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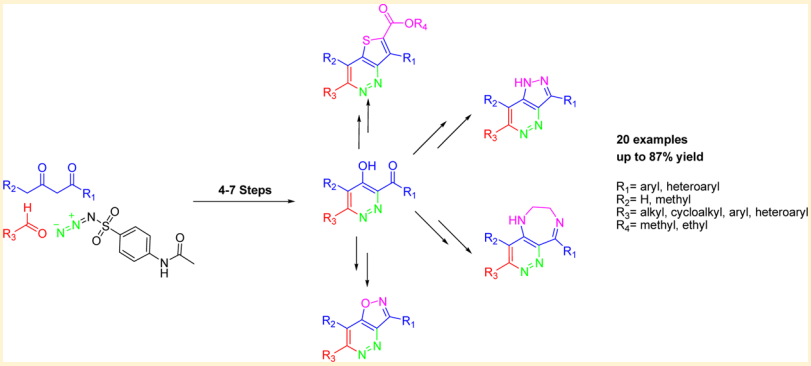
Strategy for the Synthesis of Pyridazine Heterocycles and Their Derivatives

Hassen Bel Abed,[†] Oscar Mammoliti,[‡] Omprakash Bande,[†] Guy Van Lommen,[‡] and Piet Herdewijn*[,†]

[†]Rega Institute for Medical Research, Laboratory of Medicinal Chemistry, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium

[‡]Galapagos, Laboratory of Medicinal Chemistry, Generaal De Wittelaan L11 A3, B-2800 Mechelen, Belgium

Supporting Information



ABSTRACT: The first synthesis of novel fused pyridazines has been realized starting from 1,3-diketones involving a Diaza–Wittig reaction as a key step. A convenient strategy was elaborated to access versatile pyridazine derivatives allowing the variation of substituents at position 6 of the heterocyclic ring. In a first part, pyridazines bearing an ester group were synthesized as a model to evaluate the methodology. In a second part, an improved procedure has been used for the synthesis of pyridazines bearing a ketone group and different methods of cyclization were carried out, leading to several hitherto unknown biheterocyclic compounds. This reaction scheme represents an attractive methodology for the synthesis of novel fused pyridazine derivatives.

INTRODUCTION

Recently, pyridazines have been considered by GlaxoSmithKline as one of the "most developable" heteroaromatic rings for drug design.[1] Pyridazine analogues proved to be useful ligands for different targets and have been proposed as "privileged structure" for drug discovery.[2] Several compounds with pyridazine rings demonstrate biological activity (**1**–**4**), and many examples of pyridazine structures are naturally occurring.[3] Pyridazines were recognized as selective GABA-A receptor antagonists, such as minaprine **1**.[4] Volonterio et al. developed the synthesis of pyridazine-based scaffolds such as **2** to target protein/protein interaction as α-helix mimetics.[5] 3-Amino-6-aryl-pyridazines have been considered as an interesting pharmacophore in drug discovery. Some compounds show biological activity ranging from obesity[6] or neurodegenerative diseases[7] to inflammatory pain such as the selective CB_2 agonist **3**.[8] Among kinase inhibitors, different compounds containing the diazine pyridazine have been identified. For example, compound **4** is based on a pyridazinone ring and has been identified as a potent p38 MAP inhibitor[9] (Figure 1).

The nitrogen containing heterocycle pyridazine is a key intermediate in the synthesis of several fused heterocycles used in drug discovery.[10] Fused pyridazines can be distinguished into two classes. The first one has a bridgehead nitrogen atom. Some of them can be obtained from substituted 3-amino-pyridazine, which is easily available from substituted 3-chloro-pyridazine, and further cyclized to a biheterocyclic structure. Generally rings fused to pyridazines are 5-membered rings. Triazolo[4,3-*b*]-pyridazine such as PIM-1 inhibitor **5**[11] can be considered as an example of this class of fused pyridazines. These derivatives were obtained after hydrazinolysis and cyclization of substituted 3-chloro-pyridazines. Another example of this class of compounds is a VEGFR2 kinase inhibitor based on a imidazo[1,2-*b*]pyridazine **6** scaffold,[12] which can be obtained by condensing substituted 3-amino-pyridazines with 2-chloro-acetaldehyde.

The second class represents pyridazines fused to a 6- or 5-membered ring, without a bridgehead nitrogen atom. Examples of this class of compounds are the phosphodiesterase 10A inhibitors **7**[13] and the melanin-concentrating hormone 1 antagonist[14] **8** (Figure 2).

As part of an ongoing project on the synthesis of small heterocycles of pharmaceutical interest,[15] a strategy for the synthesis of functionalized pyridazines by a diaza-Wittig[16] reaction has been developed. In search for operationally simple synthetic processes, we have now developed a convenient and safe method for the

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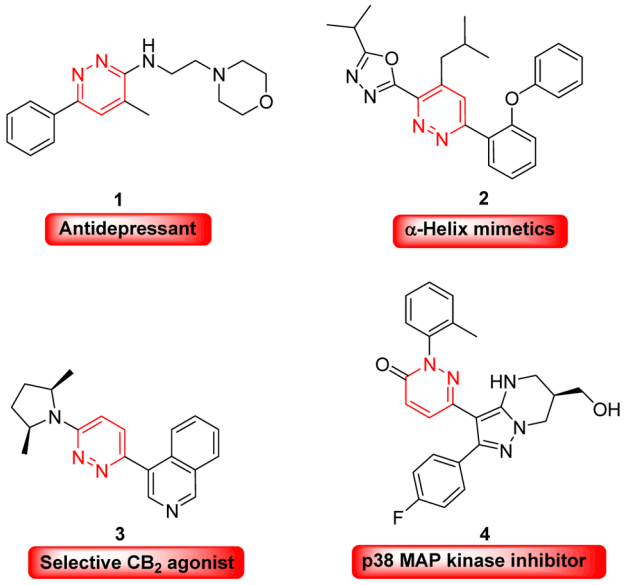

Figure 1. Biologically active pyridazine derivatives.

synthesis of 6-substituted 4-hydroxy-3-methoxycarbonyl pyridazines starting from methyl acetoacetate. We described herein the synthesis of a whole series of existing and new biheterocyclic scaffolds such as pyrazolo[4,3-*c*]pyridazines, thieno[3,2-*c*]-pyridazines, isoxazolo[4,5-*c*]pyridazines, and 5*H*,6*H*,7*H*-pyridazino[4,3-*e*][1,4]diazepine starting from α-diazo-1,3-diketone precursors.

RESULTS AND DISCUSSION

In order to explore novel heterocycles for drug design projects, we became interested in developing convenient methods for the synthesis of the pyridazine ring.[17] The synthesis of 6-substituted 4-hydroxy-3-methoxycarbonyl pyridazine derivatives was first envisioned as starting material. This compound can be obtained by the method described by Zalesov et al. using furan-4,5-dione as an intermediate.[18] However, this method has several limitations, and only aryl substituted pyridazines are accessible. A method allowing the introduction of various substituents at position 6 such as alkyls, cycloalkyls, aryls, and heteroaryls could be more valuable. Moreover, a strategy which allows modifications in a site-selective way could be appealing. The starting material chosen is the readily available methyl acetoacetate **9** which has been subjected to a diazo transfer reaction[19] with *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) in acetonitrile for 2 h at room temperature to obtain the α-diazo-β-ketoester **10** in good yields. Following the titanium aldol method developed by the Calter group,[20] the diazo derivative **10** was converted to the aldol **11** in moderate to good yields. Mild oxidation of **11** with IBX (1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide)[21] led to the α-diazo-β-ketoester, which was used without further purification. The final step to obtain the pyridazine derivatives is the diaza-Wittig reaction. Formation of the phosphazine intermediate and the subsequent diaza-Wittig reaction occur as a tandem process with HMPT (hexamethyl phosphorus triamide) in dichloromethane at room temperature for 16 h to afford the pyridazine **12** in good yields (Scheme 1).

Due to the toxicity[22] of HMPT used for the diaza-Wittig reaction, an improvement of the method to synthesize pyridazines has been investigated. Different phosphines have been screened to convert the derivative **11c** into the pyridazine **12c** after oxidation with IBX. A first attempt to replace HMPT by triphenylphosphine was not successful. In fact, after two days of reaction in diethyl ether at room temperature, no α-diazo-β-ketoester was converted into the corresponding pyridazine (Table 1, entry 2). An increase of the temperature to 60 °C by using tetrahydrofuran as a solvent led to the same result (Table 1, entry 3). By using triethyl phosphite, the pyridazine was obtained in a lower yield than with HMPT (Table 1, entry 4). Triethylphosphine allowed the formation of the pyridazine in 5 h in dichloromethane (Table 1, entry 5). Due to the toxicity and facile oxidation of triethylphosphine,[23] the tributylphosphine was explored and the pyridazine was obtained in less than 1 h at room temperature (Table 1, entry 6) in good yields. Diisopropyl ether (*i*-Pr_2O) proved to be the best solvent for this reaction, allowing the pyridazine **12c** to be obtained as a precipitate in less than 30 min in high yields (Table 1, entry 8). This modification represents an improved and safe method for the synthesis of the pyridazine derivatives **12**.

The selection of appropriate aldehydes (R_1CHO, Scheme 1) allows the synthesis of pyridazine with different substituents at position 6 such as alkyl (Table 2, entry 1), cycloalkyl (Table 2, entry 2), aryl (Table 2, entry 3), and heteroaryl (Table 2, entry 4).

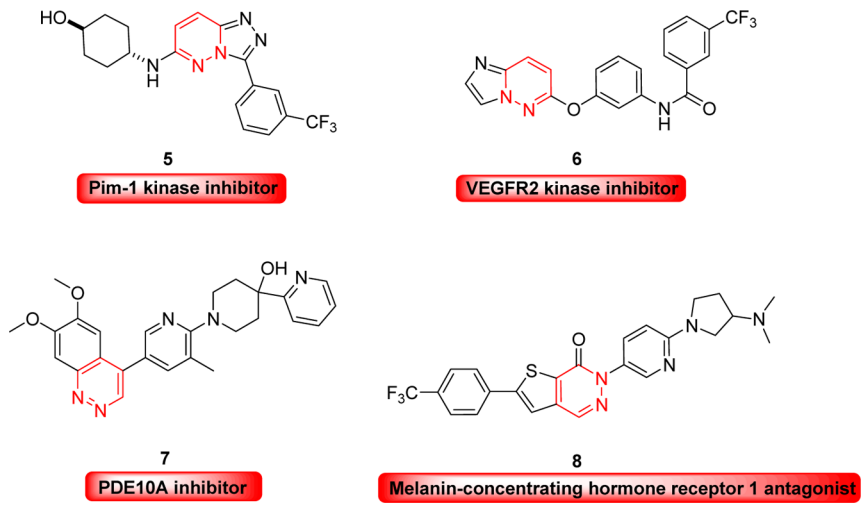

Figure 2. Biologically active fused pyridazine derivatives.

