Diastereoselective Synthesis of Dimethyl (4*R**,4a′*R**,7a′*R**)-1-Aryl-6′-benzoyl-4a′-methyl-5-oxo-1,4′,4a′,5,5′,6′-hexahydrospiro[pyrazole-4,7′-pyrrolo[3,4-*c*]pyridazine]-3′,7a′(1′*H*)-dicarboxylates

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Dedicated to Professor Volker Jäger on the occasion of his 65th birthday

Abstract: Methyl (*Z*)-2-(benzoylamino)-3-(dimethylamino)propenoate (**1**) reacted with trimethylenemethane (**2**) to produce methyl (*Z*)-2-[benzoyl(2-methylallyl)amino]-3-(dimethylamino)propenoate (**3**), which was then converted into pyrazole derivatives **11a**–**h** by a consecutive exchange of the dimethylamino group with hydrazine derivates **9a**–**h** and cyclization to the ester group. Reactions of pyrazoles **11a**–**g** with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**6**) resulted in the diastereoselective formation of 1-aryl-6′-benzoyl-4a′-methyl-5-oxo-1,4′,4a′,5,5′,6′-hexahydrospiro[pyrazole-4,7′-pyrrolo[3,4-*c*]pyridazine]-3′,7a′(1′*H*)-dicarboxylates **12a**–**g**. This represents a simple new pathway to novel heterocyclic systems. On the other hand, when (dimethylamino)propenoate **3** reacted with aniline hydrochloride (**4**), followed by the cycloaddition of 1,2,4,5-tetrazine **6**, dimethyl (*E*)- and (*Z*)-4-({benzoyl[1-(methoxycarbonyl)-2-(phenylamino)vinyl]amino}methyl)-4-methyl-1,4-dihydropyridazine-3,6-dicarboxylates (**7**) and (**8**) were formed, respectively.

Key words: spiro[pyrazole-4,7′-pyrrolo[3,4-*c*]pyridazine], 1,2,4,5-tetrazine, heterocycles, diastereoselectivity, cycloadditions

There have been only a few reports of the synthesis of systems with a similar heterocyclic backbone to that of spiro[pyrazole-4,7′-pyrrolo[3,4-*c*]pyridazine], which is reported in this paper. A well-reported route to similar spiro systems is to employ a consecutive Pschorr–Sandmeyer reaction. In this manner, racemic epimers (3′*S**,4′*R**)- and (3′*S**,4′*S**)-4′-hydroxy-2,5′-dimethyl-2′-phenyl-2′,4-dihydrospiro[isoindoline-1,3′-[3*H*]pyrazol]-3-ones,[1] and (3*S**,4*R**)- and (3*S**,4*S**)-4-chloro-2,4-dihydro-1′,3′,5,5′-tetramethyl-2-phenylspiro[3*H*-pyrazole-3,4′-[1*H*]pyrrolo[3,4-*c*]pyrazol]-6′(5′*H*)-one[2] have been prepared.

In the last decades, 2-[(trimethylsilyl)methyl]allyl acetate has proven to be a very useful reagent in palladium-catalyzed reactions with alkenes possessing an adjacent ester group to produce methylenecyclopentane derivatives, while reactions with ketones result in 3-methylenetetrahydrofurans.[3] Within this context, we have recently reported highly stereoselective [3+2] cycloadditions of trimethylenemethane to 3-(arylamino)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones leading to 4′-methylenedihydro-3′*H*-spiro[bicyclo[2.2.1]heptane-2,2′-furans] and further reductions of these cycloadducts yielding novel non-racemic amines, diamines, and amino alcohols.[4] Further [4+2] cycloaddition reactions of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate to systems possessing an exocyclic C=C bond leads to the formation of spirodihydropyridazines,[5–7] thus expanding the wide applicability of 1,2,4,5-tetrazines as useful electron-poor dienes in inverse-demand [4+2] cycloadditions to various electron-rich dienophiles.

So far, 3-(dimethylamino)propenoates have been shown to be widely applicable in the synthesis of various heterocyclic systems,[8] including some natural products and their analogues, such as aplysinopsins,[9] meridianines,[10] and dipodazines and tryprostatins.[11] Recently, we have reported on regiospecific [2+2] cycloadditions of electron-poor acetylenes to (*Z*)-2-(acylamino)-3-(dimethylamino)propenoates.[12] On the other hand, no attempt has been reported on employing 3-(dimethylamino)propenoates in cycloadditions with the trimethylenemethane precursor.

When methyl (*Z*)-2-(benzoylamino)-3-(dimethylamino)propenoate (**1**) reacted with trimethylenemethane (**2**) in the presence of palladium(II) acetate and triisopropyl phosphite, the reaction proceeded by attaching a 2-methylallyl moiety on to the nitrogen atom of the benzoylamino group resulting in the formation of methyl (*Z*)-2-[benzoyl(2-methylallyl)amino]-3-(dimethylamino)propenoate (**3**) (Scheme 1), the structure of which was confirmed by X-ray crystal structure analysis (Figure 1).[13]

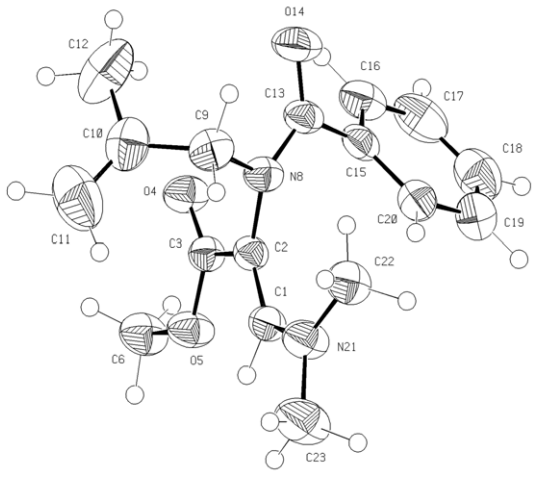

Figure 1 ORTEP view of compound **3**

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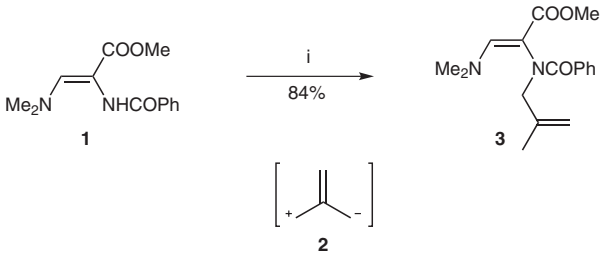


Scheme 1 *Reagents and conditions*: (i) trimethylenemethane (**2**) {from 2-[(trimethylsilyl)methyl]allyl acetate}, $Pd(OAc)_2$, $(i\text{-}PrO)_3PO$, anhyd toluene, anhyd THF, reflux.

The dimethylamino group of the (dimethylamino)propenoate **3** exhibits the same reactivity as in other (dimethylamino)propenoates reported previously. In this manner, it was easily exchanged by aniline **4** in an acid-catalyzed reaction, producing methyl (*Z*)-2-[benzoyl(2-methylallyl)amino]-3-(phenylamino)propenoate (**5**). Reacting propenoate **5** with 1,2,4,5-tetrazine **6** gave two products (Scheme 2) that were successfully separated by column chromatography. The ^{1}H NMR spectra of the two isolated products revealed that each contains a mixture of two isomers, which are in both cases in approximately the same ratio. It appears that the two separated products are the isomers (*E*)-**7** and (*Z*)-**8**, where the NH protons of the *E*-isomer **7** appear at a lower field (δ = 9.51 and 9.62) due to hydrogen bond formation with the carbonyl oxygen of the ester group, while those of the *Z*-isomers **8** appear at higher field (δ = 7.40), because in this case no hydrogen bond can be formed.

The two sets of signals in the ^{1}H NMR of *E*-isomer **7** and *Z*-isomer **8** appear to be due to rotational restrictions around the C4–C1′ bond, resulting in the observation of rotamers **7** and **7′**, and **8** and **8′**. The possibility of tautomerism of the dihydropyridazine was ruled out by the presence of characteristic chemical shifts for N1–H (*E*-isomers: δ = 7.91 and 8.02; *Z*-isomers: δ = 7.75 and 7.91) and C5–H (*E*-isomers: δ = 5.72 and 6.01; *Z*-isomers: δ = 5.64 and 6.01), thus confirming the 1,4-dihydro form in all cases. Additionally, the nature of the signals for N1–H has been, in all cases, established by addition of D_2O where these signals disappeared (Figure 2).

