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Expanding the substitution pattern of 2(1*H*)-pyrazinones via Suzuki and Heck reactions

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Abstract—Various 3,5-dichloropyrazinones were substituted at the *C*-3 position with (hetero)aryl, alkyl and alkenyl groups by means of Suzuki and Heck reactions. The methodology could be extended to reactions on the far less reactive *C*-5 position by transhalogenation of the 5-Cl substituent to a 5-Br or a 5-I group prior to performing the cross-coupling.
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1. Introduction

In the past few years, 2(1*H*)-pyrazinones started to emerge as valuable platforms in peptidomimetic chemistry. It has been shown that the diazine core is able to reduce the peptidyl features of peptide-like compounds, rendering them more interesting for pharmaceutical applications: a number of protease inhibitors have been designed around this template (Fig. 1). A pyrazinone was introduced at the P2–P3 (modified amino acid) positions of tryptase inhibitors (e.g., **1**),[1] thrombin inhibitors (e.g., **2**)[2–6] and caspase-3 inhibitors (e.g., **3**).[7] In all these cases, variation of the pyrazinone substituents representing the P1 and P4 residues led to potent compounds.

Another example is the application of a pyrazinone unit in somatostatin analogue **4** (Fig. 1) where it replaced a disulfide moiety, resulting in a compound with a high degree of antiproliferative activity.[8] The pyrazinone core also appears in an opioid-mimetic compound **5** (Fig. 1) which was shown to be able to cross epithelial tissue in the gastrointestinal tract and the blood–brain barrier, paving the way for new orally bioavailable synthetic opioid-mimetic substances.[9–11]

Considering the above mentioned applications of pyrazinone systems it is of interest to further explore the possibilities of functionalising this scaffold. Indeed, being able to modify the substitution pattern on the pyrazinone core can be advantageous if fine-tuning of pharmaceutically relevant compound properties like, e.g. lipophilicity and hydrogen bonding capacity is required.

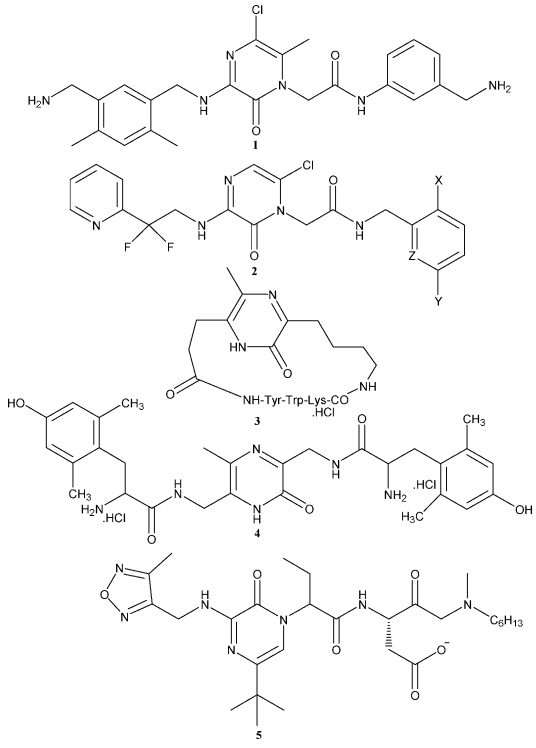

Figure 1. Pyrazinone containing compounds.

Keywords: 3- and 5-Substituted 2(1*H*)-pyrazinones; Heterocyclic compounds; Suzuki reaction; Heck reaction.
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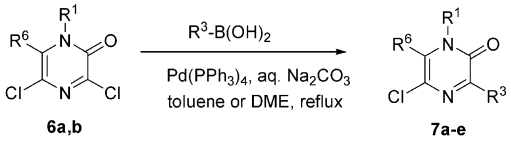
In this paper, in which we elaborate the results of a previous short communication,[12] we focus on the introduction of substituents like, e.g. alkenyl and (hetero)aryl groups at the reactive C-3 and the more challenging C-5 position of 3,5-dihalo-2(1*H*)-pyrazinones. In this respect, Suzuki and Heck cross coupling reactions using organoboron reagents or vinyl compounds appeared to be an attractive way of introducing the abovementioned functionalities. As far as the C-3 position is concerned, these methodologies are complementary to the methods described earlier.[13,14]