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Scheme 1. Synthesis of 6-Substituted 4-Hydroxy-3-methoxycarbonyl Pyridazines

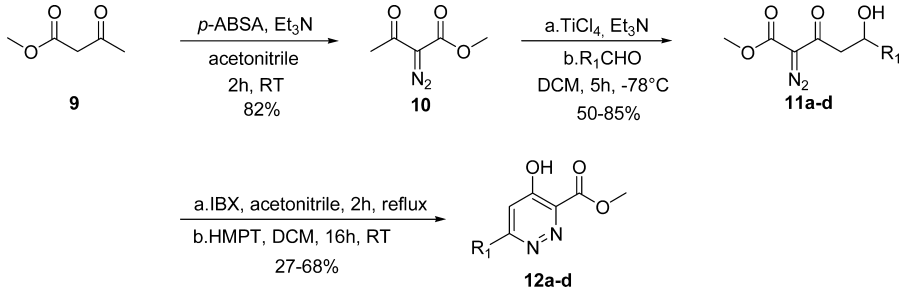
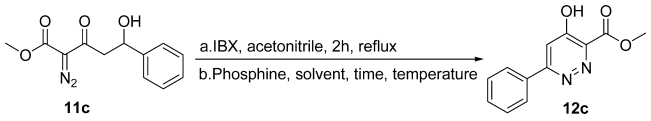


Table 1. Influence of Phosphines and Solvents on the Diaza-Wittig Reaction[a]



entry	phosphine	solvent	conditions	yield of **12c**[b] (%)
1	HMPT	CH_2Cl_2	16 h, RT	60[c]
2	$P(Ph)_3$	Et_2O	48 h, RT	*d*
3	$P(Ph)_3$	THF	16 h, 60 °C	*d*
4	$P(OEt)_3$	CH_2Cl_2	16 h, RT	37[c]
5	$P(Et)_3$	CH_2Cl_2	5 h, RT	52[c]
6	$P(n\text{-}Bu)_3$	CH_2Cl_2	1 h, RT	58[c]
7	$P(n\text{-}Bu)_3$	Et_2O	30 min, RT	53[c]
8	$P(n\text{-}Bu)_3$	$i\text{-}Pr_2O$	30 min, RT	70[e]

[a]All reactions were performed using 1 mmol of **11**c and 364 mg of IBX in refluxing acetonitrile for 2 h, followed by a filtration to obtain the *α*-diazo-*β*-ketoester. The crude compound was stirred with 183 *μ*L of phosphine following the conditions described above. [b]Isolated yield. [c]Purification by flash column chromatography on silica gel. [d]*α*-Diazo-*β*-ketoester recovered. [e]Precipitation of **12c**.

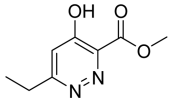
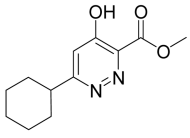
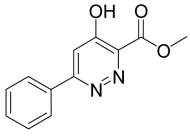
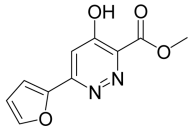
The yield of the diaza-Wittig reaction was higher with alkyl and cycloalkyl groups than aryl and heteroaryl groups. Invariably, the use of $P(n\text{-}Bu)_3$ gives higher yields of pyridazines than the use of HMPT. Some of the derivatives were obtained as precipitates (Table 2, entry 1−3) in less than 30 min of reaction.

For the building of pyridazines bearing a 3-keto group, starting material of type **13** is needed. This approach will, likewise, allow us to obtain pyridazine derivatives, useful for the formation of new bicyclic heterocycles.

The reaction scheme starts with the synthesis of *β*-hydroxy ketone. In order to avoid any side reaction during the synthetic route, R_1 has been chosen to be an aryl or heteroaryl group (Figure 3). Different methods for the synthesis of 1,3-diketone

Figure 3. Diazo derivatives.

Table 2. Synthesis of 6-Substituted 4-Hydroxy-3-methoxycarbonyl Pyridazines[a]

entry	aldehyde derivative	pyridazine		yield of **12** (%)[b] (HMPT method)	yield of **12** (%)[b] ($P(n\text{-}Bu)_3$ method)
1	propionaldehyde		**12a**	68[c]	85[d]
2	cyclohexane carboxaldehyde		**12b**	62[c]	72[d]
3	benzaldehyde		**12c**	60[c]	70[d]
4	2-furfural		**12d**	27[c]	35[c]

[a]All reactions were performed using 1 mmol of **11** and 364 mg of IBX in refluxing acetonitrile for 2 h, followed by a filtration to obtain the corresponding *α*-diazo-*β*-ketoester. The crude compound was stirred with 183 *μ*L of HMPT in dichloromethane for 16 h (HMPT method) or with 250 *μ*L of $P(n\text{-}Bu)_3$ in $i\text{-}Pr_2O$ for 30 min ($P(n\text{-}Bu)_3$ method). [b]Isolated yield. [c]Purification by flash column chromatography on silica gel. [d]Precipitation of **12**.

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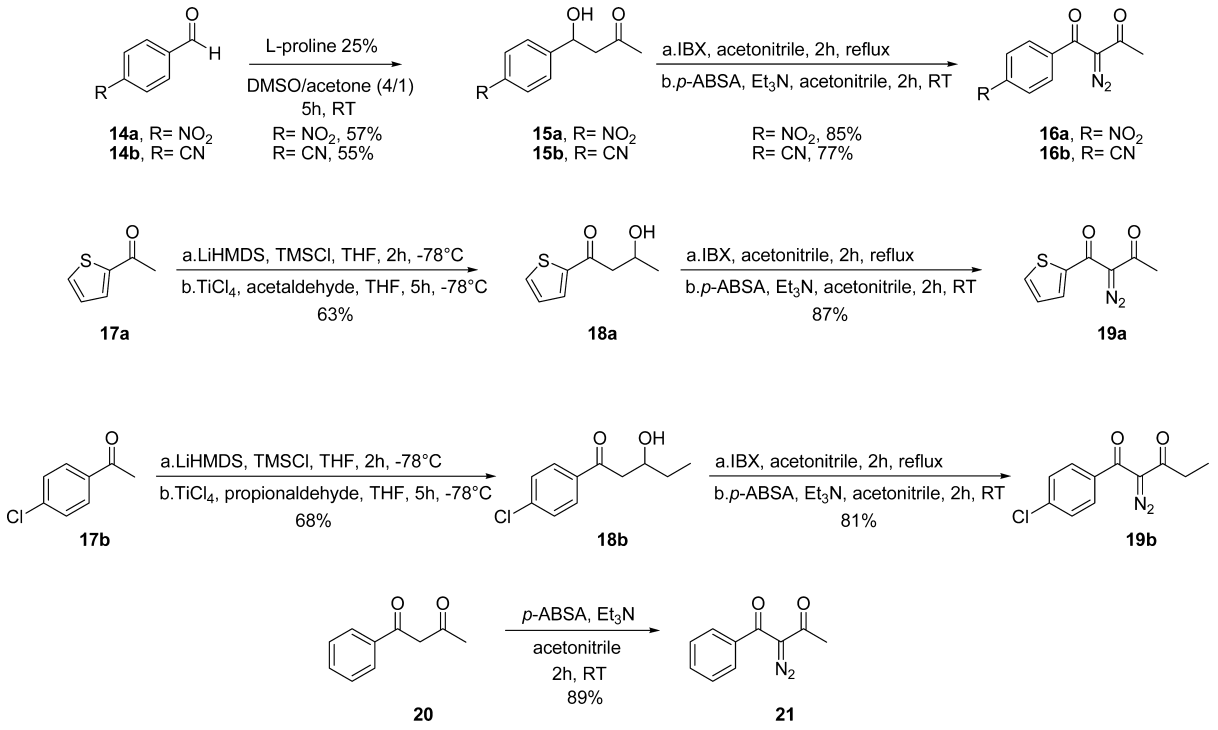
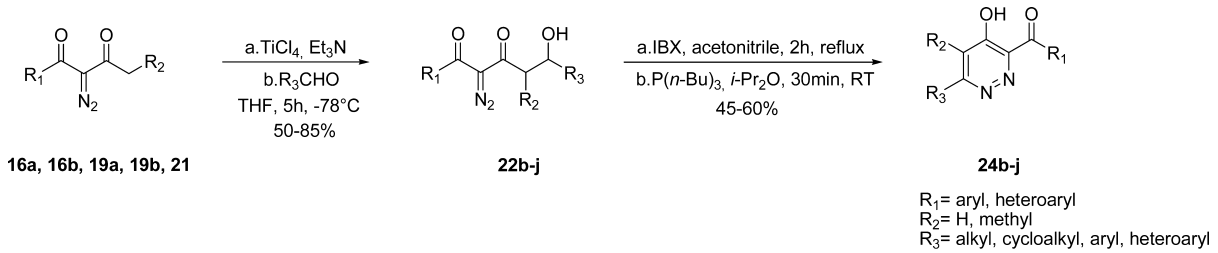
Scheme 2. Synthesis of α-Diazo-1,3-diketone



Scheme 3. Synthesis of Pyridazine Derivatives Bearing a Ketone Group



have been described in the past.[24] We have followed two different approaches. The first one is based on L-proline organocatalysis discovered by List et al.[25] This strategy was applied on aldehydes bearing an electron withdrawing group (nitro group and cyano group) **14** to afford β-hydroxy ketone **15** (Scheme 2). The final α-diazo-1,3-diketone **16** was obtained by mild oxidation with IBX, followed by a diazo transfer reaction with *p*-ABSA. However, when using other aldehydes, the reaction becomes slow and at least one day of reaction is required to afford the corresponding β-hydroxy ketone.[26]

Therefore, for the other α-diazo-1,3-diketone derivatives, a strategy based on the Mukaiyama aldol reaction[27] has been used. The acetophenone derivative **17** was converted to the corresponding silyl enol ether at −78 °C with LiHMDS and trimethylsilyl chloride. The silyl enol ether from **17** reacted with acetaldehyde or propionaldehyde in the presence of titanium tetrachloride to afford **18**. The desired diazo compound **19** was obtained after oxidation with IBX and diazo transfer reaction with *p*-ABSA.

A commercially available reagent **20** was used to synthesize the α-diazo-1,3-diketone **21** by a Regitz reaction with *p*-ABSA. Five different α-diazo-1,3-diketones, **16a**, **16b**, **19a**, **19b**, and **21**, became available in this way.

The α-diazo-1,3-diketone derivatives were used for the synthesis of pyridazines. The first step was the titanium aldol reaction to afford the β-hydroxy-α-diazo diketone **22** (Scheme 3). It should be noted that these aldol products **22** are easily degraded (water elimination)[28] to give the corresponding enone **23** (complete degradation was observed during purification by flash column chromatography on silica gel).

Derivative **22** was oxidized with IBX in refluxing acetonitrile. The crude product was used without further purification in the diaza-Wittig reaction. Treatment with tributylphosphine in diisopropyl ether for 30 min led to the desired pyridazine **24** bearing a ketone group at position 3.

This strategy led to the synthesis of nine novel pyridazine derivatives covering different substitutions, such as several aryl ketones (Table 3, entries 1−3, 5−9) and a heteroaryl ketone (Table 3, entry 4). On the pyridazine ring, it was possible to introduce various R_3 groups such as alkyl (Table 3, entry 1, 2, 4, 5, 9), cycloalkyl (Table 3, entry 8), aryl (Table 3, entry 3, 7), and heteroaryl (Table 3, entry 6). The use of **19b** allowed the synthesis of a tetrasubstituted pyridazine (Table 3, entry 5) with R_2 being a methyl group. The pyridazine analogues **24b−j** have been subjected to different cyclization methods to obtain various fused pyridazines (Scheme 4, Table 4).

