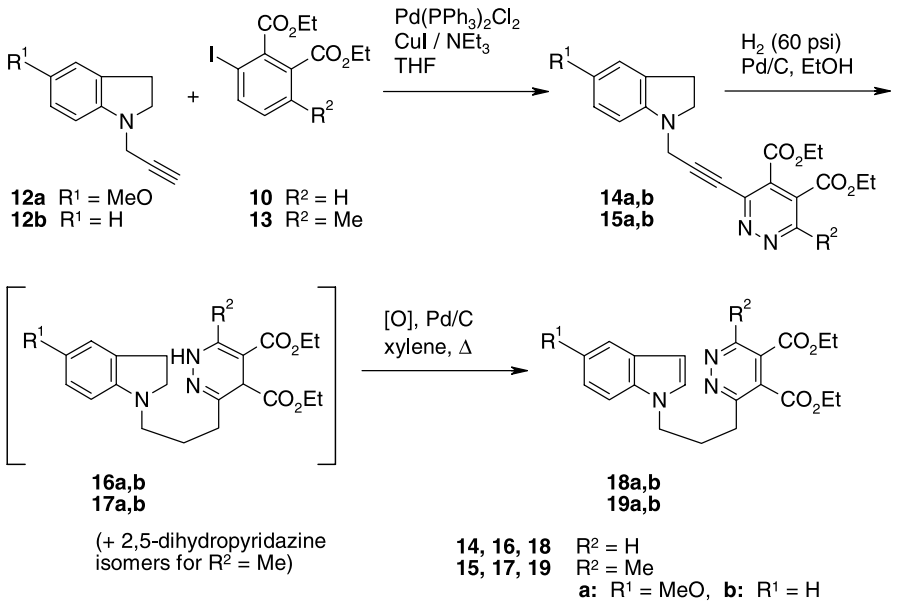
1-iodophthalazine[26] (**3**), respectively, gives the intermediate alkynes **4**, **5** which are hydrogenated to afford the desired compounds **6**, **7**. Alternatively, addition of a Grignard reagent generated from 1-(3-chloropropyl)indoles[27] (**8**) across the C(1)–N(2) bond of phthalazine, followed by dehydrogenation of the intermediate dihydrophthalazines **9** with $K_3Fe(CN)_6$ also leads to **7** in satisfactory yields.

In contrast to the smooth formation of compounds **4a** and **5a**,**b**, the palladium-catalyzed cross-coupling reaction of 5-methoxy-*N*-propargylindole (**1a**) with diethyl 3-iodopyridazine-4,5-dicarboxylate (**10**) (Scheme 2), which is easily accessible by free-radical ethoxycarbonylation of 3-iodopyridazine,[24] did not afford the desired indolylpropynylpyridazine derivative, but led to a red-colored compound which, according to its mass spectrum, is an isomer of the target propyne. Based on its spectral data (^{1}H NMR including DNOE, IR, MS, HRMS), the structure of the allene **11** was established for this compound. It proved to be very inert and all attempts failed to elaborate on the allenic structure by hydrogenation. Obviously, the alkyne/allene rearrangement is favored in this case by the increased CH acidity of the methylene group, as compared to the stable alkynes **4**, **5** which are lacking the electron-withdrawing ester functions at the diazine unit (Scheme 1).

In order to circumvent this problem, we sought to increase the electron density of the propyne synthon (thus decreasing the methylene CH acidity) by employing the corresponding indoline derivatives (**12a**, **12b**[28]) instead of the indoles (**1a**,**b**) as the cross-coupling partners with the iodopyridazine diester (**10**[24] or **13**,[24] respectively; Scheme 3). Indeed, here the Sonogashira reaction smoothly affords the desired alkyne-type coupling products **14**, **15** without any trace of an allenic rearrangement product. Catalytic hydrogenation of the triple bond in **14**, **15** was found to result in concomitant reduction of the highly electron-poor pyridazine ring, giving the corresponding dihydropyridazine



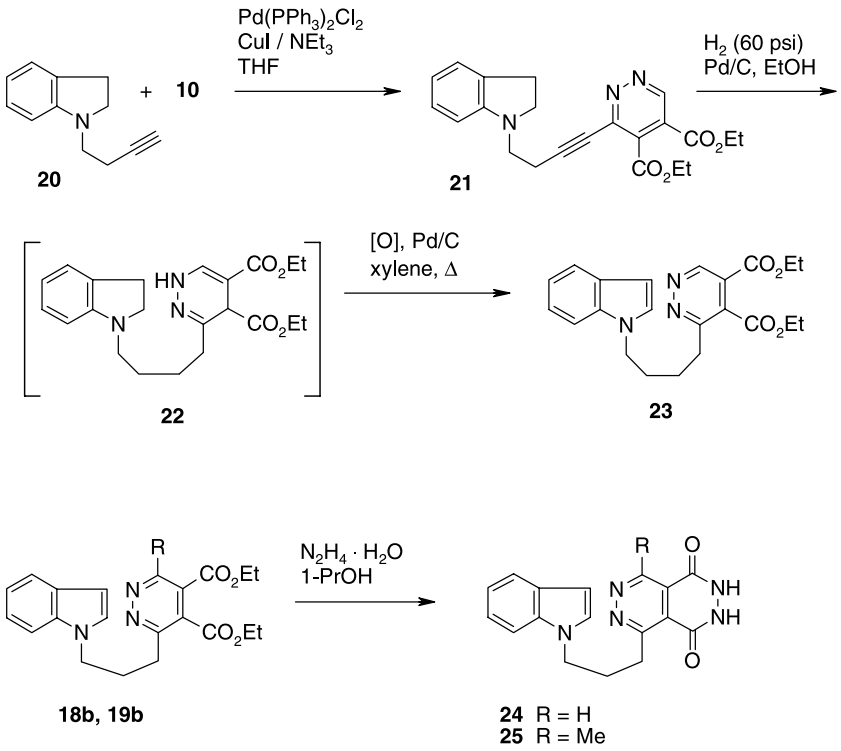
Scheme 2.



Scheme 3.

derivatives: in the case of the 3,4,5-trisubstituted pyridazines, the structure of the 1,4-dihydropyridazines **16** was established by their ^{1}H NMR spectra (coupling of the NH proton with pyridazine 6-H, J=4.2 Hz), whereas the tetrasubstituted pyridazines afforded unseparable mixtures of 1,4-dihydropyridazines (**17**) and their 2,5-dihydropyridazine isomers. Heating these compounds in xylene in the presence of air oxygen with palladium/carbon as the catalyst effects the required dehydrogenation/aromatization of the indole as well as of the pyridazine subunits to give compounds **18**, **19**. Thus, both the dienophile and the diene parts of the molecules can be generated conveniently from the precursors **16** or **17**, respectively, in a single step (Scheme 3).

In an analogous fashion, a cycloaddition candidate with a four-carbon tether chain (compound **23**, see Scheme 4) was prepared, starting from 1-(but-3-yn-1-yl)indole (**20**) and the iodopyridazine **10**. Catalytic hydrogenation, like in the transformation of **14** into **18** via **16**, results in the formation of a 1,4-dihydropyridazine intermediate (**22**) which is then dehydrogenated to give **23**. Moreover, refluxing of the



Scheme 4.

diesters **18b**, **19b** with hydrazine hydrate in 1-propanol smoothly affords the corresponding pyridazino[4,5-*d*]-pyridazinedione derivatives **24**, **25** (Scheme 4) as another type of candidates for the envisaged intramolecular cycloaddition step.

Application of the Grignard pathway (as described for the preparation of **7** from **8**, see above) to the pyrido[3,4-*d*]pyridazine ring system gave the desired compound only in low yield, together with other isomers. However, using the Sonogashira coupling route, starting from 1-chloro-pyrido[3,4-*d*]pyridazine[29] (**26**) and 1-prop-2-yn-1-ylindoline[28] (**12b**) provides a convenient access also to a cycloaddition educt with a pyrido[3,4-*d*]pyridazine system (compound **28**) as the diene unit (Scheme 5).

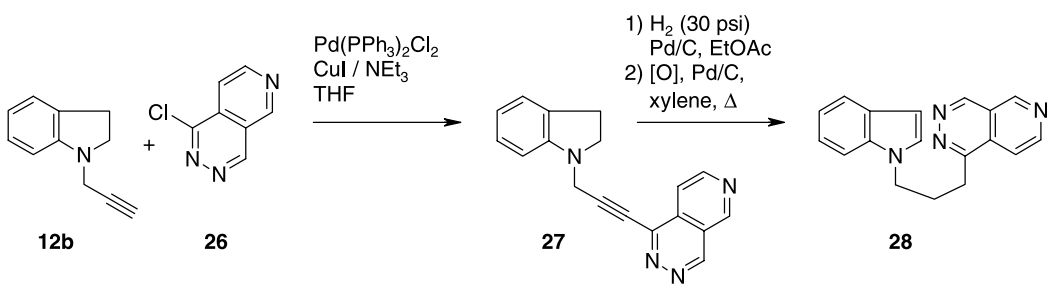
2.2. Intramolecular [4+2] cycloaddition reactions

Thermally induced intramolecular IDA reactions of the indolylalkylpyridazines could be anticipated to require drastic conditions, taking into account the lower degree of electron deficiency of these 1,2-diazine compounds as compared to structurally related 1,2,4-triazines.[11] Thus, 1,3,5-triisopropylbenzene (TIPB; bp=232 °C) was chosen as the solvent for all cycloaddition attempts to ensure sufficiently high reaction temperatures. All reactions were run under argon atmosphere in order to minimize formation of decomposition products.

Surprisingly, even the unactivated monocyclic pyridazine (compound **6a**; cf. Table 1, entry 1) was found to undergo an IDA reaction, albeit very slowly (2 weeks of refluxing) and giving a very low yield (8%) of the corresponding carbazole (**29**) besides substantial amounts of polymeric material. Obviously, compound **29** results from air oxidation/dehydrogenation of the initially formed dihydrocarbazole product (see Scheme 6) during work-up. With a phthalazine system as the diazadiene (compounds **7a**,**b**, entries 2 and 3), reactions are complete after 4 days at 232 °C, but the yields of the pentacyclic products **30a**,**b** are still rather low (mainly because of decomposition). Introduction of an additional nitrogen atom into the bicyclic diazadiene (i.e., replacement of the phthalazine by a pyrido[3,4-*d*]pyridazine structure, compound **28**) markedly increases the reaction rate (reaction time: 15 h; entry 4), however with no improvement of product yield (compound **31**). Substantially better yields are obtained with the very electron-poor pyridazinediesters **18a**,**b** and **19a**,**b**, respectively (products of type **32**, **33**; entries 5–8). Whereas the presence of an electron-donating methoxy group at the dienophilic indole subunit (**18a** and **19a**) does not significantly influence yields and reaction times as compared to the 5-unsubstituted indoles (**18b** and **19b**), the trisubstituted pyridazines **18** react considerably faster and give higher yields of carbazole products than the tetrasubstituted cyclization educts **19**, obviously as a consequence of the different degree of steric hindrance around the diazadiene structures. Expectedly, elongation of the tether chain by one methylene unit as in compound **23** leads to a marked decrease in reactivity, which is reflected by a longer reaction time and lower yield (product **34**; entry 9), as a result of the lower degree of 'entropic assistance'.