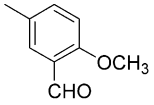
2. Results and discussion

2.1. Functionalisation of the *C*-3 position

2.1.1. Coupling with boron reagents. We first tried introducing (hetero)aryl- and alkenylboronic acids on 3,5-dichloro-2(1*H*)-pyrazinones. In agreement with earlier observations made in the Stille reaction, the initial oxidative addition occurs exclusively at the *C*-3 position of the pyrazinone. We used coupling conditions that were optimised previously for the Suzuki coupling of π-deficient heteroaryl chlorides.[15,16] The best results were obtained using tetrakis(triphenyl-phosphine)palladium(0) as a catalyst, aqueous Na_2CO_3 as the base and toluene as solvent. Thus reaction of pyrazinones **6a**[17] and **6b**[18] with 1.2 equiv of arylboronic acid and 3 mol % of tetrakis in toluene under reflux conditions produced 3-aryl-2(1*H*)-pyrazinones **7a** and **7b**,**c** in good yields (Scheme 1). After completion of the reaction and extractive workup, the mixture was subjected to column chromatography. A similar cross-coupling reaction of pyrazinones **6a** and **6b** with (*E*)-2-phenylethenylboronic acid produced the corresponding 3-(2-phenylethenyl)pyrazinones **7d** and **7e** in 87 and 98% yield, respectively. In the latter two reactions, the coupling succeeded in dimethoxyethane (DME) but not in toluene.

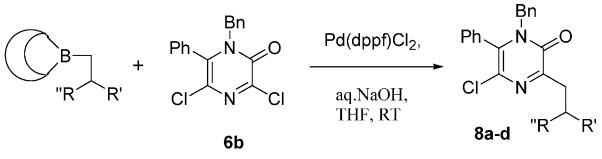


6a,b 7a-e

	R^1	R^3	R^6	Solvent	Yield%
7a	Ph	Ph	CH_3	Toluene	92
7b	Bn		Ph	Toluene	65
7c	Bn		Ph	Toluene	70
7d	Ph		CH_3	DME	87
7e	Bn		Ph	DME	98

Scheme 1. Suzuki-coupling of (hetero)aryl- and 1-alkenylboronic acid at C-3 of 2(1*H*)-pyrazinones **6a**,**b** to form 3-(hetero)aryl- and (*E*)-3-(2-phenylethenyl)-5-chloro-2(1*H*)-pyrazinones **7a–e**.

As a second class of boron containing reagents, alkyl-9-BBN derivatives were submitted to the coupling reaction with pyrazinones (Scheme 2).[19–21] The latter boron derivatives were prepared in situ by adding 9-BBN (solution in THF) to a THF solution of alkenes under argon atmosphere. The mixture was stirred for 6 h at room temperature before the 2(1*H*)-pyrazinone, $Pd(dppf)Cl_2$ and aqueous NaOH were added. The reaction was allowed to proceed at room temperature for 16 h after which complete conversion into 3-substituted products **8a–d** was observed. From the results displayed, it is apparent that primary alkyl-9-BBN reagents having either a single (phenyl, alkyl, trimethylsilyl) or double (cyclohexyl branching) substitution in β-position of the alkyl group attached to boron, all react well with 3,5-dichloro-2(1*H*)-pyrazinone **6b** to give the corresponding products **8a–d** in moderate to good yield. However, no coupling was observed in the reaction of **6b** with the secondary cyclopentyl-9-BBN reagent prepared from cyclopentene.