The first scaffold investigated was the pyrazolo[4,3-*c*]pyridazine **25**. After chlorination of **24** with phosphorus oxychloride, the crude product was refluxed with hydrazine hydrate in ethanol for 4 h to lead to the desired product **25** (method A).

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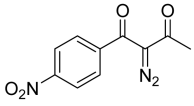
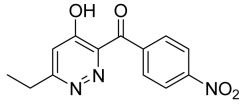
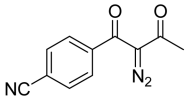
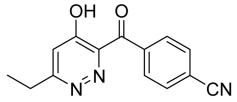
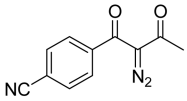
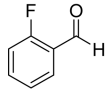
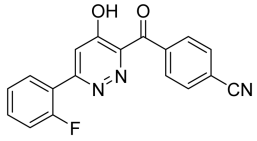
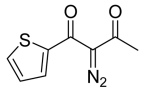
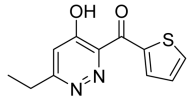
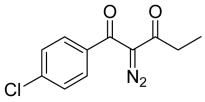
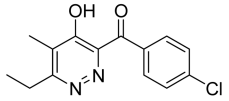
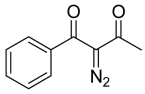
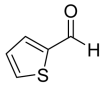
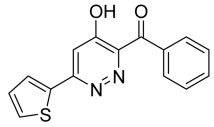
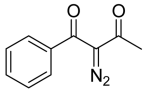
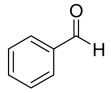
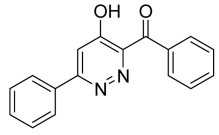
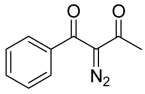
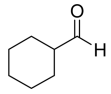
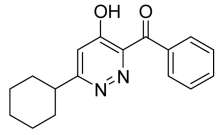
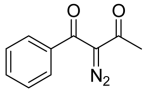
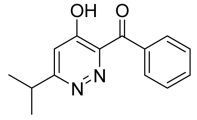
Table 3. Synthesis of 6-Substituted 4-Hydroxypyridazines Bearing a Ketone Group on Position 3[a]

entry	α-diazo-1,3-diketone		aldehyde derivative	pyridazine		yield of **24** (%)[b]
1		**16a**			**24b**	60[c]
2		**16b**			**24c**	57[c]
3		**16b**			**24d**	45[d]
4		**19a**			**24e**	55[c]
5		**19b**			**24f**	57[c]
6		**21**			**24g**	53[d]
7		**21**			**24h**	48[d]
8		**21**			**24i**	52[d]
9		**21**			**24j**	55[c]

[a]All reactions were performed using 1 mmol of **22** and 364 mg of IBX in refluxing acetonitrile for 2 h, followed by a filtration to obtain the corresponding α-diazo-β-ketoester. The crude compound was stirred with 250 μL of P(*n*-Bu)$_3$ in *i*-Pr$_2$O for 30 min at room temperature. [b]Isolated yield. [c]Precipitation of **24**. [d]Purification by flash column chromatography on silica gel.

A condensation of the methyl thioglycolate on the chlorinated pyridazine in refluxing ethanol for 16 h led to the thieno[3,2-*c*]pyridazine **26** (method B); only **26d** contained a methyl ester group, whereas the other derivatives synthesized (**26a**, **26b**, and **26c**) bore an ethyl ester group due to possible transesterification with ethanol during the reaction.

In our search for novel scaffolds, we described the first synthesis of 5*H*,6*H*,7*H*-pyridazino[4,3-*e*][1,4]diazepine **27**. Treatment of **24** with $POCl_3$, followed by a cyclization with ethylene diamine in refluxing ethanol for 16 h, led to the fused pyridazine **27** (method C). Another novel scaffold that was synthesized with this strategy is isoxazolo[4,5-*c*]pyridazine **28**. The ketone of the chlorinated pyridazine was converted into an oxime with hydroxylamine hydrochloride and finally cyclized by heating at 40 °C for 2 h with sodium hydride in tetrahydrofuran to afford **28** (method D).

CONCLUSION

In conclusion, we have developed a synthetic scheme for the synthesis of pyridazine derivatives bearing an ester group **12** starting from methyl acetoacetate **9**. The method has been improved by replacing HMPT by P(*n*-Bu)$_3$ to perform the diaza-Wittig reaction in a shorter reaction time and with better yields. Based on this methodology and starting from 1,3-diketones **13**, it was possible to synthesize novel pyridazines bearing a ketone group **24** with different substituents at position 6. These pyridazine analogues were used for the development of a 20-member library of novel biheterocyclic compounds such as pyrazolo[4,3-*c*]pyridazine

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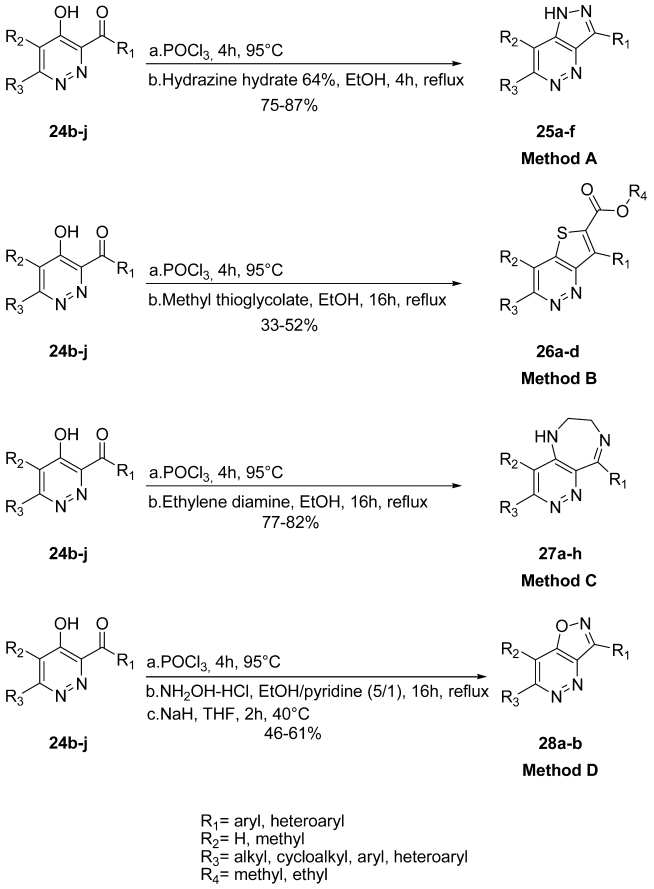
Scheme 4. Synthesis of Fused Pyridazines by Four Different Methods (A, B, C, D)



25 and thieno[3,2-*c*]pyridazine **26**. It is also the first report dealing with the synthesis of 5*H*,6*H*,7*H*-pyridazino[4,3-*e*][1,4]-diazepine **27** and isoxazolo[4,5-*c*]pyridazine **28**.

EXPERIMENTAL SECTION

For all reactions, analytical grade solvents were used. All moisture-sensitive reactions were carried out in oven-dried glassware (135 °C) under a nitrogen or argon atmosphere. Reaction temperatures are reported as bath temperature. Precoated aluminum sheets were used for TLC. Compounds were visualized with UV light (λ = 254 nm). Products were purified by flash chromatography on silica gel 63−200, 60 Å. Melting points were obtained on a melting point apparatus with open capillary tubes. ^{1}H and ^{13}C NMR spectra were recorded on 300 MHz, 500 MHz, and 600 MHz spectrometers using $CDCl_3$ and DMSO-d_6 as the solvent. The ^{1}H and ^{13}C chemical shifts were referenced to residual solvent signals at δ ^{1}H/^{13}C 7.26/77.00 ($CDCl_3$) and 2.50/39.50 (DMSO-d_6) relative to TMS as internal standard. Coupling constants J [Hz] were directly taken from the spectra. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). High resolution mass spectra were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer. Samples were infused at 3 μL/min, and spectra were obtained in positive (or negative) ionization mode with a resolution of 15000 (fwhm) using leucine enkephalin as lock mass. Electrospray MS spectra were obtained on a LC/MS spectrometer. All the LC/MS analysis methods use MeCN/H_2O gradients. Water contains either 0.1% TFA or 0.1% NH_3.

Methyl 2-Diazo-3-oxobutanoate (10). To a solution of compound **9** (5 g, 43.06 mmol) in 30 mL of acetonitrile under argon at 0 °C were added successively triethylamine (7.8 mL, 55.98 mmol) and *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (10.4 g, 43.06 mmol). The mixture was stirred for 2 h, allowed to warm to room temperature, diluted with 100 mL of Et_2O/*n*-hexane (1:1), and then filtered. The filtrate was concentrated and the residue purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:2) to afford the desired compound **10** (5 g, 35.18 mmol, 82% yield) as yellow oil. Data for **10**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.65 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 189.3, 161.5, 52.3, 27.9.

General Procedure for the Preparation of 11a−d by Titanium Aldol Reaction. To a solution of **10** (1 g, 7.04 mmol) in 50 mL of CH_2Cl_2 under argon at −78 °C was added dropwise $TiCl_4$ (849 μL, 7.74 mmol) followed by Et_3N (1.08 mL, 7.74 mmol). The resulting red solution was stirred at −78 °C for 1 h, after which a solution of aldehyde (6.34 mmol) in CH_2Cl_2 was slowly added. The reaction mixture was stirred at −78 °C for 4 h, and then the reaction was quenched with 50 mL of saturated aqueous NH_4Cl and warmed to room temperature. The organic layer was separated and then washed with 40 mL of saturated aqueous $NaHCO_3$. The aqueous layers were extracted with 50 mL of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The product was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:3) to afford the aldol product **11**.

*Methyl 2-diazo-5-hydroxy-3-oxoheptanoate (**11a**):* yellow oil, 1.2 g (85% yield); synthesized from propionaldehyde. Spectral and analytical data were in agreement with previous reports.[15b]

*Methyl 5-cyclohexyl-2-diazo-5-hydroxy-3-oxopentanoate (**11b**):* yellow oil, 1.3 g (73% yield); synthesized from cyclohexane carboxaldehyde. Spectral and analytical data were in agreement with previous reports.[15b]

*Methyl 2-diazo-5-hydroxy-3-oxo-5-phenylpentanoate (**11c**):* yellow oil, 1.3 g (75% yield); synthesized from benzaldehyde. Spectral and analytical data were in agreement with previous reports.[15b]

*Methyl 2-diazo-5-(furan-2-yl)-5-hydroxy-3-oxopentanoate (**11d**):* yellow oil, 840 mg (50% yield); synthesized from 2-furfural. Spectral and analytical data were in agreement with previous reports.[15b]

HMPT Method: Preparation of Pyridazine Derivatives 12a−d. To a solution of **11** (1 mmol) in 10 mL of acetonitrile under argon was added IBX (1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide) (364 mg, 1.3 mmol). The mixture was refluxed for 2 h and was allowed to warm to room temperature and then filtered. The filtrate was concentrated to afford the α-diazo-β-ketoester used directly without further purification for the next step.

To a solution of α-diazo-β-ketoester in 10 mL of CH_2Cl_2 was added HMPT (hexamethylphosphorous triamide) (183 μL, 1 mmol). The reaction mixture was stirred under argon at room temperature for 16 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with the addition of water. The organic layer was washed with water (2 × 10 mL), dried over Na_2SO_4, and concentrated in vacuo. A purification by flash column chromatography on silica gel (EtOAc/*n*-hexane = 9:1) afforded the desired pyridazine **12**.