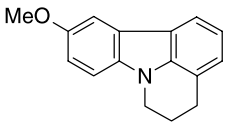
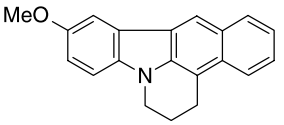
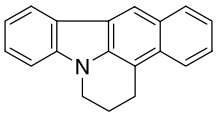
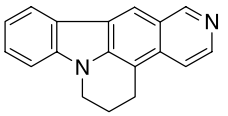
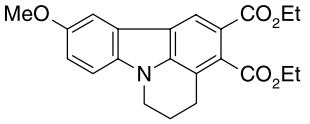
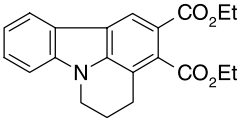
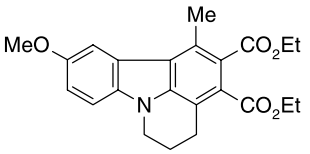
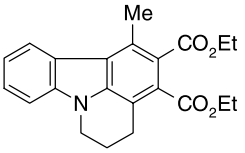
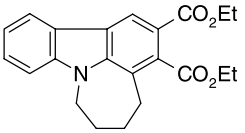
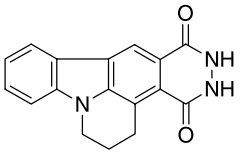
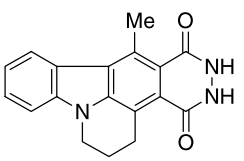
In all cases where pyridazinedicarboxylic acid diesters (compounds of type **18**, **19**, and **23**) were employed in the IDA reaction, we observed the formation of small amounts of side products in which one of the two ester groups is replaced by hydrogen, as exemplified by the isolation and characterization of ethyl 10-methoxy-5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazole-3-carboxylate[30] from the cycloaddition of compound **18a**. As a possible explanation for this side reaction, one may assume partial hydrolysis of the diester by traces of water, followed by thermally induced decarboxylation.[31] Moreover, we investigated the possibility of performing the sequence starting from the indoline-tethered dihydropyridazines **16**, **17** via the aromatic pyridazines **18**, **19** into the carbazoles **32**, **33** as a one-pot reaction by refluxing the starting material in TIPB in the presence of air oxygen with palladium/carbon as a catalyst. Indeed, the expected domino reaction (double dehydrogenation–cycloaddition–cycloreversion–dehydrogenation) takes place under these conditions, as the formation of the corresponding carbazoles could be detected by GLC–MS and TLC. However, yields are very low and large amounts of decomposition products are formed, so that this one-pot variant is of no preparative use.

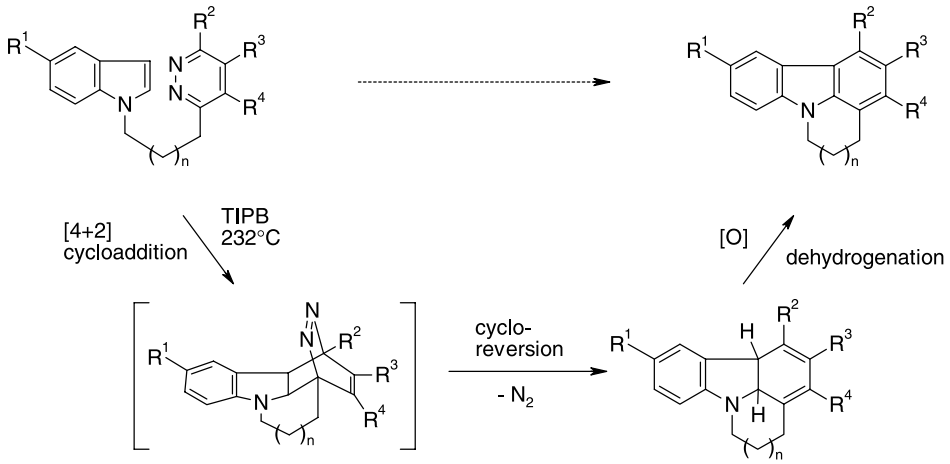
The highest yields of cycloaddition products (75 and 64% for compounds **35** and **36**, respectively) were obtained on employment of the pyridazine-fused pyridazinediones **24** and **25** as diazadienes (entries 10 and 11), and also the observed conversion rates were higher with these educts. Even with compound **25**, in which the diazadiene structure is sterically more crowded than in **24**, the transformation is complete within 24 h of refluxing, as compared to 50 h for the esters **19**. Inspection of the energy gaps between the involved frontier molecular orbitals (calculated with the PM3 method[32]) indicates a slight advantage for the bicyclic pyridazines **24** (ΔE: 6.89 eV) and **25** (ΔE: 6.93 eV) towards their monocyclic counterparts **18b** (ΔE: 7.11 eV) and **19b** (ΔE: 7.16 eV).[33] Moreover, a beneficial effect on reaction rates may be assumed to arise from the forced coplanarity of the CO groups with the pyridazine ring in **24** and **25**,



Scheme 5.

Table 1. Intramolecular [4+2] cycloaddition reactions of indolylalkylpyridazines

Entry	Educt	Product	Structure	Time	Yield (%)
1	**6a**	**29**		14 d	8
2	**7a**	**30a**		4 d	8
3	**7b**	**30b**		4 d	25
4	**28**	**31**		15 h	21
5	**18a**	**32a**		17 h	51
6	**18b**	**32b**		17 h	55
7	**19a**	**33a**		50 h	41
8	**19b**	**33b**		50 h	43
9	**23**	**34**		67 h	36
10	**24**	**35**		17 h	75
11	**25**	**36**		24 h	64



Scheme 6. General pathway of the cycloaddition reactions (for individual structures, see Table 1).

minimizing steric hindrance at this part of the diene structure, again in comparison to the esters **18**, **19**.

Cycloaddition products **29**–**34** were isolated by column chromatography whereas compounds **35** and **36** precipitated from the reaction mixtures. In all cases, the structures of the polycyclic products follow unambiguously from their elemental compositions and spectral data. In particular, the marked downfield shift of the carbazole proton which initially was 4-H in the indole precursor proved to be a convenient diagnostic tool in combination with significant NOE's which can be observed between this particular carbazole H at ring A and the neighbouring substituent R^2 (either H or CH_3) at ring C.

3. Conclusion

It can be stated that, despite its relatively high LUMO energy (as compared to 1,2,4-triazine and 1,2,4,5-tetrazine), the 1,2-diazine system is able to act as a diazadiene in intramolecular inverse-electron-demand Diels–Alder reactions with appropriately tethered indole dienophiles. Whereas unactivated pyridazines undergo these thermally induced [4+2] cycloaddition reactions only very sluggishly, the examples with more electron-deficient pyridazines, especially pyridazinediesters and pyridazino[4,5-*d*]pyridazinediones clearly demonstrate the synthetic usefulness of the intramolecular IDA strategy for the construction of polycyclic carbazoles. The target ring systems, which are of interest as core structures of new antitumour agents, are difficult to prepare via other routes[34] or (as in the case of compounds **30**, **35/36**) represent previously unknown ring systems.

4. Experimental

4.1. General

Melting points were determined on a Kofler hot-stage microscope (Reichert) and are uncorrected. Silica gel plates (Merck, KGF_{254}) and silica gel 60 (Merck, 0.063–0.200 mm) were used for TLC and column chromatography. Medium-pressure liquid chromatography (MPLC) was carried out on Merck LiChroprep Si 60 (0.040–0.063 mm) with UV detection at 280 nm. Analytical grade solvents (Merck) were used, petroleum ether (PE) refers to the fraction of bp 50–70 °C. 1,3,5-Triisopropylbenzene (TIPB) was stored over Linde molecular sieves (0.4 nm). IR spectra were measured for KBr pellets on a Perkin–Elmer 1605 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Varian Unity-Plus 300 spectrometer at 300 MHz. Mass spectra were obtained on a Hewlett–Packard 5890A/5970B GC-MSD or on a Shimadzu QP5050A DI 50 instrument. High-resolution mass spectra were measured on a Finnigan MAT 8230 at the Department of Organic Chemistry, University of Vienna. Microanalyses were performed at the Department of Physical Chemistry (Microanalytical Laboratory), University of Vienna. For semiempirical MO calculations, the MOPAC program as contained in the SYBYL 6.9 software package (Tripos Inc.) was used.

4.2. Preparation of cycloaddition educts

4.2.1. 5-Methoxy-1-prop-2-yn-1-yl-1*H*-indole (1a). To a solution of 5-methoxyindole (1.47 g, 10 mmol) and propargyl bromide (2.23 g of a 80% solution in toluene, 15 mmol) in toluene (30 mL) were added tetrabutylammonium bromide (0.161 g, 0.5 mmol) and 50% aqueous NaOH (6 mL). The two-phase mixture was vigorously stirred at rt for 1 h. Toluene (10 mL) was added and the layers were separated. The organic layer was washed with water, dried over Na_2SO_4, and the solvent was removed in vacuo to give an oil which slowly solidified. Recrystallization from ether/PE gave **1a** as yellow crystals (1.40 g, 74%): mp 65–69 °C. IR 3246, 2958, 2833, 2122, 1618, 1575, 1487, 1432, 1240, 1154, 1027, 840, 798, 725, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.32 (d, J_{6-7}=8.9 Hz, 1H, 7-H), 7.19 (d, J_{2-3}=3.2 Hz, 1H, 2-H), 7.13 (d, J_{4-6}=2.4 Hz, 1H, 4-H), 6.94 (dd, J_{6-7}=8.9 Hz, J_{4-6}=2.4 Hz, 1H, 6-H), 6.48 (d, J_{2-3}=3.2 Hz, 1H, 3-H), 4.85 (d, J=2.4 Hz, 2H, NCH_2-CCH), 3.88 (s, 3H, OCH_3), 2.41 (t, J=2.4 Hz, 1H, NCH_2CCH); MS (EI, 70 eV) *m*/*z* 185 (M^+, 100%), 170 (86), 146 (19), 142 (22), 115 (25), 103 (23), 89 (11), 76 (26), 63 (18), 51 (24). Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.56; H, 6.16; N, 7.48.