In the next step of this research (dimethylamino)propenoate **3** reacted with a series of hydrazines **9a**–**h**. Under the conditions of acidic catalysis the dimethylamino group was exchanged by hydrazines to afford **10a**–**h**,

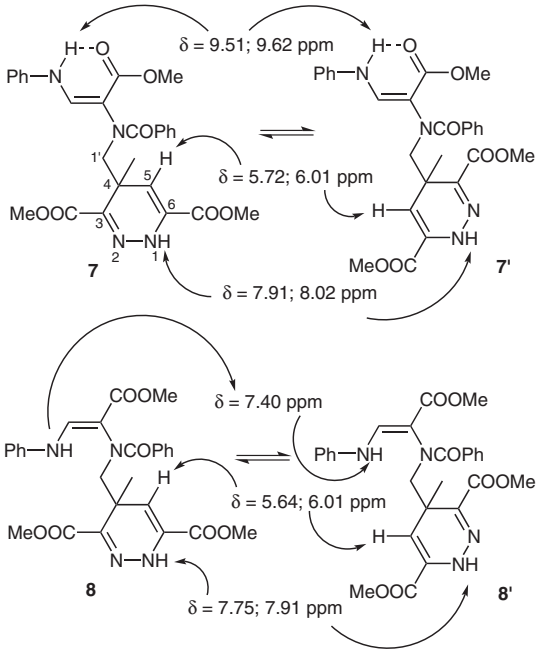
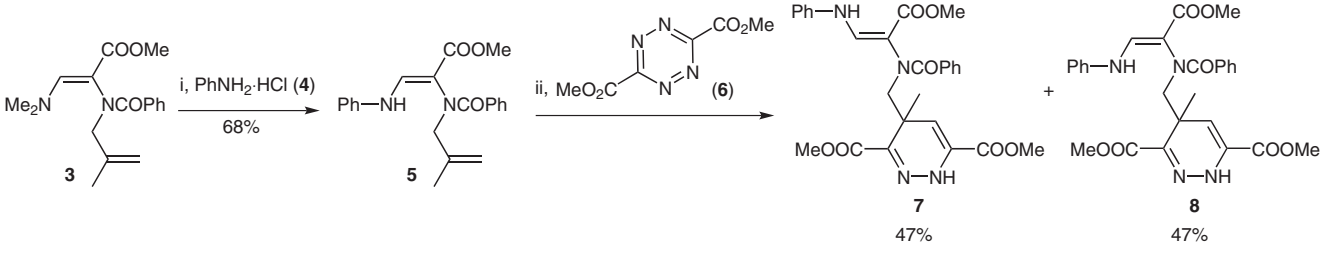
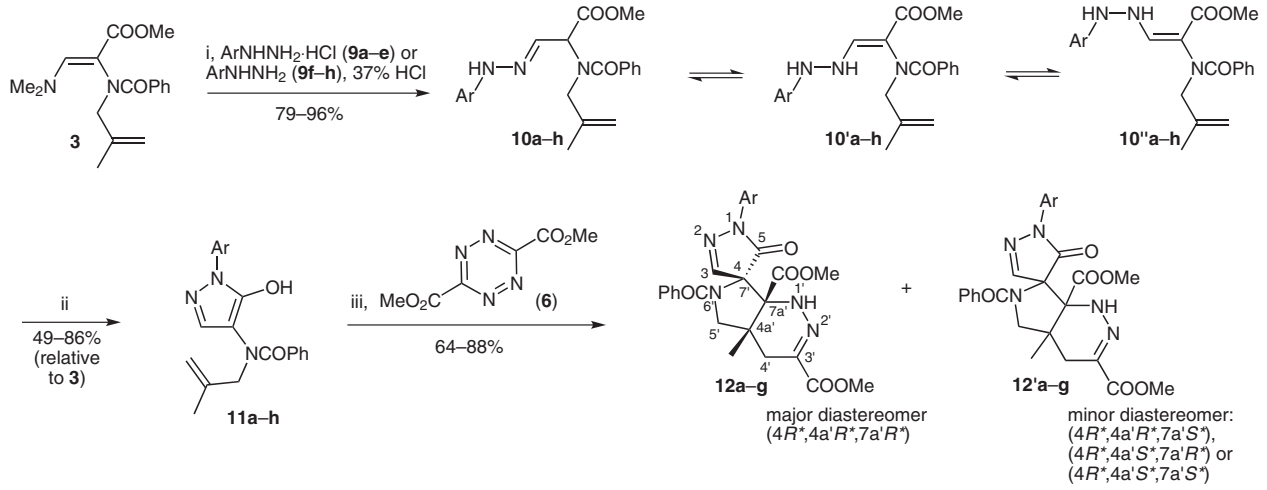


Figure 2 ^{1}H NMR chemical shifts of certain protons in **7** and **8**, and their rotamers **7′** and **8′**

10′a–**e**,**g**, and **10″a**–**e**,**g**. Further cyclization to the ester group did not take place under these conditions. In most cases the products appeared as mixtures of three forms: the hydrazono form **10**, the (*Z*)-hydrazino form **10′** and the (*E*)-hydrazino form **10″**. In the reaction with hydrazines **9f** and **9h** only the hydrazono forms **10f**,**h** were isolated. The structures of the tautomeric forms of intermediates **10a**–**h**, **10′a**–**e**,**g**, and **10″a**–**e**,**g** were determined by HRMS and ^{1}H NMR spectra. These intermediates were cyclized into pyrazole derivatives **11a**–**h** in the presence of triethylamine by heating to reflux in ethanol. When the pyrazole derivatives **11a**–**g** reacted with 1,2,4,5-tetrazine **6** an unexpected type of products was formed. Namely, [4+2] cycloaddition of 1,2,4,5-tetrazine **6** to the C=C bond of the 2-methylallyl moiety was followed by intramolecular cyclization resulting in the formation of dimethyl (4*R**,4a′*R**,7a′*R**)-1-aryl-6′-benzoyl-4a′-methyl-5-oxo-1,4′,4a′,5,5′,6′-hexahydrospiro[pyrazole-4,7′-pyrrolo[3,4-*c*]pyridazine]-3′,7a′(1′*H*)-dicarboxylates **12a**–**g** (Scheme 3). In these reactions, three new stereogenic centers are formed, therefore, four diastereomeric pairs of enantiomers can be formed. In fact these reactions proceeded with a relatively high diastereoselectivity, producing only two diasteromeric pairs of enantiomers, of which



Scheme 2 *Reagents and conditions*: (i) EtOH, reflux; (ii) toluene, reflux.



9-12: **a** Ar = Ph, **b** Ar = 4-MeC_6H_4, **c** Ar = 4-FC_6H_4, **d** Ar = 4-$MeOC_6H_4$, **e** Ar = 3-ClC_6H_4, **f** Ar = 4-$O_2NC_6H_4$, **g** Ar = 4-$HO_2CC_6H_4$, **h** Ar = 6-phenylpyridazin-3-yl

Scheme 3 *Reagents and conditions*: (i) EtOH, reflux; (ii) Et_3N, EtOH, reflux; (iii) MeCN, reflux.

the major diastereomers **12a**–**g** were formed with a diastereomeric ratio ranging between 75:25 and 85:15. The structure of the major isomers was determined by X-ray diffraction of product **12a** (Figure 3).[14] This proved that (4*R**,4a′*R**,7a′*R**)-diastereomers are formed. While the minor isomer **12′** formed is one of the three other possible diastereomers: the (4*R**,4a′*R**,7a′*S**)-, (4*R**,4a′*S**,7a′*R**)-, or (4*R**,4a′*S**,7a′*S**)-isomer. In all cases the major diastereomers **12a**–**g** can be obtained in a pure form by crystallizing the reaction mixture once or twice from a mixture of ethyl acetate and petroleum ether.