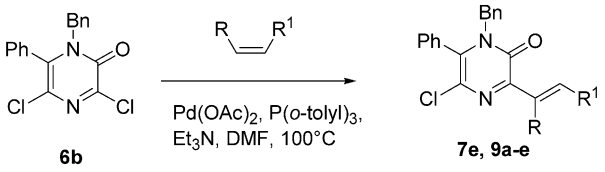


6b 8a-d

	R'	R"	Yield %
8a	H	Ph	60
8b	H	$(CH_2)_3CH_3$	30
8c		$-CH_2(CH_2)_3CH_2-$	80
8d	H	$CH_2Si(CH_3)_3$	40

Scheme 2. Pd-catalysed cross-coupling of alkyl-9-BBN derivatives at the C-3 position of 2(1*H*)-pyrazinone **6b** to form 3-alkyl-5-chloro-2(1*H*)-pyrazinones **8a–d**.

2.1.2. Heck reactions. Applying the Heck reaction to 3,5-dichloro-2(1*H*)-pyrazinones provides a direct method for preparing 3-alkenyl-5-chloro-2(1*H*)-pyrazinones. Thus reaction of pyrazinone **6b** with various alkenes afforded the corresponding 3-alkenyl substituted products **7e** and **9a–e** in good yield. The best conditions consisted of using 3 mol % of $Pd(OAc)_2$, 7 mol % of tri-*o*-tolylphosphine and 2 equiv of triethylamine in DMF at 100 °C. Less satisfactory results or no conversion at all were observed when replacing DMF with acetonitrile (Scheme 3). To avoid evaporation and/or oxidation of volatile vinylic starting materials, the reaction was carried out under argon in a capped heavy-walled glass tube heated in an oil bath. Styrene, methyl acrylate, and acrylonitrile reacted in the expected way to produce **7e**, **9a**, and **9b** in 80, 75, and 70% yield, respectively. A lower yield was observed in the reaction of **6b** with 1-hexene and cyclohexene. The reaction of **6b** with ethyl vinyl ether afforded the enol ether product **9c** that was isolated in 87% yield by flash chromatography. The (*E*)-configuration of the double bond was established by the magnitude of the coupling constant between the two vinylic protons in **7e**, and **9a**,**b**,**d** (16 Hz) and in the enol ether product **9c** (12 Hz).

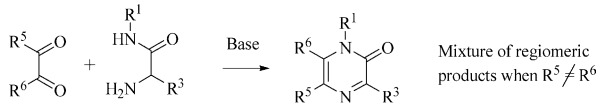


	R	R^1	AcCN Yield%	DMF Yield%
7e	H	Ph	60	80
9a	H	CO_2CH_3	50	75
9b	H	CN	-	70
9c	H	OC_2H_5	-	87
9d	H	C_4H_9	-	53
9e	$-CH_2(CH_2)_2CH_2-$		-	50

Scheme 3. Heck reaction at C-3 position of 2(1*H*)-pyrazinone **6b** to form 3-vinyl-5-chloro-2(1*H*)-pyrazinones **7e** and **9a–e.**

2.2. Functionalisation of the *C*-5 position

2.2.1. Attempts to functionalise the 5-chloro compounds. From previous research in our group, it is known that in contrast to the easy reaction of the 3-imidoyl chloride function, analogous substitution at the vinylic *C*-5-chloro position of 3,5-dichloro-2(1*H*)-pyrazinones via, e.g. Stille reaction is much more difficult. In fact, this has only been achieved by us in an indirect way via isomerisation of 6-alkyl- or 6-benzyl-5-chloro-3-methoxy-2(1*H*)-pyrazinones to form the tautomeric 6-alkylidene/benzylidene-5-chloro-3,6-dihydropyrazin-2(1*H*)-ones having a reactive 5-imidoyl chloride group: subsequent reaction with organotin reagents or amines then produced the corresponding 5-alkyl/aryl or 5-amino-alkylidene/benzylidene-3,6-dihydropyrazin-2(1*H*)-ones, respectively.[22] Alternatively, 2(1*H*)-pyrazinones bearing a 5-alkyl substituent (and their 5-H analogues) can be obtained directly by base-catalyzed condensation of 1,2-dicarbonyl compounds with various α-amino *N*-substituted carboxamide derivatives (Scheme 4).[23] However, this reaction is only interesting in the case that R^5 and R^6 are the same, since otherwise a mixture of regiomeric pyrazinones is formed.