4.2.2. 5-Methoxy-1-(3-pyridazin-3-ylprop-2-yn-1-yl)-1*H*-indole (4a). To a solution of **1a** (0.601 g, 3.25 mmol)

and 3-iodopyridazine[24,25] (**2**) (0.536 g, 2.6 mmol) in THF (6 mL) were added triethylamine (1.0 mL, 7.2 mmol), CuI (0.015 g, 0.08 mmol) and $Pd(PPh_3)_2Cl_2$ (0.055 g, 0.08 mmol). The mixture was flushed with argon, then it was stirred under argon at rt for 5 h. The solid material was removed by filtration and carefully rinsed with THF. The combined filtrate and washings were concentrated under reduced pressure, and the residue was subjected to column chromatography (EtOAc/PE, 4:1) to afford **4a** (0.320 g, 46%) as brownish crystals: mp 95–98 °C (from EtOAc). IR 3050, 2914, 2837, 2234, 1620, 1571, 1488, 1438, 1242, 1151, 1132, 1025, 803, 720, 596 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.13 (dd, J_{5-6}=5.1 Hz, J_{4-6}=1.7 Hz, 1H, pyridazine 6-H), 7.50 (dd, J_{4-5}=8.4 Hz, J_{4-6}=1.7 Hz, 1H, pyridazine 4-H), 7.45–7.35 (m, 2H, pyridazine 5-H, indole 7-H), 7.23 (d, J_{2-3}=3.0 Hz, 1H, indole 2-H), 7.12 (d, J_{4-6}=2.6 Hz, 1H, indole 4-H), 6.94 (dd, J_{6-7}=8.7 Hz, J_{4-6}=2.6 Hz, 1H, indole 6-H), 6.49 (d, J_{2-3}=3.0 Hz, 1H, indole 3-H), 5.17 (s, 2H, NCH_2), 3.87 (s, 3H, OCH_3); MS (EI, 70 eV) *m/z* 263 (M^+, 100%), 248 (15), 220 (76), 192 (22), 166 (9), 140 (9), 110 (7), 89 (8), 76 (10), 63 (15), 51 (8); HRMS (EI, 70 eV) *m/z* 263.1070 (M^+ calcd for $C_{16}H_{13}N_3O$: 263.1059). Anal. Calcd for $C_{16}H_{13}N_3O$. $0.3H_2O$: C, 71.52; H, 5.10; N, 15.64. Found: C, 71.59; H, 5.08; N, 15.51.

4.2.3. 1-[3-(5-Methoxy-1*H*-indol-1-yl)prop-1-yn-1-yl]phthalazine (5a). This compound was prepared as described for **4a**, starting from 1-iodophthalazine[26] (**3**) (0.666 g, 2.6 mmol) instead of **2**. Chromatographic work-up (EtOAc) afforded **5a** (0.400 g, 49%) as brownish crystals: mp 143–145 °C (from EtOAc). IR 3091, 2954, 2831, 2242, 1621, 1485, 1396, 1239, 1150, 1028, 758, 593 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.46 (s, 1H, phthalazine 4-H), 8.12–8.04 (m, 1H, phthalazine 8-H), 7.98–7.80 (m, 3H, phthalazine 5-H, 6-H, 7-H), 7.46 (d, J_{6-7}=8.8 Hz, 1H, indole 7-H), 7.30 (d, J_{2-3}=3.1 Hz, 1H, indole 2-H), 7.15 (d, J_{4-6}=2.4 Hz, 1H, indole 4-H), 6.96 (dd, J_{6-7}=8.8 Hz, J_{4-6}=2.4 Hz, 1H, indole 6-H), 6.52 (d, J_{2-3}=3.1 Hz, 1H, indole 3-H), 5.29 (s, 2H, NCH_2), 3.87 (s, 3H, OCH_3); MS (EI, 70 eV) *m/z* 313 (M^+, 4%), 170 (100), 156 (12), 115 (11), 102 (12), 76 (12), 69 (37), 63 (10), 51 (14). Anal. Calcd for $C_{20}H_{15}N_3O$: C, 76.66; H, 4.82; N, 13.41. Found: C, 76.43; H, 5.05; N, 13.12.

4.2.4. 1-[3-(1*H*-Indol-1-yl)prop-1-yn-1-yl]phthalazine (5b). This compound was prepared as described for **4a**, starting from 1-iodophthalazine[26] (**3**) (0.666 g, 2.6 mmol) instead of **2** and 1-prop-2-yn-1-yl-1*H*-indole[35] (**1b**) (0.504 g, 3.25 mmol) instead of **1a**. Chromatographic work-up (EtOAc) afforded **5b** (0.400 g, 54%) as brownish crystals: mp 145–148 °C (from EtOAc). IR 3053, 2952, 2238, 1483, 1463, 1353, 1187, 749, 731, 594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.45 (s, 1H, phthalazine 4-H), 8.10–8.04 (m, 1H, phthalazine 8-H), 7.97–7.80 (m, 3H, phthalazine 5-H, 6-H, 7-H), 7.68 (d, J_{4-5}=7.8 Hz, 1H, indole 4-H), 7.56 (d, J_{6-7}=8.1 Hz, 1H, indole 7-H), 7.35–7.26 (m, 2H, indole 2-H, 6-H), 7.22–7.14 (m, 1H, indole 5-H), 6.60 (d, J_{2-3}=3.3 Hz, 1H, indole 3-H), 5.32 (s, 2H, NCH_2); MS (EI, 70 eV) *m/z* 283 (M^+, 88%), 282 (100), 266 (6), 255 (39), 228 (6), 154 (23), 139 (63), 128 (20), 116 (22), 113 (27), 101 (7), 89 (47), 75 (11), 63 (41), 50 (13), 43 (32). Anal. Calcd for $C_{19}H_{13}N_3$. $0.2H_2O$: C, 79.53; H, 4.71; N, 14.64. Found: C, 79.52; H, 4.77; N, 14.59.

4.2.5. 5-Methoxy-1-(3-pyridazin-3-ylpropyl)-1*H*-indole (6a). A solution of **4a** (0.200 g, 0.76 mmol) in EtOAc (100 mL), containing Pd/C catalyst (10%, 0.065 g), was hydrogenated in a Parr apparatus at a pressure of 50 psi until TLC (EtOAc) indicated the end of the reaction (65 h). The catalyst was filtered off and washed with EtOAc and EtOH. The combined filtrate and washings were concentrated under reduced pressure and the residue was purified by MPLC (EtOAc) to give **6a** (0.118 g, 58%) as a pale yellow oil. IR 2936, 2830, 1621, 1576, 1488, 1449, 1437, 1239, 1151, 1031, 801, 722 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.05 (dd, J_{5-6}=4.9 Hz, J_{4-6}=1.8 Hz, 1H, pyridazine 6-H), 7.35 (dd, J_{4-5}=8.4 Hz, J_{5-6}=4.9 Hz, 1H, pyridazine 5-H), 7.24–7.16 (m, 2H, pyridazine 4-H, indole 7-H), 7.12–7.06 (m, 2H, indole 2-H, 4-H), 6.87 (dd, J_{6-7}=9.0 Hz, J_{4-6}=2.4 Hz, 1H, indole 6-H), 6.40 (d, J_{2-3}=3.0 Hz, 1H, indole 3-H), 4.24 (t, J=6.6 Hz, 2H, $NCH_2CH_2CH_2$), 3.86 (s, 3H, OCH_3), 2.98 (t, J=7.5 Hz, 2H, $NCH_2CH_2CH_2$), 2.48–2.35 (m, 2H, $NCH_2CH_2CH_2$); MS (EI, 70 eV) *m/z* 267 (M^+, 25%), 173 (100), 158 (39), 130 (13), 121 (17), 117 (25), 103 (12), 94 (49), 77 (11); HRMS (EI, 70 eV) *m/z* 267.1383 (M^+ calcd for $C_{16}H_{17}N_3O$: 267.1372).

4.2.6. 1-(3-Chloropropyl)-5-methoxy-1*H*-indole (8a). A mixture of 5-methoxyindole (2.94 g, 20 mmol) and finely powdered KOH (85%; 1.72 g, 26 mmol) in DMSO (47 mL) was sonicated in an ultrasound cleaning bath for 10 min. It was cooled to 0 °C, and 1-bromo-3-chloropropane (9.42 g, 60 mmol) was added dropwise. The mixture was stirred at rt for 4 h, then it was poured into ice-water (100 mL) and extracted with EtOAc. The organic layer was washed with water and brine, and dried over Na_2SO_4. The volatile components were removed in vacuo (first 10 mbar, then 10^{-2} mbar) and the residue was subjected to column chromatography (EtOAc/PE, 1:9) to afford **8a** (4.26 g, 96%) as a colorless oil. IR 2994, 2945, 2830, 1622, 1488, 1449, 1239, 1151, 1031, 802, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27 (d, J_{6-7}=9.0 Hz, 1H, 7-H), 7.15–7.09 (m, 2H, 2-H, 4-H), 6.90 (dd, J_{6-7}=9.0 Hz, J_{4-6}=2.4 Hz, 1H, 6-H), 6.44 (d, J_{2-3}=3.3 Hz, 1H, 3-H), 4.31 (t, J=6.3 Hz, 2H, $NCH_2CH_2CH_2$), 3.87 (s, 3H, OCH_3), 3.46 (t, J=6.1 Hz, 2H, $NCH_2CH_2CH_2$), 2.32–2.20 (m, 2H, $NCH_2CH_2CH_2$); MS (EI, 70 eV) *m/z* 225 (M^+, 11%), 223 (M^+, 35), 208 (12), 160 (100), 145 (16), 130 (7), 117 (49), 103 (14), 89 (15), 76 (15), 63 (12), 51 (16); HRMS (EI, 70 eV) *m/z* 223.0768 (M^+ calcd for $C_{12}H_{14}ClNO$: 223.0764).

4.2.7. 1-[3-(5-Methoxy-1*H*-indol-1-yl)propyl]phthalazine (7a). *Method A*. A solution of **5a** (0.160 g, 0.51 mmol) in EtOAc (100 mL), containing Pd/C catalyst (10%, 0.040 g), was hydrogenated in a Parr apparatus at a pressure of 50 psi until TLC (EtOAc) indicated the end of the reaction (65 h). The catalyst was filtered off and washed with EtOAc and EtOH. The combined filtrate and washings were concentrated under reduced pressure and the residue was purified by MPLC (EtOAc) to give **7a** (0.065 g, 40%) as a pale yellow oil.

Method B. Magnesium turnings (0.60 g, 25 mmol) were suspended in dry THF (5 mL) and the reaction was initiated by addition of 1,2-dibromoethane (0.26 mL, 3 mmol). Then, a solution of **8a** (3.00 g, 13.5 mmol) in dry THF (10 mL) was added dropwise, and the mixture was refluxed for 0.5 h.

A solution of phthalazine (1.17 g, 9 mmol) in dry THF (10 mL) was added dropwise, and refluxing was continued for 5 h. After cooling, the mixture was poured into a solution of NH_4Cl (3.4 g) in ice-water (100 mL), and it was exhaustively extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and evaporated in vacuo to afford an oily residue (containing the dihydrophthalazine **9a**) which was immediately used for the following step without purification: the residue was dissolved in toluene (10 mL) and a solution of $K_3Fe(CN)_6$ (13.5 g, 41 mmol) in water (63 mL) as well as a solution of KOH (6.75 g, 120 mmol) in water (32 mL) were added. The mixture was vigorously stirred at rt for 2 h, then it was neutralized with AcOH and exhaustively extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and evaporated in vacuo. The residue was subjected to MPLC (EtOAc) to give **7a** (1.64 g, 57%) as a pale yellow oil. IR 2935, 2830, 1620, 1488, 1449, 1238, 1151, 1031, 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.41 (s, 1H, phthalazine 4-H), 7.97–7.90 (m, 1H, phthalazine 5-H), 7.89–7.70 (m, 3H, phthalazine 6-H, 7-H, 8-H), 7.23 (d, J_{6-7}=8.8 Hz, 1H, indole 7-H), 7.14 (d, J_{2-3}=3.0 Hz, 1H, indole 2-H), 7.11 (d, J_{4-6}=2.5 Hz, 1H, indole 4-H), 6.84 (dd, J_{6-7}=8.8 Hz, J_{4-6}=2.5 Hz, 1H, indole 6-H), 6.43 (d, J_{2-3}=3.0 Hz, 1H, indole 3-H), 4.34 (t, J=6.7 Hz, 2H, $NCH_2CH_2CH_2$), 3.86 (s, 3H, OCH_3), 3.29 (t, J=7.5 Hz, 2H, $NCH_2CH_2CH_2$), 2.60–2.46 (m, 2H, $NCH_2CH_2CH_2$); MS (EI, 70 eV) *m/z* 317 (M^+, 6%), 173 (34), 158 (15), 144 (100), 130 (6), 117 (12), 103 (5); HRMS (EI, 70 eV) *m/z* 317.1533 (M^+ calcd for $C_{20}H_{19}N_3O$: 317.1528).