P(*n*-Bu)$_3$ Method: Preparation of Pyridazine Derivatives 12a−d. To a solution of **11** (1 mmol) in 10 mL of acetonitrile under argon was added IBX (1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide) (364 mg, 1.3 mmol). The mixture was refluxed for 2 h and was allowed to warm to room temperature and then filtered. The filtrate was concentrated to afford the α-diazo-β-ketoester used directly without further purification for the next step.

To a solution of α-diazo-β-ketoester in 20 mL of *i*-Pr_2O was added P(*n*-Bu)$_3$ (250 μL, 1 mmol). The reaction mixture was stirred under argon at room temperature for 30 min, after which time a precipitate was formed. The suspension was filtered, washed with *i*-Pr_2O, and dried to afford **12**.

*Methyl 6-ethyl-4-hydroxypyridazine-3-carboxylate (**12a**):* white solid, 124 mg (68% yield with HMPT method) and 155 mg (85% yield with P(*n*-Bu)$_3$ method); mp 179−182 °C. Spectral and analytical data were in agreement with previous reports.[15b]

*Methyl 6-cyclohexyl-4-hydroxypyridazine-3-carboxylate (**12b**):* beige solid, 146 mg (62% yield with HMPT method) and 170 mg (72% yield with P(*n*-Bu)$_3$ method); mp 215−217 °C. Spectral and analytical data were in agreement with previous reports.[15b]

*Methyl 4-hydroxy-6-phenylpyridazine-3-carboxylate (**12c**):* pale yellow solid, 138 mg (60% yield with HMPT method) and 161 mg (70% yield with P(*n*-Bu)$_3$ method); mp 211−212 °C. Spectral and analytical data were in agreement with previous reports.[15b]

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*Methyl 6-(furan-2-yl)-4-hydroxypyridazine-3-carboxylate (**12d**):* brown solid, 59 mg (27% yield with HMPT method) and 77 mg (35% yield with $P(n\text{-}Bu)_3$ method; a purification by flash column chromatography on silica gel (EtOAc/*n*-hexane = 9:1) afforded the

Table 4. Synthesis of Fused Pyridazine Analogues

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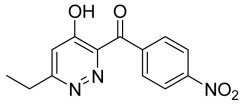
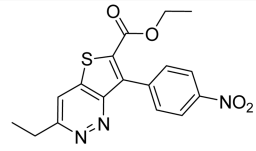
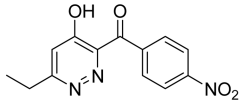
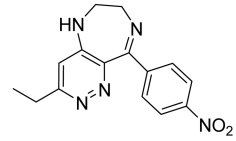
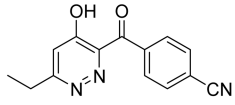
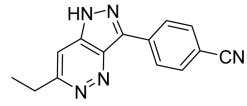
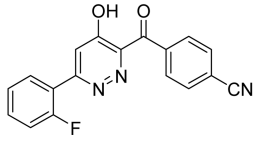
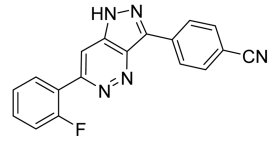
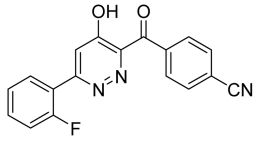
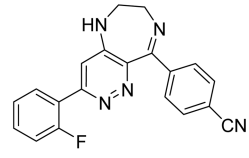
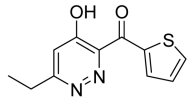
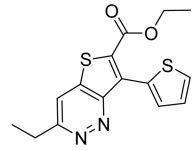
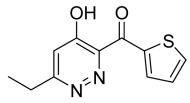
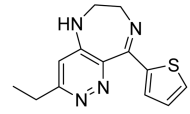
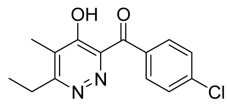
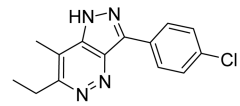
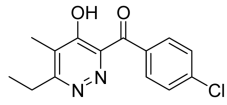
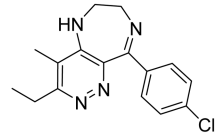
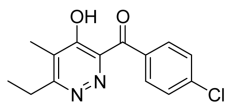
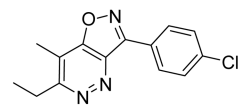
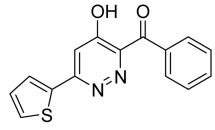
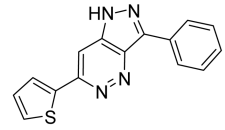
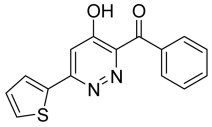
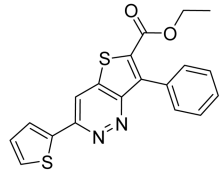
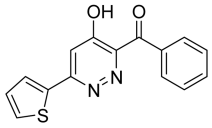
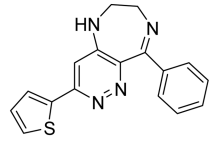
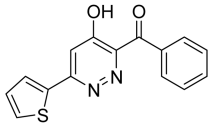
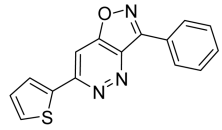
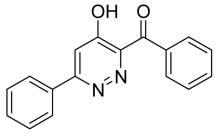
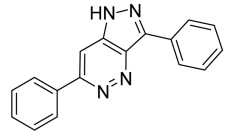
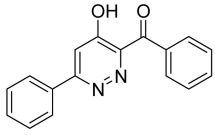
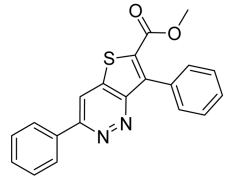
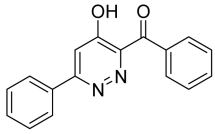
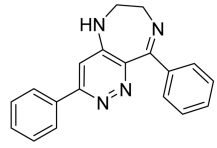
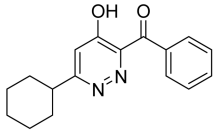
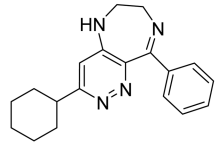
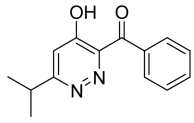
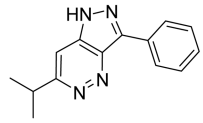
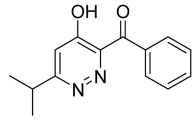
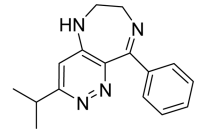
1		**24b**	B[b]		**26a**	52
2		**24b**	C[c]		**27a**	77
3		**24c**	A[d]		**25a**	83
4		**24d**	A[d]		**25b**	79
5		**24d**	C[c]		**27b**	79
6		**24e**	B[b]		**26b**	38
7		**24e**	C[c]		**27c**	81
8		**24f**	A[d]		**25c**	87
9		**24f**	C[c]		**27d**	82
10		**24f**	D[e]		**28a**	61
11		**24g**	A[d]		**25d**	81

dx.doi.org/10.1021/jo400989q | *J. Org. Chem.* 2013, 78, 7845−7858

Table 4. continued

entry	pyridazine		method	fused pyridazine		yield (%)[a]
12		**24g**	B[b]		**26c**	33
13		**24g**	C[c]		**27e**	79
14		**24g**	D[e]		**28b**	46
15		**24h**	A[d]		**25e**	79
16		**24h**	B[b]		**26d**	41
17		**24h**	C[d]		**27f**	77
18		**24i**	C[c]		**27g**	79
19		**24j**	A[d]		**25f**	75
20		**24j**	C[c]		**27h**	78

[a]Isolated yield. [b]Synthesis of thieno[3,2-*c*]pyridazine **26** with method B, see the Experimental Section for details. [c]Synthesis of 5*H*,6*H*,7*H*-pyridazino[4,3-*e*][1,4]diazepine **27** with method C, see the Experimental Section for details. [d]Synthesis of pyrazolo[4,3-*c*]pyridazine **25** with method A, see the Experimental Section for details. [e]Synthesis of isoxazolo[4,5-*c*]pyridazine **28** with method D, see the Experimental Section for details.

desired pyridazine **12d**); mp 192−195 °C. Spectral and analytical data were in agreement with previous reports.[15b]

General Procedure for the Preparation of β-Hydroxy Ketone Derivatives 15a,b by Organocatalysis. To a solution of aldehyde **14** (1 mmol) in a mixture of DMSO (4 mL) and acetone (1 mL) was added L-proline (29 mg, 0.25 mmol). The resulting mixture was stirred under argon at room temperature for 5 h. The reaction mixture was treated with 10 mL of saturated aqueous NH_4Cl, the layers were separated, and the aqueous layer was extracted several times with EtOAc, dried over Na_2SO_4, and concentrated in vacuo. A purification by flash column

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chromatography on silica gel (EtOAc/*n*-hexane = 1:2) afforded the desired aldol product **15**.

*4-Hydroxy-4-(4-nitrophenyl)butan-2-one (**15a**):* pink solid, 119 mg (57% yield); mp 65−68 °C. Data for **15a**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.19 (d, J = 8.7 Hz, 2H), 7.64 (d, J = 8.7 Hz, 2H), 5.70 (d, J = 4.8 Hz, 1H), 5.13−5.16 (m, 1H), 2.75 (d, J = 6.6 Hz, 2H), 2.14 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 206.3, 153.3, 146.5, 127.0, 123.4, 68.1, 52.4, 30.4; HRMS calcd for $C_{10}H_{11}NO_4$ [M + Na]$^+$ 232.0581, found 232.0584.

*4-(1-Hydroxy-3-oxobutyl)benzonitrile (**15b**):* beige solid, 104 mg (55% yield); mp 83−88 °C. Data for **15b**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.82 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 5.65 (d, J = 4.7 Hz, 1H), 5.10−5.13 (m, 1H), 2.76 (d, J = 5.8 Hz, 2H), 2.16 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 151.1, 132.2, 126.8, 119.0, 109.7, 68.3, 52.4, 30.4; HRMS calcd for $C_{11}H_{11}NO_2$ [M + Na]$^+$ 212.0682, found 212.0677.

General Procedure for the Preparation of β-Hydroxy Ketone Derivatives 18a,b by Mukaiyama Aldol Reaction. To a solution of ketone **17** (1 mmol) in 10 mL of THF under argon at −78 °C was slowly added a solution of 1 M LiHMDS (1.2 mL, 1.2 mmol), and the reaction mixture was stirred for 1 h at −78 °C, prior to the addition of chlorotrimethylsilane (153 μL, 1.2 mmol) in THF. The mixture was further stirred for 1 h and then allowed to warm up to room temperature. The reaction was first quenched with 10 mL of saturated aqueous NH_4Cl. After addition of EtOAc (20 mL), the layers were separated, and the aqueous layer was extracted several times with EtOAc, dried over Na_2SO_4, and concentrated in vacuo to afford the corresponding silyl enol ether used directly without further purification for the next step.