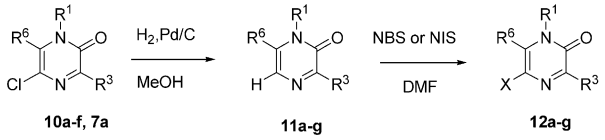
Scheme 4. Synthesis of 5-alkyl and 5-aryl-2(1*H*)-pyrazinones.

Thus exploring the possibilities for substitution at *C*-5 of the pyrazinone system via the methods described above for the *C*-3 position would be of great interest.

Similarly however as with our failure in effecting Stille couplings at the *C*-5 position, we were not successful in substituting the otherwise easily accessible 3-substituted 5-chloropyrazinones by means of a Suzuki-coupling methodology using $Pd(PPh_3)_4$ catalyst and aqueous Na_2CO_3 in either toluene or DME at reflux temperature. Not even a trace of the 5-aryl substituted compounds was formed. Other conditions involving the use of $Pd_2(dba)_3$, combined with P(*t*-Bu)$_3$ and CsF or KF in THF or dioxane, i.e. the conditions used for the synthesis of biaryl compounds starting from an aryl chloride,[24] were also unsuccessful.

A single-case solution to this reactivity issue has been reported by Kaval et al. who achieved a microwave enhanced Suzuki coupling reaction of phenylboronic acid with 1-benzyl-3,5-dichloro-2(1*H*)-pyrazinone to form the corresponding 3,5-diphenyl pyrazinone.[14] We followed a more general approach towards solving the problem by increasing the reactivity of the substrate: indeed, 5-bromo or 5-iodo-2(1*H*)-pyrazinones had to be better candidates as precursors for 5-aryl/alkenyl substituted compounds in this type of coupling reactions.

2.2.2. Synthesis of 5-Br and 5-I pyrazinones. To the best of our knowledge, the synthesis of 3-substituted 5-iodo-2(1*H*)-pyrazinones bearing various substituents at the *N*-1 position has not yet been described. However, 3,6-disubstituted 5-halo-2-pyrazinols have been prepared by halogenation at *C*-5 of the corresponding 2-pyrazinols.[25] Accordingly, we studied the analogous halogenation of 3-methoxy, 3-phenyl and 3-methyl-2(1*H*)-pyrazinones **11a–g** with *N*-bromo and *N*-iodosuccinimide (NBS, NIS) in DMF. The required 5-unsubstituted starting compounds **11a–g** were generated by hydrogenolysis of pyrazinones **10a–f** and **7a** using 10% Pd/C in methanol (Scheme 5).[26–28]



Start. Comp.	Prod.	R^1	R^3	R^6	X	Yield
11a (10a)	**12a**	Bn	OCH_3	CH_3	Br	75
11b (10b)	**12b**	Bn	OCH_3	H	Br	75
11b (10b)	**12b'**	Bn	OCH_3	H	I	75
11c (10c)	**12c**	Bn	OCH_3	Ph	Br	82
11d (10d)	**12d**	Ph	OCH_3	CH_3	Br	73
11d (10d)	**12d'**	Ph	OCH_3	CH_3	I	78
11e (10e)	**12e**	Bn	CH_3	Ph	Br	75
11f (10f)	**12f**	Bn	Ph	H	I	72
11g (7a)	**12g**	Ph	Ph	CH_3	I	66

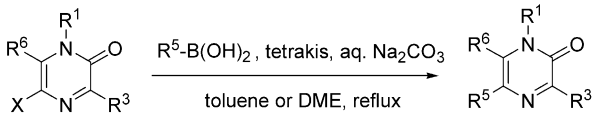
Scheme 5. 5-Bromination and 5-iodination of 2(1*H*)-pyrazinones.