4.2.8. 1-[3-(1*H*-Indol-1-yl)propyl]phthalazine (7b). *Method A*. Catalytic hydrogenation of **5b** (0.200 g, 0.71 mmol) as described for the preparation of **7a** from **5a** gave **7b** (0.110 g, 54%) as a pale yellow oil.

Method B. Grignard reaction and subsequent oxidation, as described for the preparation of **7a** from **8a**, starting from 1-(3-chloropropyl)-1*H*-indole[27] (**8b**) (2.60 g, 13.5 mmol) afforded **7b** (1.32 g, 51%) as a pale yellow oil. IR 3095, 2951, 2927, 1509, 1454, 1444, 1309, 1224, 756, 743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.44 (s, 1H, phthalazine 4-H), 7.99–7.92 (m, 1H, phthalazine 5-H), 7.91–7.73 (m, 3H, phthalazine 6-H, 7-H, 8-H), 7.67 (d, J_{4-5}=7.6 Hz, 1H, indole 4-H), 7.37 (d, J_{6-7}=8.4 Hz, 1H, indole 7-H), 7.26–7.17 (m, 2H, indole 2-H, 6-H), 7.17–7.08 (m, 1H, indole 5-H), 6.54 (d, J_{2-3}=3.0 Hz, 1H, indole 3-H), 4.41 (t, J=6.6 Hz, 2H, $NCH_2CH_2CH_2$), 3.33 (t, J=7.3 Hz, 2H, $NCH_2CH_2CH_2$), 2.66–2.51 (m, 2H, $NCH_2CH_2CH_2$); MS (EI, 70 eV) *m/z* 287 (M^+, 3%), 144 (100), 130 (6), 117 (7), 103 (6), 89 (8), 77 (10), 63 (5), 51 (4); HRMS (EI, 70 eV) *m/z* 287.1427 (M^+ calcd for $C_{19}H_{17}N_3$: 287.1422).

4.2.9. Diethyl 3-[3-(5-methoxy-1*H*-indol-1-yl)propa-1,2-dien-1-yl]pyridazine-4,5-dicarboxylate (11). To a solution of diethyl 3-iodopyridazine-4,5-dicarboxylate[24] (**10**) (2.70 g, 7.71 mmol) and **1a** (1.78 g, 9.64 mmol) in THF (16 mL) were added triethylamine (3.0 mL, 21.6 mmol), CuI (0.044 g, 0.23 mmol) and $Pd(PPh_3)_2Cl_2$ (0.162 g, 0.23 mmol). The mixture was flushed with argon, then it was refluxed under argon for 3 h. Another portion of **1a** (0.71 g, 3.86 mmol) was added and refluxing was continued for 3 h. The solid material was removed by filtration and carefully rinsed with THF. The combined filtrate and washings were concentrated under reduced pressure, and the residue was taken up in warm toluene (100 mL, 50 °C) and filtered again. Removal of the solvent in vacuo gave an oil which was subjected to column chromatography (toluene/EtOAc, 39:1) to afford the allene **11** (1.63 g, 52%) as a dark-red oil. IR 2981, 2934, 1739, 1715, 1548, 1473, 1263, 1187, 1032, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.62 (s, 1H, pyridazine 6-H, shows positive NOE on irradiation of the quartet at 4.40 ppm), 7.45 (d, J_{2-3}=3.5 Hz, 1H, indole 2-H), 7.20–7.10 (m, 3H, NC*H*CCH, indole 4-H, 7-H), 6.94–6.86 (m, 2H, NCHCC*H*, indole 6-H, shows positive NOE on irradiation of the quartet at 4.59 ppm), 6.72 (d, J_{2-3}=3.5 Hz, 1H, indole 3-H), 4.59 (q, J=7.1 Hz, 2H, pyridazine 4-$CO_2CH_2CH_3$, 4.40 (q, J=7.1 Hz, 2H, pyridazine 5-$CO_2CH_2CH_3$, 3.88 (s, 3H, OCH_3), 1.49 (t, J=7.1 Hz, 3H, pyridazine 4-$CO_2CH_2CH_3$), 1.40 (t, J=7.1 Hz, 3H, pyridazine 5-$CO_2CH_2CH_3$, shows positive NOE on irradiation of the quartet at 4.40 ppm); MS (EI, 70 eV) *m/z* 407 (M^+, 100%), 379 (15), 351 (10), 307 (20), 292 (7), 264 (19), 246 (8), 218 (12), 192 (18), 164 (8), 132 (7), 103 (6), 88 (6); HRMS (EI, 70 eV) *m/z* 407.1488 (M^+ calcd for $C_{22}H_{21}N_3O_5$: 407.1481).

4.2.10. 5-Methoxy-1-prop-2-yn-1-ylindoline (12a). To a solution of 5-methoxyindoline[36] (1.50 g, 10.8 mmol) in toluene (20 mL) were added Na_2CO_3 (2.42 g, 22.8 mmol) and propargyl bromide (2.64 g of a 80% solution in toluene, 17.1 mmol), and the mixture was stirred under argon at rt for 20 h. The inorganic material was removed by filtration and the filtrate was evaporated in vacuo. Column chromatography (neutral Al_2O_3; EtOAc/PE, 1:19) of the residue gave **12a** (1.44 g, 68%) as a pale yellow oil which slowly solidified: mp 46–48 °C. IR 3262, 2930, 2844, 2105, 1593, 1490, 1433, 1288, 1238, 1137, 1026, 868, 801, 655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.79–6.75 (m, 1H, 4-H), 6.71–6.64 (m, 1H, 6-H), 6.53 (d, J_{6-7}=8.4 Hz, 1H, 7-H), 3.89 (d, J=2.4 Hz, 2H, NCH_2CCH), 3.76 (s, 3H, OCH_3), 3.39 (t, J_{2-3}=8.0 Hz, 2H, 2-H), 2.95 (t, J_{2-3}=8.0 Hz, 2H, 3-H), 2.15 (t, J=2.4 Hz, 1H, NCH_2CCH); MS (EI, 70 eV) *m/z* 187 (M^+, 66%), 172 (69), 148 (100), 133 (71), 117 (36), 104 (39), 91 (23), 77 (28), 63 (17), 51 (18). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.94; H, 7.11; N, 7.47.

4.2.11. Diethyl 3-[3-(5-methoxy-2,3-dihydro-1*H*-indol-1-yl)prop-1-yn-1-yl]pyridazine-4,5-dicarboxylate (14a). To a solution of **12a** (0.608 g, 3.25 mmol) and diethyl 3-iodopyridazine-4,5-dicarboxylate[24] (**10**) (0.910 g, 2.6 mmol) in THF (6 mL) were added triethylamine (1.0 mL, 7.2 mmol), CuI (0.015 g, 0.08 mmol) and $Pd(PPh_3)_2Cl_2$ (0.055 g, 0.08 mmol). The mixture was flushed with argon, then it was stirred under argon at rt for 7 h. The solid material was removed by filtration and carefully rinsed with THF. The combined filtrate and washings were concentrated under reduced pressure, and the residue was subjected to column chromatography (EtOAc/PE, 2:3) to afford **14a** (0.734 g, 69%) as a brownish oil. IR 2982, 2937, 2832, 2235, 1735, 1491, 1337, 1291, 1237, 1026, 804 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.53 (s, 1H, pyridazine 6-H), 6.79–6.40 (m, 1H, indoline 4-H), 6.67 (dd, J_{6-7}=8.4 Hz, J_{4-6}=2.7 Hz, 1H, indoline 6-H), 6.54 (d, J_{6-7}=8.4 Hz, 1H, indoline 7-H), 4.43 (q, J=7.2 Hz, 2H, CH_2CH_3), 4.21 (s, 2H, propargyl CH_2), 4.18 (q, J=7.2 Hz,

2H, CH_2CH$_3$), 3.75 (s, 3H, OCH$_3$), 3.46 (t, J_{2-3}=8.0 Hz, 2H, indoline 2-H), 2.98 (t, J_{2-3}=8.0 Hz, 2H, indoline 3-H), 1.40 (t, J=7.2 Hz, 3H, CH$_2$CH_3), 1.27 (t, J=7.2 Hz, 3H, CH$_2$CH_3); MS (EI, 70 eV) m/z 409 (M$^+$, 8%), 262 (11), 233 (12), 148 (28), 133 (18), 77 (12), 58 (100); HRMS (EI, 70 eV) m/z 409.1656 (M$^+$ calcd for $C_{22}H_{23}N_3O_5$: 409.1638).

4.2.12. Diethyl 3-[3-(2,3-dihydro-1*H*-indol-1-yl)prop-1-yn-1-yl]pyridazine-4,5-dicarboxylate (14b). This compound was prepared as described for **14a**, starting from 1-prop-2-yn-1-ylindoline[28] (**12b**) (0.510 g, 3.25 mmol) instead of **12a**. Column chromatography (EtOAc/PE, 1:3) gave **14b** (0.757 g, 77%) as a brownish oil. IR 2981, 2849, 2236, 1734, 1487, 1286, 1024, 750 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 9.53 (s, 1H, pyridazine 6-H), 7.16–7.07 (m, 2H, indoline 4-H, 6-H), 6.79–6.71 (m, 1H, indoline 5-H), 6.61 (d, J_{6-7}=7.8 Hz, 1H, indoline 7-H), 4.42 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 4.27 (s, 2H, propargyl CH$_2$), 4.14 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 3.51 (t, J_{2-3}=8.0 Hz, 2H, indoline 2-H), 3.02 (t, J_{2-3}=8.0 Hz, 2H, indoline 3-H), 1.39 (t, J=7.2 Hz, 3H, CH$_2$CH_3), 1.25 (t, J=7.2 Hz, 3H, CH$_2$CH_3); MS (EI, 70 eV) m/z 379 (M$^+$, 11%), 304 (9), 262 (53), 233 (100), 205 (20), 188 (30), 160 (19), 118 (72), 91 (43), 65 (14); HRMS (EI, 70 eV) m/z 379.1517 (M$^+$ calcd for $C_{21}H_{21}N_3O_4$: 379.1532).