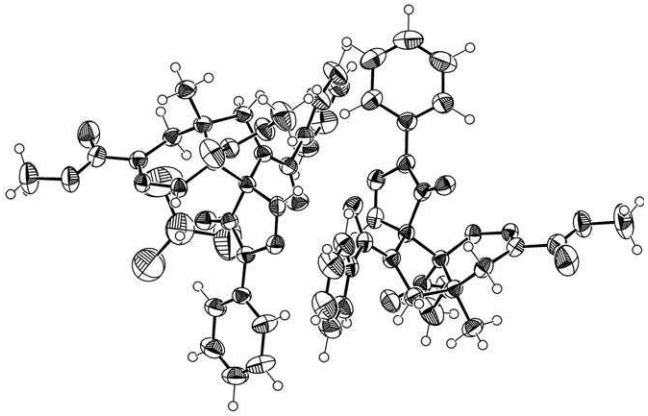
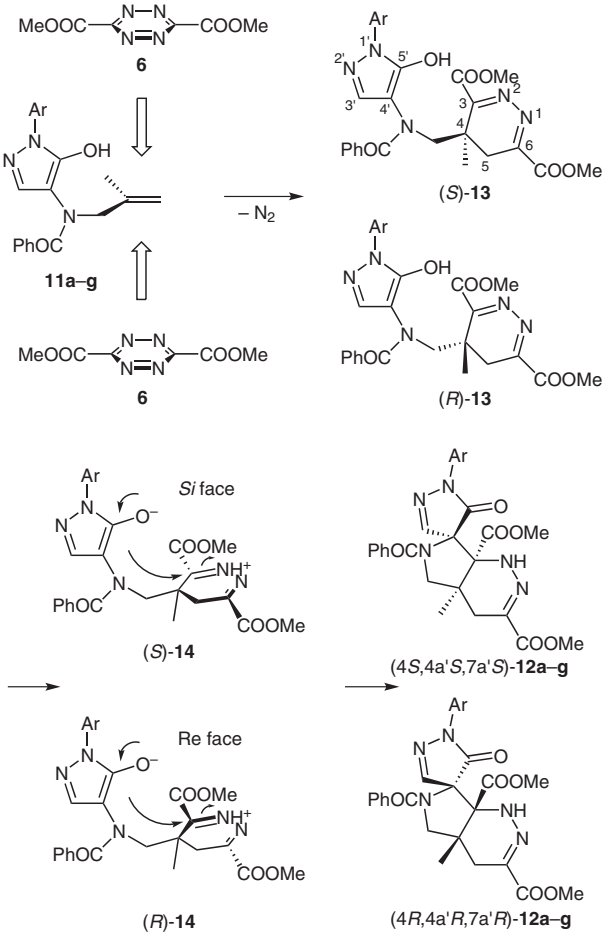


Figure 3 ORTEP view of compound **12a**

To explain the predominant formation of the major (4*R**,4a′*R**,7a′*R**)-diastereomers **12a**–**g** an easy mechanistic route can be envisioned. In the first stage, the [4+2] cycloaddition of 1,2,4,5-tetrazine **6** can proceed from both sides of the C=C bond, resulting in the formation of racemic dimethyl 4-{[(1-aryl-5-hydroxy-1*H*-pyrazol-4-yl)benzoylamino]methyl}-4-methyl-4,5-dihydropyridazine-3,6-dicarboxylates **13**. The transfer of a proton from the acidic hydroxy group to the dihydropyridazine nitrogen atom makes the pyrazole C4′ atom more nucleophilic. In the last stage, the nucleophilic attack of the pyrazole takes place on the opposite side from the methyl group, pushing the carboxylate to the side of the methyl group. In other words, (*S*)-**14** undergoes nucleophilic attack from the *Si* face, while in the case of (*R*)-**14** the attack takes place from the *Re* face (Scheme 4).



Scheme 4 Proposed mechanism of the formation of **12a**–**g**

In conclusion, a new type of (dimethylamino)propenoate reagent **3** has been prepared, which gave rise to the synthesis of new pyrazole derivatives **11a–h** and additionally a synthetic route to a new heterocyclic systems, spiro[pyrazole-4,7′-pyrrolo[3,4-*c*]pyridazines] **12**, has been developed by [4+2] cycloaddition reactions of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**6**) to pyrazoles **11**.

Melting points were determined on a Kofler micro hot stage. NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H, and 75.5 MHz for ^{13}C nucleus, using DMSO-d_6 and $CDCl_3$ as solvents and TMS as the internal standard. Microwave irradiations were performed on CEM Corporation Discover microwave unit. Mass spectra were recorder on an AutoSpecQ and Qtof-premier spectrometers, IR spectra on a Perkin-Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin-Elmer CHN Analyzer 2400 II. Column chromatography (CC) was performed on silica gel (Fluka, silica gel 60, 0.04–0.06 mm). Petroleum ether = PE.

2-[(Trimethylsilyl)methyl]allyl acetate (**2**), aniline hydrochloride (**4**) and hydrazines **9a–h** are commercially available (Sigma-Aldrich). Methyl (*Z*)-2-(benzoylamino)-3-(dimethylamino)propenoate[15] (**1**) and dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate[16] (**6**) were prepared according to literature procedures.

Methyl (*Z*)-2-[Benzoyl(2-methylallyl)amino]-3-(dimethylamino)propenoate (3)

A soln of methyl (*Z*)-2-(benzoylamino)-3-(dimethylamino)propenoate (**1**, 7.448 g, 30 mmol) and 2-[(trimethylsilyl)methyl]allyl acetate [precursor of trimethylenemethane (**2**)] (6.85 mL, 33 mmol) in anhyd toluene (60 mL) was heated to boiling point. Then a soln of (*i*-PrO)$_3$P (4.44 mL, 18 mmol) and $Pd(OAc)_2$ (0.680 g, 3 mmol) in anhyd THF (30 mL) was added through the condenser. The mixture was refluxed for 100 min. Volatile components were evaporated in vacuo and the residue was purified by column chromatography (silica gel, EtOAc–PE, 2:1). Fractions containing the product were combined and evaporated in vacuo. The product was recrystallized (EtOAc–PE). Experimental, analytical, and spectral data for compound **3** are given in Tables 1– 4.

Methyl (*Z*)-2-[Benzoyl(2-methylallyl)amino]-3-(phenylamino)propenoate (5)

Aniline hydrochloride (**4**, 0.129 g, 1 mmol) was added to a soln of **3** (0.302 g, 1 mmol) in EtOH (2 mL). The mixture was refluxed for 4.5 h. H_2O (10 drops) was added and the soln cooled to 4 °C. The precipitated product was collected by filtration. Experimental, analytical, and spectral data for compound **5** are given in Tables 1– 4.

Dimethyl (*E*)-4-[({Benzoyl[1-(methoxycarbonyl)-2-(phenylamino)vinyl]amino)methyl]-4-methyl-1,4-dihydropyridazine-3,6-dicarboxylate (7), Dimethyl (*Z*)-4-[({Benzoyl[1-(methoxycarbonyl)-2-(phenylamino)vinyl]amino)methyl]-4-methyl-1,4-dihydropyridazine-3,6-dicarboxylate (8), and Their Rotamers 7′ and 8′

Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**6**, 0.163 g, 0.825 mmol) was added to a soln of **5** (0.263 g, 0.75 mmol) in toluene (5 mL). The mixture was refluxed for 2 h. Volatile components were evaporated in vacuo and the residue was purified by column chromatography (silica gel, EtOAc–PE, 1:1) isolating two products. Fractions containing individual products were evaporated in vacuo to obtain *E*- and *Z*-isomers as mixtures of two rotamers. Experimental, analytical, and spectral data for compounds **7**, **7′**, **8**, and **8′** are given in Tables 1– 4.

***N*-(1-Aryl-5-hydroxy-1*H*-pyrazol-4-yl)-*N*-(2-methylallyl)benzamides 11a–h through Methyl 3-(2-Arylhydrazono)-2-[benzoyl(2-methylallyl)amino]propenoates 10a–h, Methyl (*Z*)-3-(2-Arylhydrazinyl)-2-[benzoyl(2-methylallyl)amino]propenoates 10′a–h, and Methyl (*E*)-3-(2-Arylhydrazinyl)-2-[benzoyl(2-methylallyl)amino]propenoates 10″a–h; General Procedure**

Hydrazine hydrochloride **9a–e** (2.4 mmol) or hydrazine **9f–h** (2.4 mmol) and 37% aq HCl (6 drops, ca. 2 mmol) was added to a soln of **3** (0.604 g, 2 mmol) in EtOH (6 mL). The mixture was refluxed for 2–16 h. Volatile components were evaporated in vacuo and the residue was purified by column chromatography (silica gel). Fractions containing the product were combined and evaporated in vacuo to give a crude mixture of 3-(2-arylhydrazono)propenoate **10a–h** and 3-(2-arylhydrazinyl)propenoates **10′a–h** and **10″a–h**.

No further purification of such a mixture was undertaken. Et_3N (0.420 mL, 3 mmol) was added to a soln of a crude mixture of **10**, **10′**, and **10″** in EtOH (5 mL). The mixture was refluxed for 1–8 h and at the end acidified with 1 M HCl (3.5 mL). The precipitated products **11a–f**,**h** were collected by filtration. Product **11g** did not precipitate. In order to isolate product **11g** volatile components were evaporated in vacuo, the residue was dissolved in 1 M $NaHSO_4$ and the product extraction with EtOAc. Experimental, analytical, and spectral data for compounds **10a–h**, **10′a–h**, **10″a–h**, and **11a–h** are given in Tables 1– 4.