To a solution of silyl enol ether in 10 mL of CH_2Cl_2 under argon at −78 °C was added acetaldehyde (85 μL, 1.5 mmol) for **18a** or propionaldehyde for **18b** (110 μL, 1.5 mmol) followed by a slow addition of $TiCl_4$ (121 μL, 1.1 mmol). The resulting red solution was stirred at −78 °C for 5 h, and then the reaction was quenched with 10 mL of saturated aqueous NH_4Cl and warmed to room temperature. The organic layer was separated and then washed with 15 mL of saturated aqueous $NaHCO_3$. The aqueous layers were extracted with 20 mL of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The product was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:3) to obtain the desired β-hydroxy ketone **18**.

*3-Hydroxy-1-(thiophene-2-yl)butan-1-one (**18a**):* colorless oil, 107 mg (63% yield). Data for **18a**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (d, J = 4.9 Hz, 1H), 7.94 (d, J = 3.8 Hz, 1H), 7.24 (t, J = 4.8 Hz, 1H), 4.70 (d, J = 4.9 Hz, 1H), 4.15−4.17 (m, 1H), 2.85−3.09 (m, 2H), 1.14 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 192.1, 144.7, 134.9, 133.6, 128.8, 63.8, 48.4, 23.8; HRMS calcd for $C_8H_{10}O_2S$ [M + Na]$^+$ 193.0294, found 193.0297.

*1-(4-Chlorophenyl)-3-hydroxypentan-1-one (**18b**):* yellow oil, 145 mg (68% yield). Data for **18b**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.97 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 4.62 (d, J = 5.5 Hz, 1H), 3.89−3.95 (m, 1H), 3.90−3.94 (m, 1H), 2.94−3.10 (m, 2H), 1.40−1.48 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.5, 138.0, 136.0, 130.1, 128.8, 68.6, 45.9, 30.2, 10.0; HRMS calcd for $C_{11}H_{13}ClO_2$ [M + Na]$^+$ 235.0497, found 235.0502.

General Procedure for the Preparation of α-Diazo-1,3-diketones 16a, 16b, 19a, and 19b. To a solution of β-hydroxy ketone (**15a**, **15b**, **18a**, **18b**) (1 mmol) in 10 mL of acetonitrile under argon at 0 °C was added IBX (1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide) (364 mg, 1.3 mmol). The mixture was refluxed for 2 h and was allowed to warm to room temperature and then filtered. The filtrate was concentrated to afford the 1,3-diketone used directly without further purification for the next step.

To a solution of 1,3-diketone in 15 mL of acetonitrile under argon at 0 °C were added successively triethylamine (181 μL, 1.3 mmol) and *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (240 mg, 1 mmol). The mixture was stirred for 2 h, allowed to warm to room temperature, diluted with a mixture of diethyl ether/hexane (1/1, 30 mL), and then filtered. The filtrate was concentrated and the residue purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:4) to afford the α-diazo-1,3-diketones **16a**, **16b**, **19a**, and **19b**.

*2-Diazo-1-(4-nitrophenyl)butane-1,3-dione (**16a**):* yellow solid, 198 mg (85% yield); mp 84−87 °C. Data for **16a**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.34 (d, J = 8.7 Hz, 2H), 7.95 (d, J = 8.7 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.8, 184.0, 149.3, 142.9, 129.1, 123.9, 84.8, 28.7.

*4-(2-Diazo-3-oxobutanoyl)benzonitrile (**16b**):* beige solid, 164 mg (77% yield); mp 106−110 °C. Data for **16b**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.01 (d, J = 8.2 Hz, 2H), 7.87 (d, J = 8.3 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 189.0, 184.2, 141.4, 132.8, 128.4, 118.2, 114.4, 84.6, 28.7.

*2-Diazo-1-(thiophene-2-yl)butane-1,3-dione (**19a**):* yellow oil, 169 mg (87% yield). Data for **19a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69−7.70 (m, 1H), 7.60−7.61 (m, 1H), 7.15−7.16 (m, 1H), 2.60 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.8, 175.1, 141.9, 133.5, 130.4, 127.9, 81.7, 29.3.

*1-(4-Chlorophenyl)-2-diazopentane-1,3-dione (**19b**):* pale yellow solid, 192 mg (81% yield); mp 88−92 °C. Data for **19b**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.75 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 2.86 (q, J = 7.3 Hz, 2H), 1.05 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 192.6, 184.1, 137.2, 136.4, 129.6, 128.8, 83.2, 33.8, 8.2.

2-Diazo-1-phenylbutane-1,3-dione (21). To a solution of compound **20** (3 g, 18.50 mmol) in 50 mL of acetonitrile under argon at 0 °C were added successively triethylamine (3.3 mL, 24.05 mmol) and *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (4.4 g, 18.50 mmol). The mixture was stirred for 2 h and was allowed to warm to room temperature, diluted with 100 mL of Et_2O/*n*-hexane (1:1), and then filtered. The filtrate was concentrated and the residue purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:3) to afford the desired compound **21** (3.1 g, 16.45 mmol, 89% yield) as yellow solid; mp 78−81 °C. Data for **21**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.73 (d, J = 7.2 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.52−7.55 (m, 2H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 189.8, 185.0, 137.5, 132.5, 128.8, 127.6, 83.6, 28.8.

General Procedure for the Preparation of 22b−j by Titanium Aldol Reaction. To a solution of α-diazo-1,3-diketone (**16a**, **16b**, **19a**, **19b**, and **21**) (1 mmol) in 10 mL of CH_2Cl_2 under argon at −78 °C was added dropwise $TiCl_4$ (121 μL, 1.1 mmol) followed by Et_3N (153 μL, 1.1 mmol). The resulting red solution was stirred at −78 °C for 1 h, after which a solution of aldehyde (0.9 mmol) in CH_2Cl_2 was slowly added. The reaction mixture was stirred at −78 °C for 4 h, and then the reaction was quenched with 10 mL of saturated aqueous NH_4Cl and warmed to room temperature. The organic layer was separated and then washed with 15 mL of saturated aqueous $NaHCO_3$. The aqueous layers were extracted with 20 mL of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The product was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:3) to afford the aldol product **22**.

*2-Diazo-5-hydroxy-1-(4-nitrophenyl)heptane-1,3-dione (**22b**):* yellow oil, 201 mg (69% yield). Data for **22b**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.33 (d, J = 8.1 Hz, 2H), 7.92 (d, J = 8.4 Hz, 2H), 4.75−4.77 (m, 1H), 3.82−3.87 (m, 1H), 2.86−2.91 (m, 2H), 1.37−1.47 (m, 2H), 0.88 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 190.0, 184.3, 149.3, 143.1, 129.1, 123.8, 85.2, 68.4, 47.9, 30.0, 10.0; HRMS calcd for $C_{13}H_{13}N_3O_5$ [M + Na]$^+$ 314.0748, found 314.0752.

*4-(2-Diazo-5-hydroxy-3-oxoheptanoyl)benzonitrile (**22c**):* yellow oil, 220 mg (81% yield). Data for **22c**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.99 (d, J = 8.1 Hz, 2H), 7.84 (d, J = 8.5 Hz, 2H), 4.73−4.75 (m, 1H), 3.85−3.87 (m, 1H), 2.83−2.93 (m, 2H), 1.30−1.46 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 190.1, 184.5, 141.5, 132.7, 128.4, 118.2, 114.4, 84.8, 68.4, 47.9, 30.0, 10.0; HRMS calcd for $C_{14}H_{13}N_3O_3$ [M + Na]$^+$ 294.0849, found 294.0849.

*4-[2-Diazo-5-(2-fluorophenyl)-5-hydroxy-3-oxopentanoyl]-benzonitrile (**22d**):* yellow oil, 169 mg (50% yield). Data for **22d**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, J = 8.6 Hz, 2H), 7.83 (d, J = 8.6 Hz, 2H), 7.52−7.56 (m, 1H), 7.29−7.34 (m, 1H), 7.20−7.23 (m, 1H), 7.12−7.16 (m, 1H), 5.63 (d, J = 4.9 Hz, 1H), 5.34−5.38 (m, 1H), 3.36 (m, 1H), 3.01 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 189.0, 184.4, 160.0, 158.0, 141.3, 132.8, 131.7, 129.0, 128.4, 127.9, 124.5, 118.2, 115.1, 114.4, 84.8, 62.8, 48.5; HRMS calcd for $C_{18}H_{12}FN_3O_3$ [M + Na]$^+$ 360.0755, found 360.0761.

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*2-Diazo-5-hydroxy-1-(thiophene-2-yl)heptane-1,3-dione (**22e**):* yellow oil, 194 mg (77% yield). Data for **22e**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.04−8.05 (m, 1H), 7.92−7.93 (m, 1H), 7.23−7.25 (m, 1H), 4.66 (d, J = 5.7 Hz, 1H), 3.84−3.88 (m, 1H), 2.91−2.98 (m, 2H), 1.33−1.48 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 175.4, 141.8, 134.6, 132.0, 128.4, 82.4, 68.3, 48.0, 30.0, 10.0; HRMS calcd for $C_{11}H_{12}N_2O_3S$ [M + Na]$^+$ 275.0461, found 275.0468.

*1-(4-Chlorophenyl)-2-diazo-5-hydroxy-4-methylheptane-1,3-dione (**22f**):* yellow oil, 186 mg (63% yield); Inseparable diastereomeric mixture. Data for **22f** (major isomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 8.7 Hz, 2H), 7.47 (d, J = 8.7 Hz, 2H), 4.60−4.67 (m, 1H), 4.18 (d, J = 4.8 Hz, 1H), 3.10−3.16 (m, 1H), 1.63−1.72 (m, 2H), 0.98−1.20 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.3, 171.6, 140.3, 133.5, 130.5, 128.8, 84.3, 57.4, 36.3, 23.0, 13.2, 10.0; HRMS calcd for $C_{14}H_{15}ClN_2O_3$ [M + Na]$^+$ 317.0664, found 317.0657.

*2-Diazo-5-hydroxy-1-phenyl-5-(thiophene-2-yl)pentane-1,3-dione (**22g**):* yellow oil, 171 mg (57% yield). Data for **22g**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.73 (m, 2H), 7.60 (m, 1H), 7.51 (t, J = 7.7 Hz, 2H), 7.41 (dd, J = 4.9, 1.3 Hz, 1H), 6.97−7.02 (m, 2H), 5.88−5.90 (m, 1H), 5.38−5.40 (m, 1H), 3.24−3.46 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 189.7, 185.1, 149.7, 137.5, 132.6, 128.8, 127.7, 126.8, 124.5, 123.2, 83.9, 65.2, 50.4; HRMS calcd for $C_{15}H_{12}N_2O_3S$ [M + Na]$^+$ 323.0461, found 323.0460.

*2-Diazo-5-hydroxy-1,5-diphenylpentane-1,3-dione (**22h**):* yellow oil, 153 mg (52% yield). Data for **22h**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.46−7.60 (m, 3H), 7.4−7.44 (m, 4H), 7.28−7.42 (m, 3H), 5.28 (m, 1H), 3.56 (m, 1H), 3.33−3.44 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 192.4, 184.7, 142.6, 136.7, 132.6, 128.7, 128.2, 127.4, 127.1, 125.5, 83.6, 70.3, 49.4; HRMS calcd for $C_{17}H_{14}N_2O_3$ [M + Na]$^+$ 317.0897, found 317.0901.