4.2.13. Diethyl 3-[3-(5-methoxy-2,3-dihydro-1*H*-indol-1-yl)prop-1-yn-1-yl]-6-methylpyridazine-4,5-dicarboxylate (15a). This compound was prepared as described for **14a**, starting from diethyl 3-iodo-6-methylpyridazine-4,5-dicarboxylate[24] (**13**) (0.946 g, 2.6 mmol) instead of **10**. Column chromatography (EtOAc/PE, 2:3) gave **15b** (0.970 g, 88%) as a brownish oil. IR 2982, 2936, 2832, 2236, 1739, 1491, 1242, 1037 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 6.78–6.73 (m, 1H, indoline 4-H), 6.66 (dd, J_{6-7}=8.5 Hz, J_{4-6}=2.5 Hz, 1H, indoline 6-H), 6.55 (d, J_{6-7}=8.5 Hz, 1H, indoline 7-H), 4.40 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 4.20 (s, 2H, propargyl CH$_2$), 4.16 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 3.75 (s, 3H, OCH$_3$), 3.47 (t, J_{2-3}=8.0 Hz, 2H, indoline 2-H), 2.97 (t, J_{2-3}=8.0 Hz, 2H, indoline 3-H), 2.85 (s, 3H, CH$_3$), 1.37 (t, J=7.2 Hz, 3H, CH$_2$CH_3), 1.27 (t, J=7.2 Hz, 3H, CH$_2$CH_3); MS (EI, 70 eV) m/z 423 (M$^+$, 7%), 276 (10), 247 (15), 203 (11), 148 (100), 133 (77), 117 (27), 101 (19), 77 (13); HRMS (EI, 70 eV) m/z 423.1810 (M$^+$ calcd for $C_{23}H_{25}N_3O_5$: 423.1794).

4.2.14. Diethyl 3-[3-(2,3-dihydro-1*H*-indol-1-yl)prop-1-yn-1-yl]-6-methylpyridazine-4,5-dicarboxylate (15b). This compound was prepared as described for **14a**, starting from 1-prop-2-yn-1-ylindoline[28] (**12b**) (0.510 g, 3.25 mmol) instead of **12a** and diethyl 3-iodo-6-methylpyridazine-4,5-dicarboxylate[24] (**13**) (0.946 g, 2.6 mmol) instead of **10**. Column chromatography (EtOAc/PE, 1:2) gave **15b** (0.980 g, 96%) as a brownish oil. IR 2981, 2936, 2846, 2235, 1739, 1488, 1386, 1244, 1036, 750 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.16–7.06 (m, 2H, indoline 4-H, 6-H), 6.78–6.69 (m, 1H, indoline 5-H), 6.62 (d, J_{6-7}=7.8 Hz, 1H, indoline 7-H), 4.39 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 4.25 (s, 2H, propargyl CH$_2$), 4.12 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 3.51 (t, J_{2-3}=8.0 Hz, 2H, indoline 2-H), 3.00 (t, J_{2-3}=8.2 Hz, 2H, indoline 3-H), 2.85 (s, 3H, CH$_3$), 1.37 (t, J=7.2 Hz, 3H, CH$_2$CH_3), 1.24 (t, J=7.2 Hz, 3H, CH$_2$CH_3); MS (EI, 70 eV) m/z 393 (M$^+$, 11%), 347 (7), 318 (14), 276 (70), 247 (100), 219 (21), 203 (50), 174 (17), 147 (14), 132 (27), 118 (50), 91 (52), 65 (16); HRMS (EI, 70 eV) m/z 393.1682 (M$^+$ calcd for $C_{22}H_{23}N_3O_4$: 393.1689).

4.2.15. Diethyl 3-[3-(5-methoxy-1*H*-indol-1-yl)propyl]-pyridazine-4,5-dicarboxylate (18a). A solution of **14a** (0.630 g, 1.54 mmol) in EtOH (200 mL) containing Pd/C catalyst (10%, 0.130 g), was hydrogenated in a Parr apparatus at a pressure of 60 psi for 45 h. The catalyst was filtered off and washed with EtOH and EtOAc. The combined filtrate and washings were concentrated under reduced pressure to afford a brown oil (0.625 g) containing the dihydropyridazine **16a**.[37] This material was dissolved in xylene (61 mL), Pd/C catalyst (10%, 0.260 g) was added, and the mixture was refluxed with vigorous stirring for 62 h (reaction monitoring by GLC–MS). The catalyst was filtered off and washed with hot EtOH and hot EtOAc. The combined filtrate and washings were concentrated under reduced pressure and the residue was subjected to column chromatography (EtOAc/PE, 1:2) to afford **18a** (0.225 g, 35%) as a brownish oil. IR 2981, 2937, 1734, 1489, 1298, 1239, 1152, 1032, 802 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 9.54 (s, 1H, pyridazine 6-H), 7.24 (d, J_{6-7}=8.9 Hz, 1H, indole 7-H), 7.11 (d, J_{2-3}=3.0 Hz, 1H, indole 2-H), 7.09 (d, J_{4-6}=2.6 Hz, 1H, indole 4-H), 6.88 (dd, J_{6-7}=8.9 Hz, J_{4-6}=2.6 Hz, 1H, indole 6-H), 6.42 (d, J_{2-3}=3.0 Hz, 1H, indole 3-H), 4.43 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 4.32–4.19 (m, 4H, CH_2CH$_3$, NCH_2CH$_2$CH$_2$), 3.85 (s, 3H, OCH$_3$), 2.98 (t, J=7.6 Hz, 2H, NCH$_2$CH$_2$CH_2), 2.50–2.35 (m, 2H, NCH$_2$CH_2CH$_2$), 1.40 (t, J=7.2 Hz, 3H, CH$_2$CH_3), 1.24 (t, J=7.2 Hz, 3H, CH$_2$CH_3); MS (EI, 70 eV) m/z 411 (M$^+$, 8%), 238 (11), 209 (10), 173 (100), 165 (15), 158 (27), 130 (9), 117 (21), 65 (7); HRMS (EI, 70 eV) m/z 411.1811 (M$^+$ calcd for $C_{22}H_{25}N_3O_5$: 411.1794).

4.2.16. Diethyl 3-[3-(1*H*-indol-1-yl)propyl]pyridazine-4,5-dicarboxylate (18b). This compound was prepared as described for **18a**, starting from **14b** (0.710 g, 1.87 mmol). Column chromatography (EtOAc/PE, 1:3) gave **18b** (0.250 g, 35%) as a pale yellow oil. IR 2980, 2936, 1733, 1464, 1369, 1297, 1201, 1013, 742 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 9.54 (s, 1H, pyridazine 6-H), 7.63 (d, J_{4-5}=7.8 Hz, 1H, indole 4-H), 7.35 (d, J_{6-7}=8.1 Hz, 1H, indole 7-H), 7.26–7.17 (m, 1H, indole 6-H), 7.14 (d, J_{2-3}=3.2 Hz, 1H, indole 2-H), 7.13–7.06 (m, 1H, indole 5-H), 6.51 (d, J_{2-3}=3.2 Hz, 1H, indole 3-H), 4.42 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 4.30 (t, J=6.6 Hz, 2H, NCH_2CH$_2$CH$_2$), 4.21 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 2.99 (t, J=7.6 Hz, 2H, NCH$_2$CH$_2$CH_2), 2.52–2.37 (m, 2H, NCH$_2$CH_2CH$_2$), 1.40 (t, J=7.2 Hz, 3H, CH$_2$CH_3), 1.22 (t, J=7.2 Hz, 3H, CH$_2$CH_3); MS (EI, 70 eV) m/z 381 (M$^+$, 16%), 335 (4), 290 (7), 264 (7), 238 (100), 209 (72), 164 (63), 143 (62), 130 (57), 94 (17), 77 (20), 63 (8); HRMS (EI, 70 eV) m/z 381.1679 (M$^+$ calcd for $C_{21}H_{23}N_3O_4$: 381.1689).

4.2.17. Diethyl 3-[3-(5-methoxy-1*H*-indol-1-yl)propyl]-6-methylpyridazine-4,5-dicarboxylate (19a). This compound was prepared as described for **18a**, starting from **15a** (0.916 g, 2.17 mmol). Column chromatography (EtOAc/PE, 1:2) gave **19a** (0.300 g, 33%) as a brownish oil. IR 2982, 2937, 1737, 1489, 1238, 1031, 802, 718 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.23 (d, J_{6-7}=8.7 Hz, 1H, indole 7-H),

7.12 (d, J_{2-3}=3.0 Hz, 1H, indole 2-H), 7.09 (d, J_{4-6}= 2.4 Hz, 1H, indole 4-H), 6.87 (dd, J_{6-7}=8.7 Hz, J_{4-6}= 2.4 Hz, 1H, indole 6-H), 6.41 (d, J_{2-3}=3.0 Hz, 1H, indole 3-H), 4.40 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 4.24 (t, J=6.6 Hz, 2H, NCH_2CH$_2$CH$_2$), 4.19 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 3.85 (s, 3H, OCH$_3$), 3.05 (t, J=7.6 Hz, 2H, NCH$_2$CH$_2$CH_2), 2.83 (s, 3H, CH$_3$), 2.45–2.30 (m, 2H, NCH$_2$CH_2CH$_2$), 1.38 (t, J=7.2 Hz, 3H, CH$_2$CH_3), 1.22 (t, J=7.2 Hz, 3H, CH$_2$CH_3); MS (EI, 70 eV) *m/z* 425 (M^+, 42%), 334 (8), 278 (11), 252 (100), 223 (57), 179 (68), 173 (52), 158 (27), 117 (28), 108 (22), 77 (14), 51 (11); HRMS (EI, 70 eV) *m/z* 425.1966 (M^+ calcd for $C_{23}H_{27}N_3O_5$: 425.1951).

4.2.18. Diethyl 3-[3-(1*H*-indol-1-yl)propyl]-6-methylpyridazine-4,5-dicarboxylate (19b). This compound was prepared as described for **18a**, starting from **15b** (0.900 g, 2.29 mmol). Column chromatography (EtOAc/PE, 1:2) gave **19b** (0.384 g, 42%) as a brownish oil. IR 2981, 2936, 1734, 1464, 1394, 1257, 1217, 1030, 743 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.63 (d, J_{4-5}=7.8 Hz, 1H, indole 4-H), 7.35 (d, J_{6-7}=8.4 Hz, 1H, indole 7-H), 7.24–7.16 (m, 1H, indole 6-H), 7.15 (d, J_{2-3}=3.3 Hz, 1H, indole 2-H), 7.13–7.06 (m, 1H, indole 5-H), 6.50 (d, J_{2-3}=3.3 Hz, 1H, indole 3-H), 4.40 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 4.29 (t, J=6.7 Hz, 2H, NCH_2CH$_2$CH$_2$), 4.16 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 3.06 (t, J=7.6 Hz, 2H, NCH$_2$CH$_2$CH_2), 2.83 (s, 3H, CH$_3$), 2.48–2.32 (m, 2H, NCH$_2$CH_2CH$_2$), 1.38 (t, J=7.2 Hz, 3H, CH$_2$CH_3), 1.20 (t, J=7.2 Hz, 3H, CH$_2$CH_3); MS (EI, 70 eV) *m/z* 395 (M^+, 8%), 304 (6), 252 (100), 223 (70), 179 (81), 143 (26), 130 (45), 108 (29), 77 (20); HRMS (EI, 70 eV) *m/z* 395.1849 (M^+ calcd for $C_{22}H_{25}N_3O_4$: 395.1845).