Dimethyl (4*R,4a′*R**,7a′*R**)-1-Aryl-6′-benzoyl-4a′-methyl-5-oxo-1,4′,4a′,5,5′,6′-hexahydrospiro[pyrazole-4,7′-pyrrolo[3,4-*c*]pyridazine]-3′,7a′(1′*H*)-dicarboxylates 12a–g; General Procedure**

Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**6**, 0.178 g, 0.9 mmol) was added to a soln of **11a–g** (0.75 mmol) in MeCN (4 mL). The mixture was refluxed for 3–5 h. Volatile components were evaporated in vacuo and the residue was crystallized EtOAc–PE). The precipitated products **12a–g** were collected by filtration. Experimental, analytical, and spectral data for compounds **12a–g** are given in Tables 1– 4.

Table 1 Experimental and Physical Data for Compounds **3**, **5**, **7**, **8**, **10**, **11**, and **12**

Compound	Ar	Time (h)	Isolation[a]	Yield (%)	Ratio of isomers[b] (%)	dr[c]	Mp (°C) (solvent)
3	–	1.67	CC: EtOAc–PE (2:1)	84	–	–	117–118 (EtOAc–PE)
5	Ph	4.5	crystallization: EtOH–H_2O	68	–	–	164–166 (EtOH–H_2O)
7, **7′**	Ph	2	CC: EtOAc–PE (1:1)	47	72:28	–	71–74 (EtOAc–PE)
8, **8′**	Ph	2	CC: EtOAc–PE, (1:1)	47	70:30	–	192–198 (EtOAc–PE)
10a, **10′a**, **10″a**	Ph	2	CC: EtOAc–PE, (1:2)	91	48:25:27	–	–

Table 1 Experimental and Physical Data for Compounds **3**, **5**, **7**, **8**, **10**, **11**, and **12** (continued)

Compound	Ar	Time (h)	Isolation[a]	Yield (%)	Ratio of isomers[b] (%)	dr[c]	Mp (°C) (solvent)
10b, **10′b**, **10″b**	4-MeC_6H_4	2	CC: EtOAc–PE, (1:2)	95	42:35:23	–	–
10c, **10′c**, **10″c**	4-FC_6H_4	5	CC: EtOAc–PE, (1:2)	96	53:24:23	–	–
10d, **10′d**, **10″d**	4-$MeOC_6H_4$	2	CC: EtOAc–PE, (1:2)	89	37:37:26	–	–
10e, **10′e**, **10″e**	3-ClC_6H_4	2	CC: EtOAc–PE, (1:2)	92	64:19:17	–	–
10f, **10′f**, **10″f**	4-$O_2NC_6H_4$	3	CC: EtOAc–PE, (2:3)	91	100:0:0	–	–
10g, **10′g**, **10″g**	4-$HO_2CC_6H_4$	16	CC: EtOAc–PE, (2:1)	79	50:36:14	–	–
10h, **10′h**, **10″h**	6-phenylpyridazin-3-yl	2	CC: EtOAc–PE, (2:1)	79	100:0:0	–	–
11a	Ph	8	crystallization: EtOH–1 M HCl	76[d]	–	–	188–192 (toluene)
11b	4-MeC_6H_4	6	crystallization: EtOH–1 M HCl	70[d]	–	–	183–185 (toluene)
11c	4-FC_6H_4	4.5	crystallization: EtOH–1 M HCl	68[d]	–	–	182–185 (toluene)
11d	4-$MeOC_6H_4$	5.5	crystallization: EtOH–1 M HCl	78[d]	–	–	178–180 (toluene)
11e	3-ClC_6H_4	3	crystallization: EtOH–1 M HCl	86[d]	–	–	188–190 (toluene)
11f	4-$O_2NC_6H_4$	1	crystallization: EtOH–1 M HCl	75[d]	–	–	186–188 (toluene)
11g	4-$HO_2CC_6H_4$	7	extraction: EtOAc–1 M $NaHSO_4$	49[d]	–	–	186–189 (toluene–DMF)
11h	6-phenylpyridazin-3-yl	1	crystallization: EtOH–1 M HCl	64[e]	–	–	235–238 (toluene)
12a	Ph	4	crystallization: EtOAc–PE	85[e]	85:15	85:15	204–206 (toluene)
12b	4-MeC_6H_4	4	crystallization: EtOAc–PE	74[e]	84:16	84:16	217–220 (toluene–DMF)
12c	4-FC_6H_4	3	crystallization: EtOAc–PE	79[e]	83:17	83:17	207–211 (toluene)
12d	4-$MeOC_6H_4$	4.5	crystallization: EtOAc–PE	70[e]	82:18	82:18	194–197 (toluene)
12e	3-ClC_6H_4	4.5	crystallization: EtOAc–PE	88[e]	83:17	83:17	178–180 (EtOAc–PE)
12f	4-$O_2NC_6H_4$	4	crystallization: EtOAc–PE	87[e]	81:19	81:19	197–200 (toluene)
12g	4-$HO_2CC_6H_4$	5	crystallization: EtOAc–PE	64[e]	75:25	75:25	180–183 (toluene–DMF)

[a] CC = column chromatography.
[b] Determined by ^1H NMR of the crude reaction mixture or after CC.
[c] Determined by ^1H NMR of the crude reaction mixture.
[d] Determined relative to **3** used in the reaction.
[e] Isolated yield after one crystallization (EtOAc–PE) resulting in higher to 100% de.

Table 2 Analytical, MS, and IR Data for Compounds **3**, **5**, **7**, **8**, **10**, **11**, and **12**[a]

Compound	MS (*m*/*z*) HRMS (*m*/*z*)	IR (cm^{-1})
3	MS (EI): 302 [M^+] MS (FAB): 303 [M + H^+]	2912, 1685, 1646, 1631, 1434, 1396, 1374, 1301, 1212, 1185, 1163, 1113, 1102, 1052, 900, 726, 705
5	–	3445, 3236, 1703, 1640, 1624, 1599, 1490, 1435, 1402, 1247, 1139, 1058, 897, 779, 762, 715
7, **7′**	MS (EI): 520 [M^+] HRMS (EI): calcd: 520.195800; found: 520.195800	3359, 2953, 1714, 1680, 1630, 1601, 1587, 1505, 1438, 1399, 1348, 1290, 1226, 1198, 1103, 757, 700
8, **8′**	MS (EI): 520 [M^+] HRMS (EI): calcd: 520.197250; found: 520.195800	3376, 3250, 2951, 1709, 1645, 1627, 1601, 1576, 1499, 1436, 1403, 1370, 1349, 1295, 1243, 1200, 1102, 761, 718, 696

Table 2 Analytical, MS, and IR Data for Compounds **3**, **5**, **7**, **8**, **10**, **11**, and **12**[a] (continued)

Compound	MS (*m*/*z*) HRMS (*m*/*z*)	IR (cm^{-1})
10a, **10′a**, **10″a**	MS (EI): 365 [M^+] HRMS (EI): calcd: 365.173942; found: 365.173020	–
10b, **10′b**, **10″b**	MS (EI): 379 [M^+] HRMS (EI): calcd: 379.189592; found: 379.188350	–
10c, **10′c**, **10″c**	MS (EI): 383 [M^+] HRMS (EI): calcd: 383.164520; found: 383.165000	–
10d, **10′d**, **10″d**	MS (EI): 395 [M^+] HRMS (EI): calcd: 395.184507; found: 395.185300	–
10e, **10′e**, **10″e**	MS (EI): 399 [M^+] HRMS (EI): calcd: 399.134970; found: 399.135500	–
10f	MS (ESI): 411.2 [M + H^+] HRMS (ESI): calcd: 411.1668; found: 411.1662	–
10g, **10′g**, **10″g**	MS (EI): 409 [M^+] HRMS (EI): calcd: 409.163771; found: 409.164550	–
10h	MS (ESI): 444.2 [M + H^+] HRMS (ESI): calcd: 444.2036; found: 444.2038	–
11a	MS (ESI): 334.2 [M + H^+] HRMS (ESI): calcd: 334.1556; found: 334.1557	3444, 3105, 2734, 1651, 1625, 1600, 1579, 1500, 1457, 1446, 1398, 1357, 1290, 1233, 916, 776, 751, 699
11b	–	3446, 3095, 2921, 1645, 1620, 1579, 1515, 1493, 1400, 1344, 1318, 1246, 924, 808, 767, 698
11c	–	3446, 3103, 1648, 1624, 1600, 1576, 1509, 1445, 1406, 1355, 1291, 1231, 832, 768, 698
11d	–	3447, 3096, 1651, 1621, 1578, 1513, 1399, 1358, 1301, 1249, 1028, 826, 766, 700
11e	–	3446, 3108, 1652, 1630, 1598, 1584, 1485, 1434, 1394, 1358, 1231, 918, 877, 792, 777, 748, 703
11f	–	3445, 3094, 1645, 1633, 1597, 1514, 1497, 1404, 1342, 1239, 1114, 850, 774, 749, 698
11g	MS (ESI): 378.1 [M + H^+] HRMS (ESI): calcd: 378.1454; found: 378.1448	3445, 3093, 1689, 1630, 1607, 1577, 1515, 1428, 1402, 1348, 1287, 1245, 1177, 855, 771, 698
11h	MS (ESI): 412.2 [M + H^+] HRMS (ESI): calcd: 412.1774; found: 412.1773	3447, 3102, 1652, 1592, 1452, 1428, 1382, 1366, 1286, 1223, 1106, 923, 744, 694
12a	–	3338, 2956, 1747, 1736, 1707, 1639, 1620, 1499, 1399, 1365, 1314, 1270, 1237, 1194, 1147, 1125, 1080, 765, 692
12b	–	3434, 3310, 1752, 1723, 1690, 1640, 1614, 1516, 1437, 1392, 1372, 1314, 1270, 1193, 1166, 1139, 1125, 825, 720
12c	MS (ESI): 522.2 [M + H^+] HRMS (ESI): calcd: 544.1608 [M + Na^+]; found: 544.1603	3308, 1755, 1728, 1690, 1639, 1613, 1510, 1439, 1393, 1372, 1314, 1269, 1216, 1194, 1156, 1143, 1124, 839, 722