*5-Cyclohexyl-2-diazo-5-hydroxy-1-phenylpentane-1,3-dione (**22i**):* yellow oil, 237 mg (79% yield). Data for **22i**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.71 (d, J = 7.3 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 4.61 (d, J = 5.8 Hz, 1H), 3.74−3.78 (m, 1H), 2.90 (d, J = 5.7 Hz, 2H), 1.59−1.76 (m, 5H), 0.95−1.28 (m, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 191.4, 185.2, 137.6, 132.5, 128.7, 127.7, 83.6, 71.0, 45.5, 43.7, 28.8, 27.6, 26.2, 25.9, 25.8; HRMS calcd for $C_{17}H_{20}N_2O_3$ [M + Na]$^+$ 323.1366, found 323.1363.

*2-Diazo-5-hydroxy-6-methyl-1-phenylheptane-1,3-dione (**22j**):* yellow oil, 221 mg (85% yield). Data for **22j**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.71 (d, J = 7.3 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 4.65 (br s, 1H), 3.76−3.78 (m, 1H), 2.85−2.95 (m, 2H), 1.60−1.64 (m, 1H), 0.85 (m, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 191.3, 185.2, 137.6, 132.5, 128.7, 127.7, 83.7, 71.5, 45.4, 33.6, 18.7, 17.5; HRMS calcd for $C_{14}H_{16}N_2O_3$ [M + Na]$^+$ 283.1053, found 283.1052.

General Procedure for the Preparation of Pyridazine Derivatives 24b−j. To a solution of **22** (1 mmol) in 10 mL of acetonitrile under argon was added IBX (1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide) (364 mg, 1.3 mmol). The mixture was refluxed for 2 h and was allowed to warm to room temperature and then filtered. The filtrate was concentrated and used directly without further purification for the next step.

To the previously prepared crude in 15 mL of *i*-Pr_2O was added P(*n*-Bu)$_3$ (250 μL, 1.0 mmol). The reaction mixture was stirred under argon at room temperature for 30 min, after which time a precipitate was formed. The suspension was filtered, washed with *i*-Pr_2O, and dried to afford **24b**, **24c**, **24e**, **24f**, and **24j**. **24d**, **24g**, **24h**, and **24i** were purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 8:2) due to no formation of precipitate.

*6-Ethyl-3-(4-nitrobenzoyl)pyridazin-4-ol (**24b**):* brown solid, 164 mg (60% yield); mp 241−244 °C. Data for **24b**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.54 (br s, 1H), 8.34 (d, J = 8.5 Hz, 2H), 8.05 (d, J = 8.4 Hz, 2H), 6.47 (s, 1H), 2.63 (q, J = 7.4 Hz, 2H), 1.24 (t, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.0, 152.7, 150.4, 140.2, 130.6, 124.1, 116.5, 24.3, 12.5; HRMS calcd for $C_{13}H_{11}N_3O_4$ [M + H]$^+$ 274.0822, found 274.0829.

*4-(6-Ethyl-4-hydroxypyridazine-3-carbonyl)benzonitrile (**24c**):* yellow solid, 144 mg (57% yield); mp 233−235 °C. Data for **24c**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.55 (br s, 1H), 8.02 (d, J = 8.3 Hz, 2H), 7.96 (d, J = 8.3 Hz, 2H), 6.46 (s, 1H), 2.62 (q, J = 7.6 Hz, 2H), 1.24 (t, J = 7.6 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 191.9, 169.1, 156.8, 152.8, 138.7, 133.0, 129.8, 118.1, 116.3, 115.9, 24.1, 12.5; HRMS calcd for $C_{14}H_{11}N_3O_2$ [M + H]$^+$ 254.0924, found 254.0928.

*4-[6-(4-Fluorophenyl)-4-hydroxypyridazine-3-carbonyl]-benzonitrile (**24d**):* beige solid, 144 mg (45% yield); mp 237−240 °C. Data for **24d**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.94 (br s, 1H), 8.05 (m, 4H), 7.73−7.76 (m, 1H), 7.66−7.69 (m, 1H), 7.46−7.49 (m, 1H), 7.43−7.45 (m, 1H), 6.78 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 191.7, 159.9, 158.3, 152.9, 138.7, 133.4, 133.3, 133.0, 130.9, 130.0, 125.9, 118.9, 118.2, 116.6, 116.5, 116.0; HRMS calcd for $C_{18}H_{10}FN_3O_2$ [M + H]$^+$ 320.0830, found 320.0831.

*6-Ethyl-3-(thiophene-2-carbonyl)pyridazin-4-ol (**24e**):* orange solid, 129 mg (55% yield); mp 236−239 °C. Data for **24e**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.41 (br s, 1H), 8.13−8.14 (m, 1H), 7.69−7.70 (m, 1H), 7.24−7.26 (m, 1H), 6.42 (s, 1H), 2.61 (q, J = 7.6 Hz, 2H), 1.23 (t, J = 7.7 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 184.0, 169.1, 156.5, 153.0, 142.2, 136.8, 136.5, 129.1, 116.0, 24.1, 12.5; HRMS calcd for $C_{11}H_{10}N_2O_2S$ [M + H]$^+$ 235.0536, found 235.0540.

*3-(4-Chlorobenzoyl)-6-ethyl-5-methylpyridazin-4-ol (**24f**):* colorless oil, 158 mg (57% yield). Data for **24f**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.37 (br s, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.5 Hz, 2H), 2.69 (q, J = 7.3 Hz, 2H), 1.95 (s, 3H), 1.22 (t, J = 7.5 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 191.9, 168.6, 153.1, 150.6, 139.0, 134.4, 131.2, 129.1, 125.5, 22.6, 12.7, 9.1; HRMS calcd for $C_{14}H_{13}ClN_2O_2$ [M + H]$^+$ 277.0738, found 277.0739.

*3-Benzoyl-6-(thiophene-2-yl)pyridazin-4-ol (**24g**):* orange solid, 150 mg (53% yield); mp 206−209 °C. Data for **24g**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.88−7.92 (m, 4H), 7.72 (t, J = 7.4 Hz, 1H), 7.57 (t, J = 7.7 Hz, 2H), 7.29−7.31 (m, 1H), 6.94 (br s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 192.4, 135.5, 134.3, 131.0, 129.6, 129.0, 128.9; HRMS calcd for $C_{15}H_{10}N_2O_2S$ [M + H]$^+$ 283.0536, found 283.0534.

*3-Benzoyl-6-phenylpyridazin-4-ol (**24h**):* brown solid, 133 mg (48% yield); mp 201−204 °C. Data for **24h**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.89 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 7.8 Hz, 2H), 7.72 (t, J = 7.4 Hz, 1H), 7.56−7.62 (m, 5H), 6.85 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 192.6, 135.4, 134.3, 131.2, 129.5, 129.3, 129.0, 127.4, 115.3; HRMS calcd for $C_{17}H_{12}N_2O_2$ [M + H]$^+$ 277.0971, found 277.0978.

*3-Benzoyl-6-cyclohexylpyridazin-4-ol (**24i**):* beige solid, 147 mg (52% yield); mp 233−235 °C. Data for **24i**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.36 (br s, 1H), 7.81 (d, J = 8.3 Hz, 2H), 7.69 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 8.1 Hz, 2H), 6.40 (s, 1H), 2.54−2.59 (m, 1H), 1.69−1.90 (m, 5H), 1.33−1.52 (m, 5H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 192.7, 159.5, 154.1, 135.4, 134.3, 129.4, 129.0, 114.2, 40.1, 31.0, 25.7, 25.1; HRMS calcd for $C_{17}H_{18}N_2O_2$ [M + H]$^+$ 283.1441, found 283.1440.

*3-Benzoyl-6-(propan-2-yl)pyridazin-4-ol (**24j**):* beige solid, 133 mg (55% yield); mp 228−231 °C. Data for **24j**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.41 (br s, 1H), 7.81 (d, J = 8.2 Hz, 2H), 7.70 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.9 Hz, 2H), 6.43 (s, 1H), 2.88−2.93 (m, 1H), 1.27 (d, J = 7.1 Hz, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 192.7, 169.3, 160.5, 154.2, 135.4, 134.3, 129.4, 129.0, 113.8, 30.3, 21.1; HRMS calcd for $C_{14}H_{14}N_2O_2$ [M + H]$^+$ 243.1128, found 243.1130.

Method A: Preparation of Pyrazolo[4,3-*c*]pyridazine Analogues 25a−f. A solution of **24** (1 mmol) in 5 mL of $POCl_3$ was heated at 95 °C for 4 h, after which the reaction mixture was cooled down to room temperature. $POCl_3$ was evaporated, and the residue was dissolved in EtOAc and washed 2 times with 20 mL of saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to afford the chlorinated pyridazine used directly without further purification for the next step.

To a solution of chlorinated pyridazine in 5 mL of EtOH was added hydrazine hydrate 64% (63 μL, 1.3 mmol) followed by Et_3N (181 μL, 1.3 mmol), and the mixture was refluxed for 4 h. After completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool to room temperature. CH_2Cl_2 was added, and the organic layer was then washed 2 times with 10 mL of saturated aqueous $NaHCO_3$ and 1 time with 10 mL of saturated aqueous NaCl. The organic layer was dried over Na_2SO_4 and concentrated in vacuo, and the residue was purified by flash

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column chromatography on silica gel (EtOAc) to obtain the desired pyrazolo[4,3-*c*]pyridazine **25**.

*4-{6-Ethyl-1H-pyrazolo[4,3-c]pyridazin-3-yl}benzonitrile (**25a**):* beige solid, 207 mg (83% yield); mp 336−338 °C. Data for **25a**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.76 (d, J = 8.5 Hz, 2H), 8.05 (d, J = 8.5 Hz, 2H), 7.80 (s, 1H), 3.16 (q, J = 7.6 Hz, 2H), 1.38 (t, J = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 159.0, 144.1, 141.0, 135.9, 133.8, 133.0, 127.3, 118.9, 111.1, 105.2, 28.9, 14.6; HRMS calcd for $C_{14}H_{11}N_5$ $[M + H]^+$ 250.1087, found 250.1089.

*4-[6-(2-Fluorophenyl)-1H-pyrazolo[4,3-c]pyridazin-3-yl]-benzonitrile (**25b**):* white solid, 249 mg (79% yield); mp 390−393 °C. Data for **25b**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 14.25 (br s, 1H), 8.78 (d, J = 8.3 Hz, 2H), 8.25 (s, 1H), 8.05−8.14 (m, 3H), 7.59−7.61 (m, 1H), 7.45 (t, J = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.7, 158.4, 149.6, 144.2, 141.3, 135.7, 133.3, 133.1, 131.7, 127.4, 125.1, 118.9, 116.7, 116.4, 111.4, 107.8; HRMS calcd for $C_{18}H_{10}FN_5$ $[M + H]^+$ 316.0993, found 316.0989.

*3-(4-Chlorophenyl)-6-ethyl-7-methyl-1H-pyrazolo[4,3-c]-pyridazine (**25c**):* beige solid, 237 mg (87% yield); mp 323−327 °C. Data for **25c**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.64 (d, J = 8.6 Hz, 2H), 7.68 (d, J = 8.6 Hz, 2H), 3.17 (q, J = 7.5 Hz, 2H), 2.61 (s, 3H), 1.37 (t, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.2, 143.6, 141.6, 134.7, 133.5, 130.6, 129.1, 128.4, 115.9, 25.6, 13.9, 12.0; HRMS calcd for $C_{14}H_{13}ClN_4$ $[M + H]^+$ 273.0901, found 273.0905.