4.2.19. 1-(But-3-yn-1-yl)indoline (20). A mixture of indoline (1.43 g, 12 mmol), Na_2CO_3 (2.54 g, 24 mmol) and but-3-yn-1-yl methanesulfonate[38] (2.66 g, 18 mmol) in toluene (20 mL) was refluxed under argon for 48 h. The inorganic material was filtered off and washed with EtOAc. The combined filtrate and washings were evaporated in vacuo and the residue was purified by column chromatography (EtOAc/PE, 1:29) to give **20** (1.83 g, 89%) as a colorless oil which slowly solidified: mp $<$ 30 °C. IR 3292, 2920, 2843, 2117, 1607, 1489, 1458, 1267, 1022, 747, 643 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.15–7.06 (m, 2H, 4-H, 6-H), 6.74–6.65 (m, 1H, 5-H), 6.52 (d, J_{6-7}=8.1 Hz, 1H, 7-H), 3.46 (t, J_{2-3}=8.4 Hz, 2H, 2-H), 3.35 (t, ^3J=7.4 Hz, 2H, NCH_2CH$_2$-CCH), 3.02 (t, J_{2-3}=8.4 Hz, 2H, 3-H), 2.51 (dt, ^3J=7.4 Hz, ^4J=2.6 Hz, 2H, NCH$_2$CH_2CCH), 2.05 (t, ^4J=2.6 Hz, 1H, NCH$_2$CH$_2$CC*H*); MS (EI, 70 eV) *m/z* 171 (M^+, 14%), 133 (11), 132 (100), 130 (13), 117 (20), 115 (6), 103 (5), 77 (10), 51 (4); HRMS (EI, 70 eV) *m/z* 171.1047 (M^+ calcd for $C_{12}H_{13}N$: 171.1048).

4.2.20. Diethyl 3-[4-(2,3-dihydro-1*H*-indol-1-yl)but-1-yn-1-yl]pyridazine-4,5-dicarboxylate (21). This compound was prepared as described for **14a**, using the alkyne **20** (0.556 g, 3.25 mmol) instead of **12a**. Column chromatography (EtOAc/PE, 1:2) afforded **21** (0.873 g, 85%) as a brownish oil. IR 2981, 2844, 2236, 1735, 1607, 1490, 1276, 1209, 1029, 747 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.57 (s, 1H, pyridazine 6-H), 7.15–7.06 (m, 2H, indoline 4-H, 6-H), 6.74–6.66 (m, 1H, indoline 5-H), 6.52 (d, J_{6-7}=8.1 Hz, 1H, indoline 7-H), 4.55–4.40 (m, 4H, CH_2CH$_3$), 3.55–3.40 (m, 4H, indoline 2-H, NCH_2CH$_2$CC), 3.03 (t, J_{2-3}=8.2 Hz, 2H, indoline 3-H), 2.83 (t, J=7.3 Hz, 2H, NCH$_2$CH_2CC), 1.50–1.35 (m, 6H, CH$_2$CH_3); MS (EI, 70 eV) *m/z* 393 (M^+, 2%), 347 (4), 318 (5), 132 (100), 130 (15), 117 (16), 77 (6); HRMS (EI, 70 eV) *m/z* 393.1674 (M^+ calcd for $C_{22}H_{23}N_3O_4$: 393.1689).

4.2.21. Diethyl 3-[4-(1*H*-indol-1-yl)butyl]pyridazine-4,5-dicarboxylate (23). This compound was prepared as described for **18a**, starting from **21** (0.815 g, 2.07 mmol); the hydrogenation time was 7 d. Column chromatography (EtOAc/PE, 1:2) gave **23** (0.410 g, 50%) as a brownish oil. IR 2936, 2870, 1733, 1464, 1297, 1193, 1019, 743 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.55 (s, 1H, pyridazine 6-H), 7.65 (d, J_{4-5}=7.8 Hz, 1H, indole 4-H), 7.36 (d, J_{6-7}=8.4 Hz, 1H, indole 7-H), 7.29–7.18 (m, 1H, indole 6-H), 7.17–7.06 (m, 2H, indole 2-H, 5-H), 6.50 (d, J_{2-3}=3.1 Hz, 1H, indole 3-H), 4.46 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 4.40 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 4.20 (t, J=6.4 Hz, 2H, NCH_2CH$_2$CH$_2$CH$_2$), 3.10 (t, J=7.2 Hz, 2H, NCH$_2$CH$_2$CH$_2$CH_2), 2.05–1.83 (m, 4H, NCH$_2$CH_2CH_2CH$_2$), 1.43 (t, J=7.2 Hz, 3H, CH$_2$CH_3), 1.34 (t, J=7.2 Hz, 3H, CH$_2$CH_3); MS (EI, 70 eV) *m/z* 395 (M^+, 13%), 322 (10), 278 (60), 233 (49), 205 (23), 156 (63), 130 (100), 117 (27), 103 (22), 77 (23); HRMS (EI, 70 eV) *m/z* 395.1857 (M^+ calcd for $C_{22}H_{25}N_3O_4$: 395.1845).

4.2.22. 5-[3-(1*H*-Indol-1-yl)propyl]-2,3-dihydropyridazino[4,5-*d*]pyridazine-1,4-dione (24). A solution of **18b** (0.191 g, 0.5 mmol) and hydrazine hydrate (100%; 0.24 mL, 5 mmol) in 1-PrOH (5 mL) was refluxed under argon for 24 h. The volatile components were removed in vacuo and the yellow residue was taken up in water (5 mL) and acidified (pH 2) with 2 N HCl. The mixture was cooled and the precipitate was collected by filtration, washed with water and EtOH, and dried in vacuo to afford **24** (0.100 g, 61%) as pale yellow crystals: mp 259–262 °C. IR 3426, 3165, 3048, 2922, 2572, 1666, 1603, 1570, 1464, 1315, 740 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.2 (br s, 2H, NH), 9.54 (s, 1H, pyridazinopyridazine 8-H), 7.61 (d, J_{4-5}=7.6 Hz, 1H, indole 4-H), 7.45 (d, J_{6-7}=8.2 Hz, 1H, indole 7-H), 7.38 (d, J_{2-3}=3.0 Hz, 1H, indole 2-H), 7.14–7.05 (m, 1H, indole 6-H), 7.02–6.93 (m, 1H, indole 5-H), 6.38 (d, J_{2-3}=3.0 Hz, 1H, indole 3-H), 4.29 (t, J=7.0 Hz, 2H, NCH_2CH$_2$CH$_2$), 3.54 (t, J=7.5 Hz, 2H, NCH$_2$CH$_2$CH_2), 2.34–2.20 (m, 2H, NCH$_2$CH_2CH$_2$); MS (EI, 70 eV) *m/z* 321 (M^+, 4%), 178 (15), 143 (100), 130 (33), 117 (16), 103 (12), 89 (13), 77 (14), 63 (10), 51 (8); HRMS (EI, 70 eV) *m/z* 321.1236 (M^+ calcd for $C_{17}H_{15}N_5O_2$: 321.1226). Anal. Calcd for $C_{17}H_{15}N_5O_2\cdot0.3H_2O$: C, 62.49; H, 4.81; N, 21.43. Found: C, 62.51; H, 4.73; N, 21.37.

4.2.23. 5-[3-(1*H*-Indol-1-yl)propyl]-8-methyl-2,3-dihydropyridazino[4,5-*d*]pyridazine-1,4-dione (25). This compound was prepared as described for **24**, starting from the diester **19b** (0.200 g, 0.51 mmol). The product **25** (0.115 g, 67%) was obtained as pale yellow crystals: mp 259–263 °C. IR 3428, 3164, 3027, 2926, 2607, 1663, 1595, 1464, 1313, 741 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.2 (br s, 2H, NH), 7.53 (d, J_{4-5}=7.8 Hz, 1H, indole 4-H), 7.46 (d, J_{6-7}=8.1 Hz, 1H, indole 7-H), 7.38 (d, J_{2-3}=3.2 Hz, 1H, indole 2-H), 7.16–7.06 (m, 1H, indole 6-H), 7.04–6.96 (m, 1H, indole 5-H), 6.40 (d, J_{2-3}=3.2 Hz, 1H, indole 3-H), 4.29 (t, J=7.0 Hz, 2H, NCH_2CH$_2$CH$_2$), 3.50 (br t,

J=6.9 Hz, 2H, $NCH_2CH_2CH_2$), 2.99 (s, 3H, CH_3), 2.34–2.18 (m, 2H, $NCH_2CH_2CH_2$); MS (EI, 70 eV) m/z 335 (M^+, 21%), 218 (8), 192 (100), 163 (16), 143 (66), 130 (40), 117 (12), 103 (15), 89 (12), 77 (22), 51 (12). Anal. Calcd for $C_{18}H_{17}N_5O_2$: C, 64.47; H, 5.11; N, 20.88. Found: C, 64.21; H, 5.22; N, 20.64.

4.2.24. 1-[3-(2,3-Dihydro-1*H*-indol-1-yl)prop-1-yn-1-yl]pyrido[3,4-*d*]pyridazine (27). To a solution of **12b**[28] (1.02 g, 6.5 mmol) and 1-chloropyrido[3,4-*d*]pyridazine[29] (**26**) (0.860 g, 5.2 mmol) in THF (12 mL) were added triethylamine (2.0 mL, 14.4 mmol), CuI (0.030 g, 0.16 mmol) and $Pd(PPh_3)_2Cl_2$ (0.110 g, 0.16 mmol). The mixture was refluxed under argon for 3 h, then the solid material was removed by filtration and carefully rinsed with THF. The combined filtrate and washings were concentrated under reduced pressure, and the residue was subjected to column chromatography (EtOAc/MeOH, 19:1) to afford **27** (1.04 g, 70%) as almost colorless crystals: mp 120–122 °C (from EtOAc/PE). IR 2920, 2835, 2224, 1606, 1484, 1359, 1242, 764, 668, 594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.54 (s, 1H, pyridopyridazine 4-H), 9.40 (s, 1H, pyridopyridazine 5-H), 8.86 (d, J_{7-8}=5.8 Hz, 1H, pyridopyridazine 7-H), 7.41 (d, J_{7-8}=5.8 Hz, 1H, pyridopyridazine 8-H), 7.24–7.15 (m, 2H, indoline 4-H, 6-H), 6.90–6.81 (m, 1H, indoline 5-H), 6.77 (d, J_{6-7}=7.7 Hz, 1H, indoline 7-H), 4.39 (s, 2H, propargyl CH_2), 3.57 (t, J_{2-3}=8.3 Hz, 2H, indoline 2-H), 3.05 (t, J_{2-3}=8.3 Hz, 2H, indoline 3-H); MS (EI, 70 eV) m/z 286 (M^+, 100%), 271 (12), 258 (7), 169 (43), 156 (12), 143 (25), 128 (17), 117 (27), 103 (14), 89 (16), 77 (35), 63 (15), 51 (19). Anal. Calcd for $C_{18}H_{14}N_4$: C, 75.51; H, 4.93; N, 19.57. Found: C, 75.65; H, 5.00; N, 19.57.