Table 2 Analytical, MS, and IR Data for Compounds **3**, **5**, **7**, **8**, **10**, **11**, and **12**[a] (continued)

Compound	MS (*m*/*z*) HRMS (*m*/*z*)	IR (cm^{-1})
12d	MS (ESI): 534.2 [M + H^+] HRMS (ESI): calcd: 534.1989; found: 534.1984	3399, 3309, 1750, 1731, 1712, 1645, 1624, 1512, 1445, 1390, 1311, 1270, 1249, 1188, 1149, 1127, 1028, 832, 722
12e	MS (ESI): 538.2 [M + H^+] HRMS (ESI): calcd: 538.1493; found: 538.1508	3315, 1733, 1728, 1707, 1640, 1594, 1483, 1438, 1398, 1358, 1311, 1273, 1243, 1190, 1127, 1078, 782, 719
12f	MS (ESI): 549.2 [M + H^+] HRMS (ESI): calcd: 549.1734; found: 549.1726	3299, 1749, 1730, 1706, 1635, 1594, 1516, 1497, 1399, 1334, 1270, 1195, 1129, 1112, 846, 751
12g	MS (ESI): 548.2 [M + H^+] HRMS (ESI): calcd: 548.1781; found: 548.1775	3448, 3338, 2958, 1729, 1701, 1682, 1670, 1637, 1606, 1515, 1395, 1356, 1315, 1276, 1250, 1183, 1131, 1086, 860, 720

[a] Anal. **3**, **5**, **7**, **7′**, **8**, **8′**, **11a**–**h**, **12a**–**d**, C ±0.29, H ±0.21, N ±0.31 except, **12e**: Calcd for $C_{26}H_{24}ClN_5O_6 \cdot 0.5\ C_4H_8O_2$ (EtOAc): C, 57.78; H, 4.85; N, 12.03. Found: C, 58.16; H, 4.76; N, 12.11; **12f**: Calcd for $C_{26}H_{24}N_6O_8 \cdot 0.5\ C_7H_8$ (toluene): C, 59.59; H, 4.75; N, 14.13. Found: C, 59.80; H, 4.80; N, 14.22; and **12g**: Calcd for $C_{27}H_{25}N_5O_8 \cdot C_3H_7NO$ (DMF): C, 58.06; H, 5.20; N, 13.54. Found: C, 58.45; H, 5.10; N, 13.29.

Table 3 ^{1}H NMR Data for Compounds **3**, **5**, **7**, **8**, **10**, **11**, and **12**[a]

Compound	^{1}H NMR δ ($CDCl_3$)[b], *J* (Hz)
3	1.90 (s, 3 H, CH_3), 3.03 (s, 6 H, NMe_2), 3.55 (s, 3 H, COOMe), 3.69 (d, *J* = 13.6, 1 H, CHH_a), 4.63 (d, *J* = 13.6, 1 H, CHH_b), 4.87 (s, 2 H, C=CH_2), 7.03 (s, 1 H, CH), 7.23–7.32 (m, 3 H, Ph), 7.40–7.45 (m, 2 H, Ph)
5	1.92 (s, 3 H, CH_3), 3.58 (s, 3 H, COOMe), 3.73 (d, *J* = 15.1, 1 H, CHH_a), 4.64 (d, *J* = 15.1, 1 H, CHH_b), 5.01 (s, 1 H, C=CHH_a), 5.05 (s, 1 H, C=CHH_b), 6.92–6.97 (m, 2 H, Ph), 7.03–7.09 (m, 1 H, Ph), 7.15 (br d, *J* = 13.7, 1 H, NH), 7.21–7.28 (m, 2 H, Ph), 7.29–7.37 (m, 3 H, Ph), 7.40–7.46 (m, 2 H, Ph), 7.72 (d, *J* = 13.6, 1 H, CH)
7	1.47 (s, 3 H, CH_3), 3.61 (s, 3 H, COOMe), 3.81 (s, 3 H, COOMe), 3.87 (s, 3 H, COOMe), 3.96 (d, *J* = 14.1, 1 H, CHH_a), 4.44 (d, *J* = 14.4, 1 H, CHH_b), 6.01 (d, *J* = 2.1, 1 H, H5), 6.68–6.72 (m, 2 H, Ph), 6.91 (d, *J* = 13.1, 1 H, C*H*NH), 6.97–7.03 (m, 1 H, Ph), 7.13–7.32 (m, 7 H, Ph), 8.02 (d, *J* = 2.0, 1 H, H1), 9.51 (d, *J* = 13.0, 1 H, CHN*H*)
7′	1.51 (s, 3 H, CH_3), 3.49 (d, *J* = 14.2, 1 H, CHH_a), 3.59 (s, 3 H, COOMe), 3.61 (s, 3 H, COOMe), 3.72 (s, 3 H, COOMe), 4.82 (d, *J* = 14.0, 1 H, CHH_b), 5.72 (d, *J* = 1.8, 1 H, H5), 6.79–6.84 (m, 2 H, Ph), 7.01–7.07 (m, 2 H, C*H*NH, Ph), 7.13–7.32 (m, 7 H, Ph), 7.91 (d, *J* = 1.9, 1 H, H1), 9.62 (d, *J* = 12.1, 1 H, CHN*H*)
8	1.42 (s, 3 H, CH_3), 3.79 (s, 3 H, COOMe), 3.80 (s, 3 H, COOMe), 3.84 (d, *J* = 14.4, 1 H, CHH_a), 3.88 (s, 3 H, COOMe), 4.49 (d, *J* = 14.6, 1 H, CHH_b), 6.01 (d, *J* = 1.7, 1 H, H5), 6.64–6.72 (m, 2 H, Ph), 6.96–7.02 (m, 1 H, Ph), 7.09 (d, *J* = 13.8, 1 H, C*H*NH), 7.15–7.34 (m, 7 H, Ph), 7.40 (d, *J* = 13.5, 1 H, CHN*H*), 7.91 (d, *J* = 1.8, 1 H, H1)
8′	1.42 (s, 3 H, CH_3), 3.33 (d, *J* = 14.4, 1 H, CHH_a), 3.63 (s, 3 H, COOMe), 3.69 (s, 3 H, COOMe), 3.91 (s, 3 H, COOMe), 4.90 (d, *J* = 14.3, 1 H, CHH_b), 5.64 (d, *J* = 2.2, 1 H, H5), 6.80–6.85 (m, 2 H, Ph), 7.00–7.04 (m, 1 H, Ph), 7.11 (d, *J* = 13.5, 1 H, C*H*NH), 7.15–7.34 (m, 7 H, Ph), 7.40 (d, *J* = 13.5, 1 H, CHN*H*), 7.75 (d, *J* = 2.2, 1 H, H1)
10a	1.71 (s, 3 H, CH_3), 3.81 (s, 3 H, COOMe), 3.89 (d, *J* = 17.7, 1 H, CHH_a), 3.97 (d, *J* = 17.7, 1 H, CHH_b), 4.57 (d, *J* = 6.3, 1 H, H2), 5.11 (s, 1 H, C=CHH_a), 5.38 (s, 1 H, C=CHH_b), 7.20–7.58 (m, 11 H, Ph, H3), 7.66 (s, 1 H, NH)
10′a	1.90 (s, 3 H, CH_3), 3.63 (s, 3 H, COOMe), 4.61 (d, *J* = 15.0, 1 H, CHH_b), 4.99 (s, 1 H, C=CHH_a), 5.80 (s, 1 H, C=CHH_b), 6.30 (d, *J* = 11.4, 1 H, CHN*H*), 6.56 (s, 1 H, N*H*Ar)
10″a	1.80 (s, 3 H, CH_3), 3.54 (d, *J* = 14.6, 1 H, CHH_a), 3.75 (s, 3 H, COOMe), 4.85 (s, 1 H, C=CHH_a), 5.87 (s, 1 H, C=CHH_b), 6.54 (s, 1 H, N*H*Ar), 6.74 (d, *J* = 10.7, 1 H, H3), 8.58 (d, *J* = 10.5, 1 H, CHN*H*)
10b	1.71 (s, 3 H, CH_3), 2.27 (s, 3 H, PhCH_3), 3.80 (s, 3 H, COOMe), 3.88 (d, *J* = 19.2, 1 H, CHH_a), 3.96 (d, *J* = 18.5, 1 H, CHH_b), 4.57 (d, *J* = 5.7, 1 H, H2), 5.10 (s, 1 H, C=CHH_a), 5.38 (s, 1 H, C=CHH_b), 6.85–6.91 (m, 2 H, H3′, H5′), 7.28–7.44 (m, 5 H, Ph), 7.48–7.54 (m, 3 H, H2′, H6′, H3), 7.58 (s, 1 H, NH)
10′b	1.89 (s, 3 H, CH_3), 2.27 (s, 3 H, PhCH_3), 3.62 (s, 3 H, COOMe), 4.58 (d, *J* = 14.7, 1 H, CHH_b), 4.98 (s, 1 H, C=CHH_a), 5.72 (s, 1 H, C=CHH_b), 6.29 (d, *J* = 11.0, 1 H, CHN*H*), 6.49 (s, 1 H, N*H*Ar)
10″b	1.80 (s, 3 H, CH_3), 2.27 (s, 3 H, PhCH_3), 3.53 (d, *J* = 14.5, 1 H, CHH_a), 3.74 (s, 3 H, COOMe), 4.85 (s, 1 H, C=CHH_a), 5.79 (s, 1 H, C=CHH_b), 6.46 (s, 1 H, N*H*Ar), 6.75 (d, *J* = 10.8, 1 H, H3), 8.56 (d, *J* = 10.6, 1 H, CHN*H*)