*3-Phenyl-6-(thiophene-2-yl)-1H-pyrazolo[4,3-c]pyridazine (**25d**):* pale yellow solid, 225 mg (81% yield); mp 345−348 °C. Data for **25d**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.94 (br s, 1H), 8.59 (d, J = 8.4 Hz, 2H), 8.35 (s, 1H), 8.06 (d, J = 3.7 Hz, 1H), 7.76 (d, J = 5.0 Hz, 1H), 7.60 (t, J = 7.9 Hz, 2H), 7.50 (m, 1H), 7.26 (m, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 148.9, 144.5, 143.2, 141.2, 133.5, 131.3, 129.4, 129.2, 129.0, 128.5, 127.0, 126.5, 101.3; HRMS calcd for $C_{15}H_{10}N_4S$ $[M + H]^+$ 279.0699, found 279.0701.

*3,6-Diphenyl-1H-pyrazolo[4,3-c]pyridazine (**25e**):* beige solid, 215 mg (79% yield); mp 332−335 °C. Data for **25e**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.96 (br s, 1H), 8.63 (d, J = 7.3 Hz, 2H), 8.34 (s, 1H), 8.30 (d, J = 7.4 Hz, 2H), 7.59−7.62 (m, 4H), 7.49−7.56 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 152.7, 144.6, 143.0, 137.0, 133.8, 131.4, 129.6, 129.2, 129.1, 129.0, 127.5, 127.0, 103.7; HRMS calcd for $C_{17}H_{12}N_4$ $[M + H]^+$ 273.1135, found 273.1133.

*3-Phenyl-6-(propan-2-yl)-1H-pyrazolo[4,3-c]pyridazine (**25f**):* beige solid, 179 mg (75% yield); mp 272−275 °C. Data for **25f**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.70 (br s, 1H), 8.58 (d, J = 8.3 Hz, 2H), 7.71 (s, 1H), 7.58 (t, J = 7.4 Hz, 2H), 7.48 (t, J = 7.4 Hz, 1H), 3.46−3.51 (m, 1H), 1.41 (d, J = 6.9 Hz, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.2, 144.3, 142.7, 133.6, 131.6, 129.0, 128.9, 126.9, 103.5, 34.4, 22.9; HRMS calcd for $C_{14}H_{14}N_4$ $[M + H]^+$ 239.1291, found 239.1293.

Method B: Preparation of Thieno[3,2-*c*]pyridazine Analogues 26a−d. A solution of **24** (1 mmol) in 5 mL of $POCl_3$ was heated at 95 °C for 4 h, after which the reaction mixture was cooled down to room temperature. $POCl_3$ was evaporated, and the residue was dissolved in EtOAc and washed 2 times with 20 mL of saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to afford the chlorinated pyridazine, used directly without further purification for the next step.

To a solution of chlorinated pyridazine in 5 mL of EtOH was added methyl thioglycolate (134 μL, 1.5 mmol) followed by Et_3N (417 μL, 3 mmol), and the mixture was refluxed for 16 h. After completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool to room temperature. CH_2Cl_2 was added, and the organic layer was then washed 2 times with 10 mL of saturated aqueous $NaHCO_3$ and 1 time with 10 mL of saturated aqueous NaCl. The organic layer was dried over Na_2SO_4 and concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:9) to obtain the desired thieno[3,2-*c*]pyridazine **26**.

*Ethyl 3-ethyl-7-(4-nitrophenyl)thieno[3,2-c]pyridazine-6-carboxylate (**26a**):* brown solid, 185 mg (52% yield); mp 143−145 °C. Data for **26a**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.36 (d, J = 8.8 Hz, 2H), 7.89 (d, J = 8.9 Hz, 2H), 4.25 (q, J = 7.0 Hz, 2H), 3.12 (q, J = 7.6 Hz, 2H), 1.36 (t, J = 7.6 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.1, 159.6, 156.4, 147.5, 139.4, 139.0, 138.0, 134.4, 132.3, 122.7, 119.6, 62.3, 28.8, 14.2, 13.8; HRMS calcd for $C_{17}H_{15}N_3O_4S$ $[M + H]^+$ 358.0856, found 358.0860.

*Ethyl 3-ethyl-7-(thiophene-2-yl)thieno[3,2-c]pyridazine-6-carboxylate (**26b**):* beige solid, 121 mg (38% yield); mp 139−142 °C. Data for **26b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81−7.83 (m, 2H), 7.58−7.59 (m, 1H), 7.19−7.21 (m, 1H), 4.39 (q, J = 7.1 Hz, 2H), 3.20 (q, J = 7.7 Hz, 2H), 1.47 (t, J = 7.7 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.8, 159.6, 156.3, 137.9, 134.5, 131.7, 131.5, 131.0, 128.7, 126.5, 118.1, 62.3, 29.4, 14.0; HRMS calcd for $C_{15}H_{14}N_2O_2S_2$ $[M + H]^+$ 319.0569, found 319.0579.

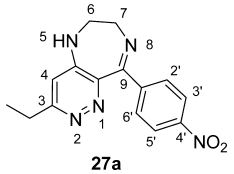
*Ethyl 7-phenyl-3-(thiophene-2-yl)thieno[3,2-c]pyridazine-6-carboxylate (**26c**):* yellow solid, 120 mg (33% yield); mp 157−161 °C. Data for **26c**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.03 (s, 1H), 7.97 (d, J = 3.4 Hz, 1H), 7.81 (d, J = 4.8 Hz, 1H), 7.59−7.61 (m, 2H), 7.51−7.53 (m, 3H), 7.29 (d, J = 4.6 Hz, 1H), 4.25 (q, J = 7.0 Hz, 2H), 1.15 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.4, 156.9, 149.5, 141.5, 140.4, 138.4, 133.5, 132.0, 130.8, 130.4, 128.9, 128.7, 127.7, 127.3, 115.8, 62.1, 13.8; HRMS calcd for $C_{19}H_{14}N_2O_2S_2$ $[M + H]^+$ 367.0569, found 367.0570.

*Methyl 3,7-diphenylthieno[3,2-c]pyridazine-6-carboxylate (**26d**):* brown solid, 148 mg (41% yield); mp 140−144 °C. Data for **26d**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.09 (s, 1H), 8.25 (d, J = 7.3 Hz, 2H), 7.60−7.64 (m, 4H), 7.53−7.57 (m, 4H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.7, 157.0, 153.2, 141.6, 138.5, 136.1, 133.1, 132.0, 130.8, 130.2, 129.3, 128.7, 127.7, 127.3, 117.9, 53.1; HRMS calcd for $C_{20}H_{14}N_2O_2S$ $[M + H]^+$ 347.0849, found 347.0846.

Method C: Preparation of 5*H*,6*H*,7*H*-Pyridazino[4,3-*e*][1,4]-diazepine Analogues 27a−h. A solution of **24** (1 mmol) in 5 mL of $POCl_3$ was heated at 95 °C for 4 h, after which the reaction mixture was cooled down to room temperature. $POCl_3$ was evaporated, and the residue was dissolved in EtOAc and washed 2 times with 20 mL of saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to afford the chlorinated pyridazine, used directly without further purification for the next step.

To a solution of chlorinated pyridazine in 5 mL of EtOH was added ethylene diamine (87 μL, 1.3 mmol) followed by Et_3N (181 μL, 1.3 mmol), and the mixture was refluxed for 16 h. After completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool to room temperature. CH_2Cl_2 was added, and the organic layer was then washed 2 times with 10 mL of saturated aqueous $NaHCO_3$ and 1 time with 10 mL of saturated aqueous NaCl. The organic layer was dried over Na_2SO_4 and concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (MeOH/EtOAc = 1:9) to obtain the desired 5*H*,6*H*,7*H*-pyridazino[4,3-*e*][1,4]diazepine **27**.

*3-Ethyl-9-(4-nitrophenyl)-5H,6H,7H-pyridazino[4,3-e][1,4]-diazepine (**27a**):* pale yellow solid, 229 mg (77% yield); mp 213-215 °C. Data for **27a**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.21 (d, J = 8.8 Hz, 2H, H3′, H5′), 7.65 (m, 3H, NH, H2′, H6′), 6.72 (s, 1H, H4), 4.10−4.11 (m, 2H, H7), 3.51−3.52 (m, 2H, H6), 2.75 (q, J = 7.6 Hz, 2H, CH_2), 1.23 (t, J = 7.6 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.0 (C9), 161.7 (C3), 148.6 (C4′), 147.3 (C), 146.6 (C), 139.8 (C1′), 130.3 (C2′, C6′), 122.7 (C3′, C5′), 109.9 (C4), 53.3 (C6), 47.5 (C7), 28.0 (CH_2), 13.4 (CH_3); HRMS calcd for $C_{15}H_{15}N_5O_2$ $[M + H]^+$ 298.1298, found 298.1306.



27a

*4-[3-(2-Fluorophenyl)-5H,6H,7H-pyridazino[4,3-e][1,4]diazepin-9-yl]benzonitrile (**27b**):* white solid, 271 mg (79% yield); mp 251−255 °C. Data for **27b**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.02−8.05 (m, 1H, H6″), 7.96−7.97 (m, 1H, NH), 7.84 (d, J = 8.2 Hz, 2H, H2′, H6′), 7.64 (d, J = 7.8 Hz, 2H, H3′, H5′), 7.53−7.57 (m, 1H, H4″), 7.36−7.41 (m, 2H, H3″, H5″), 7.32 (s, 1H, H4), 4.16−4.17 (m, 2H, H7), 3.56−3.57 (m, 2H, H6); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.0 (C9), 161.1 (C3), 159.1 (C2″), 151.8 (C), 146.5 (C), 139.8 (C1′), 131.7 (C4″),

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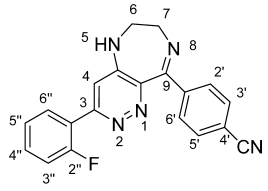
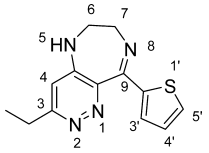
131.5 (C3′, C5′), 130.7 (C6″), 130.0 (C2′, C6′), 125.0 (C5″), 124.3 (C1″), 118.9 (C3″), 116.5 (C≡N), 112.3 (C4′), 111.0 (C4), 53.4 (C6), 47.6 (C7); HRMS calcd for $C_{20}H_{14}FN_5$ $[M + H]^+$ 344.1306, found 344.1301.



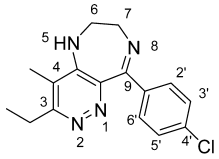
27b

*3-Ethyl-9-(thiophene-2-yl)-5H,6H,7H-pyridazino[4,3-e][1,4]-diazepine (**27c**):* yellow solid, 209 mg (81% yield); mp 185−188 °C. Data for **27c**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.58 (d, J = 4.9 Hz, 1H, H5′), 7.36 (d, J = 3.0 Hz, 1H, H3′), 7.31 (br s, 1H, NH), 7.05 (t, J = 4.0 Hz, 1H, H4′), 6.69 (s, 1H, H4), 3.98−3.99 (m, 2H, H7), 3.52−3.53 (m, 2H, H6), 2.78 (q, J = 7.6 Hz, 2H, CH_2), 1.26 (t, J = 7.6 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.6 (C9), 162.1 (C3), 146.0 (C), 145.1 (C), 139.9 (C2′), 130.5 (C3′), 129.2 (C4′), 127.2 (C5′), 110.2 (C4), 51.4 (C6), 48.3 (C7), 28.0 (CH_2), 13.4 (CH_3); HRMS calcd for $C_{13}H_{14}N_4S$ $[M + H]^+$ 259.1012, found 259.1007.