4.2.25. 1-[3-(1*H*-Indol-1-yl)propyl]pyrido[3,4-*d*]pyridazine (28). A solution of **27** (0.500 g, 1.75 mmol) in EtOAc (200 mL) containing Pd/C catalyst (5%, 0.300 g), was hydrogenated in a Parr apparatus at a pressure of 30 psi for 5 h (TLC monitoring: EtOAc/MeOH, 19:1). The catalyst was filtered off and washed with EtOH and EtOAc. The combined filtrate and washings were concentrated under reduced pressure to afford a brown oil (0.500 g) containing the intermediate. This material was dissolved in xylene (90 mL), Pd/C catalyst (10%, 0.300 g) was added, and the mixture was refluxed with vigorous stirring for 120 h (reaction monitoring by GLC–MS). The catalyst was filtered off and washed with hot EtOH and hot EtOAc. The combined filtrate and washings were concentrated under reduced pressure and the residue was subjected to column chromatography (EtOAc/MeOH, 19:1) to afford **28** (0.107 g, 21%) as a brownish oil. IR 3048, 2918, 2849, 1610, 1463, 1315, 744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.52 (s, 1H, pyridopyridazine 4-H), 9.40 (s, 1H, pyridopyridazine 5-H), 8.87 (d, J_{7-8}=5.7 Hz, 1H, pyridopyridazine 7-H), 7.63 (d, J_{4-5}=7.6 Hz, 1H, indole 4-H), 7.41 (d, J_{7-8}=5.7 Hz, 1H, pyridopyridazine 8-H), 7.30 (d, J_{6-7}=7.9 Hz, 1H, indole 7-H), 7.22–7.05 (m, 3H, indole 2-H, 5-H, 6-H), 6.50 (d, J_{2-3}=3.0 Hz, 1H, indole 3-H), 4.38 (t, J=6.4 Hz, 2H, $NCH_2CH_2CH_2$), 3.25 (t, J=7.5 Hz, 2H, $NCH_2CH_2CH_2$), 2.64–2.50 (m, 2H, $NCH_2CH_2CH_2$); MS (EI, 70 eV) m/z 288 (M^+, 11%), 145 (100), 143 (80), 130 (15), 117 (9), 103 (11), 89 (14), 77 (19), 63 (12), 51 (7); HRMS (EI, 70 eV) m/z 288.1386 (M^+ calcd for $C_{18}H_{16}N_4$: 288.1375).

4.3. Intramolecular [4+2] cycloaddition reactions. General procedure

A solution (or suspension, in the case of **24**, **25**) of 0.5 mmol of the cycloaddition educt (0.11 mmol in the case of **6a**) in 1,3,5-triisopropylbenzene (7 mL) was heated to reflux under argon for the time given in Table 1. Except in those cases where the product precipitated from the mixture (compounds **35**, **36**), the solvent was removed by Kugelrohr distillation (10^{-1} mbar, 80 °C) and the residue was subjected to column chromatography.

4.3.1. 10-Methoxy-5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazole (29). Elution with EtOAc/PE (1:19) gave **29** (0.002 g, 8%) as a brownish oil. ^1H NMR ($CDCl_3$) δ 7.86 (d, J_{1-2}=7.8 Hz, 1H, 1-H), 7.60 (d, J_{9-11}=2.4 Hz, 1H, 11-H), 7.30 (d, J_{8-9}=9.0 Hz, 1H, 8-H), 7.19–7.06 (m, 3H, 2-H, 3-H, 9-H), 4.22 (t, J_{5-6}=5.7 Hz, 2H, 6-H), 3.94 (s, 3H, OCH_3), 3.08 (t, J_{4-5}=6.1 Hz, 2H, 4-H), 2.40–2.27 (m, 2H, 5-H); MS (EI, 70 eV) m/z 237 (M^+, 71%), 222 (100), 194 (24), 166 (13), 139 (7), 119 (8); HRMS (EI, 70 eV) m/z 237.1147 (M^+ calcd for $C_{16}H_{15}NO$: 237.1154).

4.3.2. 7-Methoxy-2,3-dihydro-1*H*-benzo[*b*]pyrido[1,2,3-*lm*]carbazole (30a). Elution with EtOAc/PE (1:9) gave an oil which was triturated with PE to afford **30a** (0.012 g, 8%) as yellow crystals: mp 131–132 °C (from toluene/PE). IR 2935, 2830, 1640, 1484, 1287, 1230, 1129, 1072, 835, 742 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.39 (s, 1H, 9-H), 8.09–7.99 (m, 2H, 10-H, 13-H), 7.74 (d, J_{6-8}=2.5 Hz, 1H, 8-H, shows positive NOE on irradiation at 8.39 ppm or at 3.97 ppm), 7.55–7.47 (m, 1H, 12-H), 7.42–7.33 (m, 1H, 11-H), 7.26 (d, J_{5-6}=8.7 Hz, 1H, 5-H), 7.17 (dd, J_{5-6}=8.7 Hz, J_{6-8}=2.5 Hz, 1H, 6-H), 4.20 (t, J_{2-3}=5.8 Hz, 2H, 3-H), 3.97 (s, 3H, OCH_3), 3.37 (t, J_{1-2}=6.1 Hz, 2H, 1-H), 2.52–2.40 (m, 2H, 2-H); MS (EI, 70 eV) m/z 287 (M^+, 100%), 272 (91), 244 (16), 216 (13), 144 (17), 121 (14), 109 (9). Anal. Calcd for $C_{20}H_{17}NO$: C, 83.60; H, 5.96; N, 4.87. Found: C, 83.42; H, 6.13; N, 4.78.

4.3.3. 2,3-Dihydro-1*H*-benzo[*b*]pyrido[1,2,3-*lm*]carbazole (30b). Elution with EtOAc/PE (1:19) gave an oil which was triturated with PE to afford **30b** (0.032 g, 25%) as pale yellow crystals: mp 143 °C (from toluene/PE). IR 3052, 2936, 2854, 1637, 1607, 1475, 1364, 1240, 1131, 879, 736, 772 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.43 (s, 1H, 9-H, shows positive NOE on irradiation at 8.22 ppm), 8.22 (d, J_{7-8}=7.8 Hz, 1H, 8-H, shows positive NOE on irradiation at 8.43 ppm or at 7.28–7.20), 8.11–8.01 (m, 2H, 10-H, 13-H), 7.58–7.48 (m, 2H, 6-H, 12-H), 7.43–7.33 (m, 2H, 5-H, 11-H), 7.28–7.20 (m, 1H, 7-H), 4.24 (t, J_{2-3}=5.7 Hz, 2H, 3-H), 3.40 (t, J_{1-2}=6.0 Hz, 2H, 1-H), 2.53–2.41 (m, 2H, 2-H); MS (EI, 70 eV) m/z 257 (M^+, 100%), 254 (35), 241 (9), 229 (9), 202 (6), 129 (16), 127 (18), 121 (9), 100 (8). Anal. Calcd for $C_{19}H_{15}N$: C, 88.68; H, 5.88; N, 5.44. Found: C, 88.40; H, 5.87; N, 5.33.

4.3.4. 2,3-Dihydro-1*H*-indolo[3,2,1-*gh*][3,7]phenanthroline (31). Elution with EtOAc gave **31** (0.028 g, 21%) as a yellow oil. IR 3049, 2929, 2859, 1604, 1460, 1361, 1309, 1243, 1132, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.36 (s, 1H, 10-H), 8.46 (d, J_{12-13}=6.5 Hz, 1H, 12-H), 8.43 (s, 1H, 9-H, shows positive NOE on irradiation at 8.20 ppm), 8.20 (d,

J_{7-8}=8.0 Hz, 1H, 8-H), 7.74 (d, J_{12-13}=6.5 Hz, 1H, 13-H), 7.62–7.52 (m, 1H, 6-H), 7.37 (d, J_{5-6}=8.3 Hz, 1H, 5-H), 7.33–7.25 (m, 1H, 7-H), 4.19 (t, J_{2-3}=6.0 Hz, 2H, 3-H), 3.28 (t, J_{1-2}=6.3 Hz, 2H, 1-H), 2.48–2.35 (m, 2H, 2-H); MS (EI, 70 eV) *m/z* 258 (M^+, 100%), 255 (25), 230 (16), 202 (7), 176 (5), 128 (24), 114 (16), 101 (8), 88 (9), 75 (7), 63 (4); HRMS (EI, 70 eV) *m/z* 258.1163 (M^+ calcd for $C_{18}H_{14}N_2$: 258.1157).

4.3.5. Diethyl 10-methoxy-5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazole-2,3-dicarboxylate (32a). Elution with EtOAc/toluene (1:14) afforded **32a** (0.097 g, 51%) as a brownish oil.[30] IR 2979, 2937, 1725, 1707, 1485, 1300, 1265, 1209, 1120, 1048, 1031, 785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.58 (s, 1H, 1-H), 7.62 (d, J_{9-11}=2.4 Hz, 1H, 11-H), 7.34 (d, J_{8-9}=9.0 Hz, 1H, 8-H), 7.17 (dd, J_{8-9}=9.0 Hz, J_{9-11}=2.4 Hz, 1H, 9-H), 4.47 (q, *J*=7.2 Hz, 2H, CH_2CH_3), 4.41 (q, *J*=7.2 Hz, 2H, CH_2CH_3), 4.21 (t, J_{5-6}=5.8 Hz, 2H, 6-H), 3.95 (s, 3H, OCH_3), 3.08 (t, J_{4-5}=6.1 Hz, 2H, 4-H), 2.40–2.27 (m, 2H, 5-H), 1.49–1.38 (m, 6H, CH_2CH_3); MS (EI, 70 eV) *m/z* 381 (M^+, 51%), 336 (10), 306 (100), 292 (17), 281 (7), 264 (7), 235 (21), 221 (22), 207 (20), 191 (14), 154 (15), 135 (6), 96 (5), 73 (10); HRMS (EI, 70 eV) *m/z* 381.1583 (M^+ calcd for $C_{22}H_{23}NO_5$: 381.1576).

4.3.6. Diethyl 5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazole-2,3-dicarboxylate (32b). Elution with EtOAc/toluene (1:19) gave **32b** (0.097 g, 55%) as a brownish oil. IR 2978, 2935, 1727, 1709, 1476, 1329, 1264, 1224, 1144, 1078, 1048, 1023, 785, 747, 734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.59 (s, 1H, 1-H), 8.14 (d, J_{10-11}=8.1 Hz, 1H, 11-H), 7.58–7.48 (m, 1H, 9-H), 7.42 (d, J_{8-9}=8.1 Hz, 1H, 8-H), 7.36–7.24 (m, 1H, 10-H), 4.48 (q, *J*=7.2 Hz, 2H, CH_2CH_3), 4.41 (q, *J*=7.2 Hz, 2H, CH_2CH_3), 4.23 (t, J_{5-6}=5.7 Hz, 2H, 6-H), 3.09 (t, J_{4-5}=6.3 Hz, 2H, 4-H), 2.41–2.27 (m, 2H, 5-H), 1.51–1.47 (m, 6H, CH_2CH_3); MS (EI, 70 eV) *m/z* 351 (M^+, 29%), 305 (21), 276 (100), 204 (45), 177 (8), 151 (6); HRMS (EI, 70 eV) *m/z* 351.1467 (M^+ calcd for $C_{21}H_{21}NO_4$: 351.1471).