Table 3 ^{1}H NMR Data for Compounds **3**, **5**, **7**, **8**, **10**, **11**, and **12**[a] (continued)

Compound	^{1}H NMR δ ($CDCl_3$)[b], *J* (Hz)
10c	1.71 (s, 3 H, CH_3), 3.80 (s, 3 H, COOMe), 3.89 (d, *J* = 16.2, 1 H, CHH_a), 3.97 (d, *J* = 16.7, 1 H, CHH_b), 4.54 (d, *J* = 5.8, 1 H, H2), 5.11 (s, 1 H, C=CHH_a), 5.37 (s, 1 H, C=CHH_b), 6.85–6.95 (m, 2 H, H3′, H5′), 7.30–7.45 (m, 5 H, Ph), 7.47–7.53 (m, 2 H, H2′, H6′), 7.55 (d, *J* = 6.7, 1 H, H3), 7.68 (s, 1 H, NH)
10′c	1.89 (s, 3 H, CH_3), 3.64 (s, 3 H, COOMe), 4.57 (d, *J* = 13.4, 1 H, CHH_b), 4.97 (s, 1 H, C=CHH_a), 5.75 (s, 1 H, C=CHH_b)
10″c	1.80 (s, 3 H, CH_3), 3.53 (d, *J* = 14.3, 1 H, CHH_a), 3.76 (s, 3 H, COOMe), 4.84 (s, 1 H, C=CHH_a), 5.82 (s, 1 H, C=CHH_b), 6.71 (d, *J* = 10.7, 1 H, H3), 8.58 (d, *J* = 10.9, 1 H, CHN*H*)
10d	1.71 (s, 3 H, CH_3), 3.77 (s, 3 H, OMe), 3.80 (s, 3 H, COOMe), 3.88 (d, *J* = 18.1, 1 H, CHH_a), 3.96 (d, *J* = 17.3, 1 H, CHH_b), 4.56 (d, *J* = 5.9, 1 H, H2), 5.11 (s, 1 H, C=CHH_a), 5.38 (s, 1 H, C=CHH_b), 6.79–6.85 (m, 2 H, H3′, H5′), 7.29–7.55 (m, 9 H, Ph, H2′, H6′, H3, NH)
10′d	1.88 (s, 3 H, CH_3), 3.62 (s, 3 H, COOMe), 3.77 (s, 3 H, OMe), 4.55 (d, *J* = 14.7, 1 H, CHH_b), 4.96 (s, 1 H, C=CHH_a), 5.66 (s, 1 H, C=CHH_b), 6.31 (d, *J* = 11.2, 1 H, CHN*H*), 6.54 (s, 1 H, N*H*Ar)
10″d	1.80 (s, 3 H, CH_3), 3.53 (d, *J* = 14.3, 1 H, CHH_a), 3.74 (s, 3 H, COOMe), 3.76 (s, 3 H, OMe), 4.85 (s, 1 H, C=CHH_a), 5.73 (s, 1 H, C=CHH_b), 6.51 (s, 1 H, N*H*Ar), 6.75 (d, *J* = 10.8, 1 H, H3), 8.56 (d, *J* = 10.3, 1 H, CHN*H*)
10e	1.72 (s, 3 H, CH_3), 3.80 (s, 3 H, COOMe), 3.89 (d, *J* = 17.3, 1 H, CHH_a), 3.97 (d, *J* = 17.3, 1 H, CHH_b), 4.53 (d, *J* = 6.3, 1 H, H2), 5.12 (s, 1 H, C=CHH_a), 5.38 (s, 1 H, C=CHH_b), 6.75 (ddd, *J* = 0.9, 2.1, 8.2, 1 H, H4′ or H6′), 6.79 (ddd, *J* = 0.9, 1.9, 7.8, 1 H, H4′ or H6′), 7.02 (t, *J* = 2.0, 1 H, H2′), 7.11 (t, *J* = 8.1, 1 H, H5′), 7.30–7.54 (m, 5 H, Ph), 7.59 (d, *J* = 6.2, 1 H, H3), 7.91 (s, 1 H, NH)
10′e	1.91 (s, 3 H, CH_3), 3.63 (s, 3 H, COOMe), 4.59 (d, *J* = 15.1, 1 H, CHH_b), 4.99 (s, 1 H, C=CHH_a), 5.87 (s, 1 H, C=CHH_b), 6.42 (d, *J* = 10.8, 1 H, CHN*H*)
10″e	1.80 (s, 3 H, CH_3), 3.53 (d, *J* = 14.3, 1 H, CHH_a), 3.75 (s, 3 H, COOMe), 4.86 (s, 1 H, C=CHH_a), 5.93 (s, 1 H, C=CHH_b), 6.52 (t, *J* = 2.0, 1 H, H2′), 6.62 (s, 1 H, N*H*Ar), 6.69 (d, *J* = 10.6, 1 H, H3), 8.59 (d, *J* = 10.6, 1 H, CHN*H*)
10f	1.74 (s, 3 H, CH_3), 3.81 (s, 3 H, COOMe), 3.92 (d, *J* = 17.0, 1 H, CHH_a), 4.00 (d, *J* = 17.0, 1 H, CHH_b), 4.53 (d, *J* = 6.3, 1 H, H2), 5.14 (s, 1 H, C=CHH_a), 5.37 (s, 1 H, C=CHH_b), 6.81–6.87 (m, 2 H, H2′, H6′), 7.36–7.54 (m, 5 H, Ph), 7.84 (d, *J* = 6.4, 1 H, H3), 8.02–8.09 (m, 2 H, H3′, H5′), 9.12 (s, 1 H, NH)
10g	1.72 (s, 3 H, CH_3), 3.79 (s, 3 H, COOMe), 3.90 (d, *J* = 17.0, 1 H, CHH_a), 3.98 (d, *J* = 18.3, 1 H, CHH_b), 4.55 (d, *J* = 6.2, 1 H, H2), 5.13 (s, 1 H, C=CHH_a), 5.37 (s, 1 H, C=CHH_b), 6.90–6.97 (m, 2 H, H2′, H6′), 7.35–7.56 (m, 5 H, Ph), 7.89–7.96 (m, 2 H, H3′, H5′), 7.68 (d, *J* = 6.1, 1 H, H3), 8.40 (s, 1 H, NH), COOH exchanged
10′g	1.90 (s, 3 H, CH_3), 3.65 (s, 3 H, COOMe), 4.43 (d, *J* = 14.4, 1 H, CHH_b), 4.98 (s, 1 H, C=CHH_a), 6.21 (s, 1 H, C=CHH_b)
10″g	1.79 (s, 3 H, CH_3), 3.54 (d, *J* = 14.4, 1 H, CHH_a), 3.78 (s, 3 H, COOMe), 4.85 (s, 1 H, C=CHH_a), 6.23 (s, 1 H, C=CHH_b), 6.66 (d, *J* = 10.7, 1 H, H3), 8.66 (d, *J* = 10.9, 1 H, CHN*H*)
10h	1.71 (s, 3 H, CH_3), 3.84 (s, 3 H, COOMe), 3.90 (d, *J* = 17.0, 1 H, CHH_a), 4.01 (d, *J* = 16.9, 1 H, CHH_b), 4.63 (d, *J* = 6.3, 1 H, H2), 5.11 (s, 1 H, C=CHH_a), 5.37 (s, 1 H, C=CHH_b), 7.35–7.57 (m, 9 H, Ph, $H_{pyridazine}$), 7.78 (d, *J* = 9.34, 1 H, $H_{pyridazine}$), 7.84 (d, *J* = 6.1, 1 H, H3), 7.98–8.04 (m, 2 H, Ph), 9.46 (br s, 1 H, NH)
11a	1.64 (s, 3 H, CH_3), 4.22 (s, 2 H, CH_2), 5.02 (s, 1 H, C=CHH_a), 5.05 (s, 1 H, C=CHH_b), 7.27–7.32 (m, 1 H, Ph), 7.40–7.56 (m, 8 H, H3, Ph), 7.79–7.88 (m, 2 H, Ph), OH exchanged
11b	1.63 (s, 3 H, CH_3), 2.38 (s, 3 H, Me), 4.21 (s, 2 H, CH_2), 5.02 (s, 1 H, C=CHH_a), 5.05 (s, 1 H, C=CHH_b), 7.22–7.27 (m, 2 H, H3′, H5′), 7.38–7.56 (m, 6 H, H3, Ph), 7.64–7.70 (m, 2 H, H2′, H6′), 10.56 (br s, 1 H, OH)
11c	1.64 (s, 3 H, CH_3), 4.21 (s, 2 H, CH_2), 5.01 (s, 1 H, C=CHH_a), 5.06 (s, 1 H, C=CHH_b), 7.08–7.17 (m, 2 H, H3′, H5′), 7.38–7.56 (m, 6 H, H3, Ph), 7.74–7.82 (m, 2 H, H2′, H6′), 10.71 (br s, 1 H, OH)
11d	1.63 (s, 3 H, CH_3), 3.84 (s, 3 H, OMe), 4.21 (s, 2 H, CH_2), 5.01 (s, 1 H, C=CHH_a), 5.05 (s, 1 H, C=CHH_b), 6.94–7.00 (m, 2 H, H3′, H5′), 7.38 (s, 1 H, H3), 7.40–7.56 (m, 5 H, Ph), 7.64–7.72 (m, 2 H, H2′, H6′), 10.53 (br s, 1 H, OH)
11e	1.63 (s, 3 H, CH_3), 4.21 (s, 2 H, CH_2), 5.00 (s, 1 H, C=CHH_a), 5.06 (s, 1 H, C=CHH_b), 7.22–7.27 (m, 1 H, H4′), 7.36 (t, *J* = 8.1, 1 H, H2′), 7.40–7.56 (m, 6 H, H3, Ph), 7.77–7.81 (m, 1 H, H6′), 7.89–7.93 (m, 1 H, H2′), 10.84 (br s, 1 H, OH)
11f	1.64 (s, 3 H, CH_3), 4.23 (s, 2 H, CH_2), 5.01 (s, 1 H, C=CHH_a), 5.08 (s, 1 H, C=CHH_b), 7.43–7.58 (m, 6 H, H3, Ph), 8.12–8.18 (m, 2 H, H2′, H6′), 8.28–8.34 (m, 2 H, H3′, H5′), 11.24 (br s, 1 H, OH)
11g[c]	1.78 (s, 3 H, CH_3), 4.24 (s, 2 H, CH_2), 4.88 (s, 2 H, C=CH_2), 7.24–7.42 (m, 6 H, H3, Ph), 7.74–7.82 (m, 2 H, H2′, H6′), 7.94–8.02 (m, 2 H, H3′, H5′), 12.19 (br s, 1 H, COOH), 12.91 (br s, 1 H, OH)