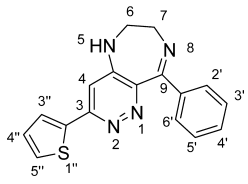
27c

*9-(4-Chlorophenyl)-3-ethyl-4-methyl-5H,6H,7H-pyridazino[4,3-e][1,4]diazepine (**27d**):* beige solid, 247 mg (82% yield); mp 242−247 °C. Data for **27d**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.38−7.39 (m, 4H, H2′, H3′, H5′, H6′), 6.64 (br s, 1H, NH), 4.01−4.04 (m, 2H, H7), 3.58−3.60 (m, 2H, H6), 2.86 (q, J = 7.6 Hz, 2H, CH_2), 2.09 (s, 3H, CH_3), 1.22 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.6 (C9), 159.7 (C3), 144.6 (C), 141.2 (C), 139.7 (C1′), 133.3 (C4′), 130.8 (C2′, C6′), 127.5 (C3′, C5′), 117.6 (C4), 52.5 (C6), 48.7 (C7), 26.7 (CH_2), 13.3 (CH_3), 11.7 (CH_3); HRMS calcd for $C_{16}H_{17}ClN_4$ $[M + H]^+$ 301.1214, found 301.1217.



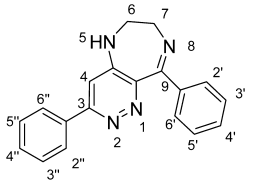
27d

*9-Phenyl-3-(thiophene-2-yl)-5H,6H,7H-pyridazino[4,3-e][1,4]-diazepine (**27e**):* white solid, 242 mg (79% yield); mp 193−196 °C. Data for **27e**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.73−7.74 (m, 1H, H5″), 7.69−7.70 (m, 1H, H3″), 7.61−7.62 (m, 1H, NH), 7.34−7.44 (m, 5H, H2′, H3′, H4′, H5′, H6′), 7.25 (s, 1H, H4), 7.21−7.23 (m, 1H, H4″), 4.07−4.08 (m, 2H, H7), 3.56−3.58 (m, 2H, H6); ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.1 (C9), 151.2 (C3), 146.7 (C), 141.8 (C), 141.0 (C2″), 140.5 (C1′), 129.5 (C4′), 129.1 (C2′, C6′), 128.7 (C3″), 128.4 (C4″), 127.5 (C3′, C5′), 126.1 (C5″), 106.2 (C4), 52.3 (C6), 48.3 (C7); HRMS calcd for $C_{17}H_{14}N_4S$ $[M + H]^+$ 307.1012, found 307.1016.



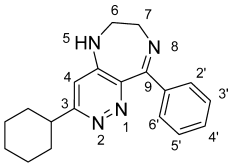
27e

*3,9-Diphenyl-5H,6H,7H-pyridazino[4,3-e][1,4]diazepine (**27f**):* yellow solid, 231 mg (77% yield); mp 186−189 °C. Data for **27f**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.01 (m, 2H, H2′, H6′), 7.60−7.61 (m, 1H, NH), 7.35−7.56 (m, 8H, H3′, H4′, H5′, H2″, H3″, H4″, H5″, H6″), 7.31 (s, 1H, H4), 4.09−4.10 (m, 2H, H7), 3.58−3.60 (m, 2H, H6); ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.3 (C9), 155.3 (C3), 146.8 (C), 141.9 (C), 140.9 (C1′), 136.3 (C1″), 129.8 (C4′), 129.1 (C2′, C6′), 129.0 (C3″, C5″), 128.7 (C4″), 127.5 (C3′, C5′), 126.7 (C2″, C6″), 108.5 (C4), 52.4 (C6), 48.3 (C7); HRMS calcd for $C_{19}H_{16}N_4$ $[M + H]^+$ 301.1448, found 301.1446.



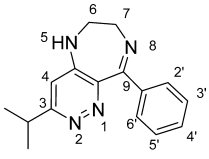
27f

*3-Cyclohexyl-9-phenyl-5H,6H,7H-pyridazino[4,3-e][1,4]diazepine (**27g**):* white solid, 242 mg (79% yield); mp 244−247 °C. Data for **27g**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.34−7.39 (m, 6H, NH, H2′, H3′, H4′, H5′, H6′), 6.67 (s, 1H, H4), 4.01−4.03 (m, 2H, H7), 3.51−3.52 (m, 2H, H6), 2.68−2.72 (m, 1H, CH), 1.70−1.90 (m, 5H, CH_2, CH_2, CH), 1.24−1.50 (m, 5H, CH_2, CH_2, CH); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.4 (C9), 164.3 (C3), 146.7 (C), 142.0 (C), 140.6 (C1′), 129.1 (C2′, C6′), 128.6 (C4′), 127.4 (C3′, C5′), 108.9 (C4), 52.3 (C6), 48.3 (C7), 43.3 (CH), 32.2 (2xCH_2), 26.1 (2xCH_2), 25.8 (CH); HRMS calcd for $C_{19}H_{22}N_4$ $[M + H]^+$ 307.1917, found 307.1909.



27g

*9-Phenyl-3-(propan-2-yl)-5H,6H,7H-pyridazino[4,3-e][1,4]-diazepine (**27h**):* white solid, 208 mg (78% yield); mp 208−212 °C. Data for **27h**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.34−7.39 (m, 6H, NH, H2′, H3′, H4′, H5′, H6′), 6.70 (s, 1H, H4), 4.01−4.02 (m, 2H, H7), 3.52−3.53 (m, 2H, H6), 3.02−3.07 (m, 1H, CH), 1.25 (d, J = 6.9 Hz, 6H, 2xCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.4 (C9), 165.2 (C3), 146.7 (C), 142.0 (C), 140.6 (C1′), 129.1 (C2′, C6′), 128.6 (C4′), 127.4 (C3′, C5′), 108.5 (C4), 52.3 (C6), 48.3 (C7), 33.5 (CH), 22.2 (2xCH_3); HRMS calcd for $C_{16}H_{18}N_4$ $[M + H]^+$ 267.1604, found 267.1602.



27h

Method D: Preparation of Isoxazolo[4,5-*c*]pyridazine Analogues 28a,b. A solution of **24** (1 mmol) in 5 mL of $POCl_3$ was heated at 95 °C for 4 h, after which the reaction mixture was cooled down to room temperature. $POCl_3$ was evaporated, and the residue was dissolved in EtOAc and washed 2 times with 20 mL of saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to afford the chlorinated pyridazine, used directly without further purification for the next step.

To a solution of chlorinated pyridazine in 5 mL of EtOH and 1 mL of pyridine was added hydroxylamine hydrochloride (208 mg, 3 mmol), and the mixture was refluxed for 16 h. After conversion of the ketone into the corresponding oxime (monitored by TLC), the reaction

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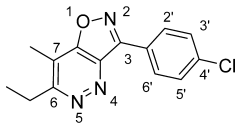
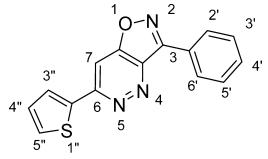
mixture was allowed to cool to room temperature. CH_2Cl_2 was added, and the organic layer was then washed 2 times with 10 mL of saturated aqueous $NaHCO_3$ and 1 time with 10 mL of saturated aqueous NaCl. The organic layer was dried over Na_2SO_4 and concentrated in vacuo; to the residue obtained dissolved in THF was slowly added NaH 60% (52 mg, 1.3 mmol) under argon at room temperature. The reaction mixture was heated at 40 °C for 2 h; after completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool to room temperature. CH_2Cl_2 was added, and the organic layer was then washed 2 times with 10 mL of saturated aqueous $NaHCO_3$ and 1 time with 10 mL of saturated aqueous NaCl. The organic layer was dried over Na_2SO_4 and concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:4) to obtain the desired isoxazolo[4,5-*c*]pyridazine **28**.

*3-(4-Chlorophenyl)-6-ethyl-7-methyl-isoxazolo[4,5-c]pyridazine (**28a**):* beige solid, 167 mg (61% yield); mp 189−192 °C. Data for **28a**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.55 (d, J = 8.7 Hz, 2H, H2′, H6′), 7.78 (d, J = 8.7 Hz, 2H, H3′, H5′), 3.20 (q, J = 7.5 Hz, 2H, CH_2), 2.60 (s, 3H, CH_3), 1.37 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.3 (C), 156.2 (C3), 154.4 (C6), 144.6 (C1′), 136.9 (C4′), 130.0 (C2′, C6′), 129.8 (C3′, C5′), 125.2 (C7), 117.3 (C), 25.8 (CH_2), 13.3 (CH_3), 10.4 (CH_3); HRMS calcd for $C_{14}H_{12}ClN_3O$ $[M + H]^+$ 274.0742, found 274.0743.



28a

*3-Phenyl-6-(thiophene-2-yl)-isoxazolo[4,5-c]pyridazine (**28b**):* orange solid, 128 mg (46% yield); mp 208−211 °C. Data for **28b**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.80 (s, 1H, H7), 8.52−8.54 (m, 2H, H2′, H6′), 8.15 (d, J = 3.7 Hz, 1H, H5″), 7.88 (d, J = 5.0 Hz, 1H, H3″), 7.71−7.72 (m, 3H, H3′, H4′, H5′), 7.32 (t, J = 5.0 Hz, 1H, H4″); ^{13}C NMR (150 MHz, DMSO-d_6) δ 156.7 (C), 155.1 (C3), 153.0 (C6), 145.9 (C2″), 139.6 (C1′), 132.1 (C4′), 131.4 (C3″), 129.5 (C2′, C6′), 128.9 (C4″), 128.7 (C5″), 128.3 (C3′, C5′), 125.9 (C7), 101.8 (C); HRMS calcd for $C_{15}H_9N_3OS$ $[M + H]^+$ 280.0539, found 280.0543.



28b

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra of compounds **10**, **15**, **16**, **18**, **19**, **21**, and **22**−**28**, as well as LC/MS analysis of compounds **24b**−**j**, **25a**−**f**, **26a**−**d**, **27a**−**h**, and **28a,b**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: piet.herdewijn@rega.kuleuven.be. Tel: +32 (0)16/33.73.87. Fax: +32 (0)16/33.73.40.

Notes

The authors declare no competing financial interest.

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(28) Degradation of the crude product **22a** (obtained from the titanium aldol reaction between **19a** and *p*-methoxybenzaldehyde) into the enone **23** during the purification by flash chromatography on silica gel. **2-Diazo-(4-methoxyphenyl)-1-(thiophene-2-yl)-pent-4-ene-1,3-dione (23):** yellow solid, 194 mg (62% yield); mp 120−123 °C. Data for **23**: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.07 (d, J = 3.9 Hz, 1H), 7.97 (d, J = 3.8 Hz, 1H), 7.56−7.74 (m, 4H), 7.26 (t, J = 3.9 Hz, 1H), 7.02 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 181.2, 175.6, 161.6, 142.1, 141.8, 134.7, 132.0, 130.6, 128.4, 126.9, 120.5, 114.7, 82.9, 55.5.