4.3.7. Diethyl 10-methoxy-1-methyl-5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazole-2,3-dicarboxylate (33a). Elution with EtOAc/toluene (1:14) afforded **33a** (0.081 g, 41%) as a brownish oil. IR 2955, 1721, 1489, 1299, 1175, 1038, 801 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.75 (d, J_{9-11}=2.5 Hz, 1H, 11-H), 7.36 (d, J_{8-9}=8.9 Hz, 1H, 8-H), 7.19 (dd, J_{8-9}=8.9 Hz, J_{9-11}=2.5 Hz, 1H, 9-H), 4.43 (q, *J*=7.2 Hz, 4H, CH_2CH_3), 4.20 (t, J_{5-6}=5.7 Hz, 2H, 6-H), 3.95 (s, 3H, OCH_3), 3.21 (t, J_{4-5}=6.3 Hz, 2H, 4-H), 2.91 (s, 3H, CH_3), 2.35–2.22 (m, 2H, 5-H), 1.46–1.35 (m, 6H, CH_2CH_3); MS (EI, 70 eV) *m/z* 395 (M^+, 44%), 350 (11), 320 (100), 306 (18), 277 (9), 249 (20), 234 (19), 207 (16), 178 (8), 161 (12), 102 (7); HRMS (EI, 70 eV) *m/z* 395.1721 (M^+ calcd for $C_{23}H_{25}NO_5$: 395.1733).

4.3.8. Diethyl 1-methyl-5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazole-2,3-dicarboxylate (33b). Elution with EtOAc/toluene (1:19) gave **33b** (0.079 g, 43%) as a brownish oil. IR 2979, 2938, 2902, 2869, 1722, 1484, 1375, 1316, 1260, 1203, 1162, 1055, 1029, 745, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.25 (d, J_{10-11}=8.1 Hz, 1H, 11-H), 7.58–7.48 (m, 1H, 9-H), 7.44 (d, J_{8-9}=8.1 Hz, 1H, 8-H), 7.34–7.25 (m, 1H, 10-H), 4.47–4.33 (m, 4H, CH_2CH_3), 4.22 (t, J_{5-6}=5.8 Hz, 2H, 6-H), 3.22 (t, J_{4-5}=6.1 Hz, 2H, 4-H), 2.92 (s, 3H, CH_3), 2.37–2.24 (m, 2H, 5-H), 1.41 (t, *J*=7.0 Hz, 6H, CH_2CH_3); MS (EI, 70 eV) *m/z* 365 (M^+, 24%), 319 (12), 290 (100), 247 (12), 218 (30), 204 (13), 180 (7), 109 (7); HRMS (EI, 70 eV) *m/z* 365.1639 (M^+ calcd for $C_{22}H_{23}NO_4$: 365.1627).

4.3.9. Diethyl 4,5,6,7-tetrahydroazepino[3,2,1-*jk*]carbazole-2,3-dicarboxylate (34). Elution with EtOAc/toluene (1:19) gave **34** (0.066 g, 36%) as a brownish oil. IR 2977, 2932, 2865, 1728, 1711, 1592, 1474, 1367, 1336, 1261, 1144, 1040, 1022, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.66 (s, 1H, 1-H), 8.15 (d, J_{11-12}=7.8 Hz, 1H, 12-H, shows positive NOE on irradiation at 8.66 ppm), 7.59–7.50 (m, 1H, 10-H), 7.45 (d, J_{9-10}=8.4 Hz, 1H, 9-H), 7.37–7.27 (m, 1H, 11-H), 4.51 (q, *J*=7.2 Hz, 2H, CH_2CH_3), 4.50–4.38 (m, 4H, 7-H, CH_2CH_3), 3.22 (t, J_{4-5}=5.8 Hz, 2H, 4-H), 2.34–2.13 (m, 4H, 5-H, 6-H), 1.52–1.40 (m, 6H, CH_2CH_3); MS (EI, 70 eV) *m/z* 365 (M^+, 15%), 319 (20), 290 (100), 246 (7), 218 (24), 204 (17), 191 (11); HRMS (EI, 70 eV) *m/z* 365.1634 (M^+ calcd for $C_{22}H_{23}NO_4$: 365.1627).

4.3.10. 2,3,11,12-Tetrahydro-1*H*-pyridazino[4,5-*b*]-pyrido[1,2,3-*lm*]carbazole-10,13-dione (35). The material which precipitated from the reaction mixture was collected by filtration and washed with EtOAc. It was then suspended in MeOH (10 mL) and refluxed for 0.5 h. After cooling, the solid was collected by filtration and dried to afford **35** (0.111 g, 75%) as almost colorless crystals: mp >330 °C (dec). IR 3404, 3154, 3018, 2937, 1645, 1625, 1474, 1328, 1246, 819, 745 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.18 (s, 2H, NH), 8.73 (s, 1H, 9-H), 8.38 (d, J_{7-8}=7.8 Hz, 1H, 8-H), 7.65 (d, J_{5-6}=8.1 Hz, 1H, 5-H), 7.64–7.53 (m, 1H, 6-H), 7.36–7.25 (m, 1H, 7-H), 4.30 (t, J_{2-3}=5.5 Hz, 2H, 3-H), 3.76 (t, J_{1-2}=6.0 Hz, 2H, 1-H), 2.40–2.15 (m, 2H, 2-H); MS (EI, 70 eV) *m/z* 291 (M^+, 100%), 246 (9), 204 (24), 177 (8), 146 (9), 102 (20), 51 (9), 44 (13). Anal. Calcd for $C_{17}H_{13}N_3O_2 \cdot 0.25H_2O$: C, 69.03; H, 4.60; N, 14.20. Found: C, 68.95; H, 4.62; N, 14.08.

4.3.11. 9-Methyl-2,3,11,12-tetrahydro-1*H*-pyridazino-[4,5-*b*]pyrido[1,2,3-*lm*]carbazole-10,13-dione (36). The material which precipitated from the reaction mixture was collected by filtration and washed with EtOAc. It was then suspended in MeOH (10 mL) and refluxed for 0.5 h. After cooling, the solid was collected by filtration and dried to afford **36** (0.098 g, 64%) as beige crystals: mp >350 °C (dec). IR 3405, 3149, 3041, 2934, 1632, 1579, 1475, 1414, 1321, 1249, 744 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.1 (br s, 2H, NH), 8.43 (d, J_{7-8}=7.8 Hz, 1H, 8-H), 7.70 (d, J_{5-6}=8.1 Hz, 1H, 5-H), 7.67–7.58 (m, 1H, 6-H), 7.40–7.30 (m, 1H, 7-H), 4.31 (t, J_{2-3}=5.7 Hz, 2H, 3-H), 3.73 (t, not resolved, 2H, 1-H), 3.44 (s, 3H, CH_3), 2.32–2.18 (m, 2H, 2-H); MS (EI, 70 eV) *m/z* 305 (M^+, 100%), 289 (17), 260 (20), 244 (9), 232 (12), 217 (21), 204 (14), 191 (11), 152 (14), 109 (12), 95 (11), 57 (10), 43 (20); HRMS (EI, 70 eV) *m/z* 305.1172 (M^+ calcd for $C_{18}H_{15}N_3O_2$: 305.1164).

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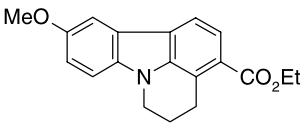
30. From the column fraction preceding the main product (**32a**), a side product was isolated. Purification of this material by MPLC (EtOAc/toluene, 1:14) gave ethyl 10-methoxy-5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazole-3-carboxylate (0.016 g, 10%) as a yellow oil. IR 2927, 2855, 1704, 1490, 1243, 1213, 1138, 1076, 1040, 815, 749 cm^{-1}; ^1H NMR ($CDCl_3$) (7.88 (d, J_{1-2}=8.2 Hz, 1H, 1-H, shows positive NOE on irradiation at 6.60 ppm), 7.81 (d, J_{1-2}=8.2 Hz, 1H, 2-H), 6.60 (d, J_{9-11}= 2.5 Hz, 1H, 11-H), 7.33 (d, J_{8-9}=8.8 Hz, 1H, H-8), 7.18 (dd, J_{8-9}=8.8 Hz, J_{9-11}=2.5 Hz, 1H, 9-H), 4.42 (q, J=7.1 Hz, 2H, CH_2CH_3), 4.22 (t, J_{5-6}=5.7 Hz, 2H, 6-H), 3.95 (s, 3H, OCH_3, shows positive NOE on irradiation at 6.60 ppm), 3.51 (t, J_{4-5}=6.3 Hz, 2H, 4-H), 2.40-2.27 (m, 2H, 5-H), 1.45 (t, J=7.1 Hz, 3H, CH_2CH_3); MS (EI, 70 eV) *m*/*z* 309 (M^*, 100%), 294 (38), 280 (22), 266 (33), 236 (15), 221 (19), 207 (12), 191 (21), 165 (9), 125 (11), 111 (10), 96 (12), 84 (10), 73 (6); HRMS (EI, 70 eV) *m*/*z* 309.1378 (M^* calcd for $C_{19}H_{19}NO_3$: 309.1365).



31. This assumption is supported by the observation that only one of the two possible monoesters is formed from pyridazines **18a**,**b** and **23**, in which one ester group is sterically more shielded than the other one, whereas from the tetrasubstituted pyridazines **19a**,**b** mixtures of both mono-decarboxylation products are formed. This is in agreement with the regioselective hydrolysis of 1-methylcarbazole-2,3-dicarboxylic acid dimethyl ester into 2-(methoxycarbonyl)-1-methyl-9*H*-carbazole-3-carboxylic acid, which was described recently[20].
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37. A sample of the intermediate **16a** was isolated by column chromatography (EtOAc/PE, 1:2) as a brownish oil. IR 3376, 2935, 2830, 1734, 1685, 1623, 1493, 1238, 1194, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.64 (br d, J_{1-6}=4.2 Hz, 1H, NH), 7.52 (d, J_{1-6}=4.2 Hz, 1H, pyridazine 6-H), 6.76–6.71 (m, 1H, indoline 4-H), 6.62 (dd, J_{6-7}=8.5 Hz, J_{4-6}=2.5 Hz, 1H, indoline 6-H, shows positive NOE on irradiation at 6.40 ppm), 6.40 (d, J_{6-7}=8.5 Hz, 1H, indoline 7-H), 4.34 (s, 1H, pyridazine 4-H), 4.25–4.10 (m, 4H, CH_2CH_3), 3.74 (s, 3H, OCH_3), 3.28 (t, J_{2-3}=8.1 Hz, 2H, indoline 2-H), 3.03 (t, J=7.2 Hz, 2H, $NCH_2CH_2CH_2$), 2.92 (t, J_{2-3}=8.1 Hz, 2H, indoline 3-H), 2.70–2.40 (m, 2H, $NCH_2CH_2CH_2$), 2.06–1.80 (m, 2H, $NCH_2CH_2CH_2$), 1.32–1.20 (m, 6H, CH_2CH_3); MS (EI, 70 eV) *m*/*z* 415 (M^*, 13%), 193 (25), 175 (47), 162 (100), 148 (10), 130 (9), 57 (7); HRMS (EI, 70 eV) *m*/*z* 415.2118 (M^* calcd for $C_{22}H_{29}N_3O_5$: 415.2107).
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