In each of the reactions studied, bromine and iodine were introduced selectively at the *C*-5 position, even when R^6 = H. Halogenation of compounds **11a–d** (3-methoxy), **11e** (3-methyl), and **11f** and **11g** (3-phenyl) provided the corresponding products **12a–d**, **12e** and **12f,g**, respectively. Presumably electrophilic attack at *C*-5 is facilitated by delocalisation of the lone pair on *N*-1. Thus bromination of the 2(1*H*)-pyrazinones by NBS in DMF already proceeded at room temperature in the dark and was completed within 1 h. In contrast, iodination of **11b**, **11d**, **11f** and **11g** by NIS in DMF occurred only at higher temperature to produce the 5-iodo compounds in yields ranging from 66 to 78%. Consistent with a better electron donation of 3-OMe to the pyrazinone ring system, iodination of the 3-OMe compounds already was completed after 8 h at 50 °C whereas

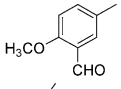
conversion of the less reactive 3-Ph-substituted pyrazinones required heating at 100 °C.

The position of the 5-halo substituent was verified by ^{1}H coupled ^{13}C NMR analysis of **12b′**, **12d**, **12d′** and **12f**, and confirmed by heteronuclear multiple bond correlation (HMBC) spectroscopy (^2J and ^3J) of **12d′**. In the ^{1}H coupled ^{13}C NMR spectrum of 6-H compound **12b′**, the methylene *C*-atom of the *N*-benzyl group appears as a triplet of quartets (tq) with $^1J=284.8$ Hz and $^3J=3.2$ Hz: these *J* values are due to coupling with the two attached protons (^1J) and to coupling with the two *ortho*-protons of the phenyl ring plus the 6-H atom on the 2(1*H*)-pyrazinone ring (^3J). For the carbonyl carbon atom *C*-2 a doublet of triplets (dt) coupling pattern was observed with $^3J=5$ and 3 Hz, which can be related to coupling of *C*-2 with H-6 and the methylene protons of the *N*-benzyl group. The carbon atom *C*-5 attached to the I-atom appears as a doublet (d, $^2J=$ 2.5 Hz) at δ 78.7 ppm, due to coupling with H-6. The *C*-6 atom in turn is detected as a doublet of triplets (dt) with $^1J=$ 189 Hz and $^3J=4.6$ Hz, due to coupling with H-6 and the methylene protons of the *N*-benzyl group.

In the ^{1}H coupled ^{13}C NMR spectrum of the *N*-Ph-6-Me compound **12d′**, *C*-2 is observed as a singlet at δ 151.4 ppm as expected. Owing to coupling with the OMe protons, *C*-3 appears as a multiplet. The quartet pattern with $^3J=7$ Hz observed for *C*-5 reveals coupling with the 6-Me group. Finally, *C*-6 appears as a quartet with $^2J=6$ Hz due to coupling with the protons of the methyl group. In the HMBC spectrum of **12d′**, protons of the 6-methyl group are correlated with *C*-5 and *C*-6 whereas those of the methoxy group are correlated with *C*-3.



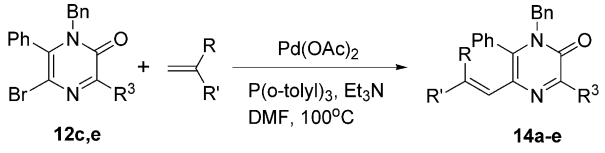
12a,b',d,d',e,f **13a-j**

Start. Comp.	Prod.	R^1	R^3	R^6	R^5	Yield %
12a	**13a**	Bn	OCH_3	CH_3	Ph	92
12a	**13b**	Bn	OCH_3	CH_3		90
12a	**13c**	Bn	OCH_3	CH_3		95
12a	**13d**	Bn	OCH_3	CH_3		80
12b'	**13e**	Bn	OCH_3	H	Ph	78
12d	**13f**	Ph	OCH_3	CH_3	Ph	94
12d'	**13f**	Ph	OCH_3	CH_3	Ph	85
12d	**13g**	Ph	OCH_3	CH_3		55
12d	**13h**	Ph	OCH_3	CH_3		95
12e	**13i**	Bn	CH_3	Ph	Ph	87
12f	**13j**	Bn	Ph	H	Ph	70

Scheme 6. Suzuki-coupling reaction of aryl- and 1-alkenylboronic acid and 5-bromo and 5-iodo-2(1*H*)-pyrazinones.