Table 3 ^{1}H NMR Data for Compounds **3**, **5**, **7**, **8**, **10**, **11**, and **12**[a] (continued)

Compound	^{1}H NMR δ ($CDCl_3$)[b], *J* (Hz)
11h	1.85 (s, 3 H, CH_2), 4.43 (s, 2 H, CH_2), 4.89–4.94 (m, 2 H, C=CH_2), 7.21–7.31 (m, 3 H, Ph), 7.45–7.51 (m, 2 H, Ph), 7.51–7.59 (m, 4 H, Ph, H5′), 7.97–8.04 (m, 2 H, Ph), 8.05 (s, 1 H, H3), 8.11 (d, *J* = 9.5, 1 H, H4′), 12.13 (br s, 1 H, OH)
12a	1.01 (s, 3 H, CH_3), 2.71 (d, *J* = 17.5, 1 H, H4′$_a$), 3.29 (d, *J* = 17.6, 1 H, H4′$_b$), 3.68 (d, *J* = 10.1, 1 H, H5′$_a$), 3.83 (s, 3 H, COOMe), 3.94 (s, 3 H, COOMe), 4.03 (d, *J* = 10.4, 1 H, H5′$_b$), 7.17–7.24 (m, 1 H, Ph), 7.32 (s, 1 H, H3), 7.34–7.50 (m, 6 H, Ph, NH), 7.52–7.58 (m, 2 H, Ph), 7.70–7.77 (m, 2 H, Ph)
12′a	1.23 (s, 3 H, CH_3), 2.47 (d, *J* = 19.0, 1 H, H4′$_a$), 3.86 (s, 3 H, COOMe), 3.91 (s, 3 H, COOMe)
12b	1.02 (s, 3 H, CH_3), 2.34 (s, 3 H, Me), 2.70 (d, *J* = 17.5, 1 H, H4′$_a$), 3.28 (d, *J* = 17.4, 1 H, H4′$_b$), 3.67 (d, *J* = 10.0, 1 H, H5′$_a$), 3.83 (s, 3 H, COOMe), 3.93 (s, 3 H, COOMe), 4.00 (d, *J* = 9.6, 1 H, H5′$_b$), 7.14–7.22 (m, 2 H, H3′, H5′), 7.30 (s, 1 H, H3), 7.38–7.50 (m, 4 H, Ph, NH), 7.50–7.56 (m, 2 H, Ph), 7.56–7.62 (m, 2 H, H2′, H6′)
12′b	1.22 (s, 3 H, CH_3), 2.52 (d, *J* = 18.1, 1 H, H4′$_a$), 3.55 (d, *J* = 9.9, 1 H, H5′$_a$), 3.86 (s, 3 H, COOMe), 3.90 (s, 3 H, COOMe), 4.21 (d, *J* = 9.8, 1 H, H5′$_b$)
12c	1.00 (s, 3 H, CH_3), 2.71 (d, *J* = 17.5, 1 H, H4′$_a$), 3.29 (d, *J* = 17.5, 1 H, H4′$_b$), 3.68 (d, *J* = 10.0, 1 H, H5′$_a$), 3.83 (s, 3 H, COOMe), 3.95 (s, 3 H, COOMe), 4.04 (d, *J* = 10.1, 1 H, H5′$_b$), 7.02–7.11 (m, 2 H, H3′, H5′), 7.30 (s, 1 H, H3), 7.35 (br s, 1 H, NH), 7.40–7.50 (m, 3 H, Ph), 7.52–7.58 (m, 2 H, Ph), 7.67–7.74 (m, 2 H, H2′, H6′)
12′c	1.23 (s, 3 H, CH_3), 2.47 (d, *J* = 19.1, 1 H, H4′$_a$), 3.56 (d, *J* = 9.8, 1 H, H5′$_a$), 3.86 (s, 3 H, COOMe), 3.91 (s, 3 H, COOMe), 4.19 (d, *J* = 9.7, 1 H, H5′$_b$)
12d	1.02 (s, 3 H, CH_3), 2.69 (d, *J* = 17.5, 1 H, H4′$_a$), 3.28 (d, *J* = 17.8, 1 H, H4′$_b$), 3.67 (d, *J* = 10.0, 1 H, H5′$_a$), 3.81 (s, 3 H, OMe), 3.83 (s, 3 H, COOMe), 3.93 (s, 3 H, COOMe), 4.00 (d, *J* = 10.2, 1 H, H5′$_b$), 6.88–6.95 (m, 2 H, H3′, H5′), 7.29 (s, 1 H, H3), 7.39–7.50 (m, 4 H, Ph, NH), 7.50–7.57 (m, 2 H, Ph), 7.57–7.64 (m, 2 H, H2′, H6′)
12′d	1.22 (s, 3 H, CH_3), 2.46 (d, *J* = 19.0, 1 H, H4′$_a$), 2.77 (d, *J* = 19.2, 1 H, H4′$_b$), 3.55 (d, *J* = 9.7, 1 H, H5′$_a$), 3.86 (s, 3 H, COOMe), 3.91 (s, 3 H, COOMe), 4.20 (d, *J* = 9.6, 1 H, H5′$_b$), 7.14 (s, 1 H, H3)
12e	0.99 (s, 3 H, CH_3), 2.72 (d, *J* = 17.5, 1 H, H4′$_a$), 3.28 (d, *J* = 17.4, 1 H, H4′$_b$), 3.69 (d, *J* = 10.1, 1 H, H5′$_a$), 3.84 (s, 3 H, COOMe), 3.95 (s, 3 H, COOMe), 4.06 (d, *J* = 10.2, 1 H, H5′$_b$), 7.14–7.19 (m, 1 H, H4′), 7.26–7.34 (m, 3 H, H2′, H3, NH), 7.40–7.58 (m, 5 H, Ph), 7.67–7.72 (m, 1 H, H6′), 7.81–7.85 (m, 1 H, H2′)
12′e	1.24 (s, 3 H, CH_3), 2.46 (d, *J* = 19.0, 1 H, H4′$_a$), 3.57 (d, *J* = 9.8, 1 H, H5′$_a$), 3.86 (s, 3 H, COOMe), 3.91 (s, 3 H, COOMe), 4.19 (d, *J* = 10.1, 1 H, H5′$_b$)
12f	0.98 (s, 3 H, CH_3), 2.75 (d, *J* = 17.5, 1 H, H4′$_a$), 3.29 (d, *J* = 17.4, 1 H, H4′$_b$), 3.72 (d, *J* = 10.1, 1 H, H5′$_a$), 3.85 (s, 3 H, COOMe), 3.99 (s, 3 H, COOMe), 4.12 (d, *J* = 10.1, 1 H, H5′$_b$), 7.24 (br s, 1 H, NH), 7.39 (s, 1 H, H3), 7.42–7.59 (m, 5 H, Ph), 7.99–8.05 (m, 2 H, H2′, H6′), 8.22–8.29 (m, 2 H, H3′, H5′)
12′f	1.27 (s, 3 H, CH_3), 2.48 (d, *J* = 19.4, 1 H, H4′$_a$), 2.78 (d, *J* = 19.1, 1 H, H4′$_b$), 3.61 (d, *J* = 9.8, 1 H, H5′$_a$), 3.87 (s, 3 H, COOMe), 3.90 (s, 3 H, COOMe), 4.18 (d, *J* = 9.9, 1 H, H5′$_b$), 7.18 (br s, 1 H, NH), 7.28 (s, 1 H, H3)
12g[c]	0.79 (s, 3 H, CH_3), 2.64 (d, *J* = 17.1, 1 H, H4′$_a$), 3.00 (d, *J* = 17.1, 1 H, H4′$_b$), 3.67 (s, 3 H, COOMe), 3.72 (d, *J* = 10.1, 1 H, H5′$_a$), 3.94 (s, 3 H, COOMe), 4.15 (d, *J* = 10.4, 1 H, H5′$_b$), 7.48–7.62 (m, 5 H, Ph), 7.82 (s, 1 H, H3), 7.82–7.87 (m, 2 H, H2′, H6′), 7.99–8.05 (m, 2 H, H3′, H5′), 9.06 (br s, 1 H, NH), 12.89 (br s, 1 H, COOH)
12′g[c]	1.31 (s, 3 H, CH_3), 3.66 (s, 3 H, COOMe), 3.71 (s, 3 H, COOMe), 9.33 (s, 1 H, NH), 12.75 (br s, 1 H, COOH)

[a] The ^{1}H NMR spectra of **10′a–e**,**g**, **10″a–e**,**g** and **12′a–g** are part spectra.
[b] Unless otherwise stated.
[c] DMSO-d_6.

Table 4 ^{13}C NMR Data for Compounds **3**, **11a–f**, and **12a–f**

Compound	Solvent	^{13}C NMR δ, *J* (Hz)
3	$CDCl_3$	21.6, 42.0, 50.9, 56.5, 102.3, 115.0, 127.0, 127.7, 129.3, 137.3, 141.4, 145.7, 168.0, 172.9
11a	DMSO-d_6	20.0, 53.8, 112.4, 120.5, 120.6, 125.7, 126.9, 127.5, 128.8, 129.0, 131.1, 136.7, 138.1, 140.7, 170.7
11b	DMSO-d_6	20.1, 20.4, 53.8, 112.4, 120.5, 120.7, 127.0, 127.5, 129.0, 129.3, 135.2, 135.9, 136.8, 137.6, 140.8, 170.7
11c	DMSO-d_6	20.1, 53.8, 107.9, 112.5, 115.7 (d, *J* = 22.8), 122.7 (d, *J* = 7.1), 127.0, 127.6, 129.0, 134.7, 136.8, 138.1, 140.7, 159.9 (d, *J* = 243), 170.7
11d	DMSO-d_6	20.1, 53.9, 55.4, 112.5, 114.1, 122.7, 127.0, 127.6, 129.1, 131.5, 136.8, 137.5, 140.8, 157.4, 170.8

Table 4 ^{13}C NMR Data for Compounds **3**, **11a–f**, and **12a–f** (continued)

Compound	Solvent	^{13}C NMR δ, *J* (Hz)
11e	DMSO-d_6	20.0, 53.7, 108.4, 112.6, 118.4, 119.6, 125.4, 127.0, 127.6, 129.1, 130.7, 133.3, 136.7, 138.9, 139.4, 140.7, 170.7
11f	DMSO-d_6	20.0, 53.6, 108.9, 112.8, 119.6, 124.9, 127.0, 127.7, 129.2, 136.6, 140.3, 140.7, 143.3, 144.0, 170.7
12a	$CDCl_3$	20.7, 29.9, 36.3, 52.4, 53.8, 60.9, 71.4, 75.6, 119.9, 125.9, 127.6, 128.7, 128.9, 131.3, 133.6, 133.8, 137.7, 146.7, 164.8, 167.9, 168.5, 169.3
12b	$CDCl_3$	20.9, 21.2, 29.9, 36.5, 52.5, 53.8, 60.9, 71.3, 75.3, 120.3, 127.7, 128.7, 129.5, 131.3, 133.6, 134.0, 135.3, 135.8, 146.4, 164.9, 167.9, 168.5, 169.3
12c	$CDCl_3$	20.8, 29.9, 36.4, 52.5, 53.9, 61.0, 71.5, 75.6, 115.7 (d, *J* = 22.7), 122.0 (d, *J* = 8.2), 127.7, 128.7, 131.4, 133.8, 133.9, 134.0, 146.8, 160.6 (d, *J* = 245), 164.8, 168.0, 168.5, 169.4
12d	$CDCl_3$	20.9, 29.9, 36.4, 52.5, 53.8, 55.7, 60.9, 71.3, 75.2, 114.3, 122.4, 127.7, 128.7, 131.1, 131.3, 133.6, 134.0, 146.4, 158.0, 164.9, 168.0, 168.5, 169.4
12e	$CDCl_3$	20.7, 29.9, 36.3, 52.5, 53.9, 61.0, 71.6, 75.9, 117.4, 119.5, 125.7, 127.7, 128.7, 130.0, 131.4, 133.6, 133.9, 134.7, 138.9, 147.1, 164.7, 167.9, 168.5, 169.4
12f	$CDCl_3$	20.7, 30.0, 36.3, 52.7, 54.1, 61.1, 72.0, 76.3, 118.6, 124.9, 127.8, 128.8, 131.7, 133.3, 134.4, 142.9, 144.6, 148.1, 164.7, 168.1, 168.6, 169.5

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(14) Crystallographic data for compound **12a** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 689403. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, CB2 1EZ, UK [fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].
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