2.2.3. Functionalisation of the 5-Br and 5-I compounds. Cross-coupling of both 5-bromo- and 5-iodopyrazinones with aryl-, heteroaryl- and 1-alkenylboronic acids in all cases proceeded well to produce the corresponding 5-aryl- and 5-alkenyl-2(1*H*)-pyrazinones. The reactions involving arylboronic acids were carried out using aqueous Na_2CO_3 and $Pd(PPh_3)_4$ and went to completion after heating in toluene or DME at reflux temperature for 18 h. The resulting 5-arylpyrazinones were isolated in excellent yields. Similar cross-coupling of **12a** and **12d** with (*E*)-2-phenylethenylboronic acid in DME afforded compounds **13d** and **13h** in 80 and 95% yield (Scheme 6).

The Heck reaction of 5-bromo-2(1*H*)-pyrazinones **12c**,**e** with alkenes was carried out in a similar way as described above for 3-chloro-2(1*H*)-pyrazinones. Thus treatment of **12c**,**e** with 3 mol % of $Pd(OAc)_2$, 7 mol % of tri-*o*-tolylphosphine and 2 equiv of triethylamine in DMF at 100 °C was found to be most effective for conversion into the 5-substituted alkenyl-2(1*H*)-pyrazinones **14a–e** (Scheme 7).



12c,e **14a-e**

	R	R′	R^3	Yield%
14a	H	Ph	CH_3	71
14b	H	CO_2CH_3	CH_3	84
14c	H	Ph	OCH_3	71
14d	H	CO_2CH_3	OCH_3	66
14e	$-CH_2(CH_2)_3CH_2-$		OCH_3	60

Scheme 7. Heck-coupling of 5-bromopyrazinones with alkenes.

3. Conclusion

The reactive 3-Cl position of 3,5-dichloropyrazinones is easily substituted by means of palladium-catalysed Suzuki and Heck reactions providing easy access to 3-(hetero)aryl, 3-alkenyl and 3-alkyl derived pyrazinone compounds. The 5-Cl atom in these systems is inert towards these cross-coupling conditions and substitution at this position therefore requires prior transhalogenation proceeding via a reduction/bromination (or iodination) sequence. The resulting 5-Br and 5-I compounds smoothly undergo the expected cross-coupling reactions.

4. Experimental

Melting points were taken using an Electrothermal IA 9000 digital melting point apparatus and were uncorrected. Infrared spectra were recorded on a Perkin–Elmer 1600 Fouriertransform IR spectrometer. Mass spectra were run using a Hewlett Packard MS-Engine 5989A apparatus for EI and CI spectra, and a Kratos MS50TC instrument for exact mass measurements performed in the EI mode at a resolution of 10000. NMR spectra were recorded on a Bruker AMX 300 and 400. They were taken using $CDCl_3$ as

a solvent and the ^{1}H and ^{13}C chemical shifts are reported in ppm relative to TMS.

The 2(1*H*)-pyrazinones **6a** and **6b** were prepared as described previously.[17,18]

4.1. Synthesis of 3-(hetero)aryl, 3-alkenyl-2(1*H*)-pyrazinones 7a–e via Suzuki-coupling reaction

General procedure. A mixture of pyrazinone **6a** and **6b** (1 mmol) and 28 mg of tetrakis $Pd(PPh_3)_4$ (2.5 mol %) in dry toluene or DME (for the synthesis of 3-alkenyl-2(1*H*)-pyrazinones) was stirred under nitrogen for 10 min. Following addition of (hetero)aryl boronic acid (1.5 mmol), the mixture was stirred further for 10 min whereupon 2 M aqueous sodium carbonate (3 mL) was added. The reaction mixture was then heated at reflux for 18 h (1.5 h for the synthesis of 3-alkenyl-2(1*H*)-pyrazinones) and cooled to RT. The mixture was distributed between 50 mL of water and CH_2Cl_2 (50 mL) and the aqueous phase further extracted with CH_2Cl_2 two times (50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to afford a pale residue, which was subjected to column chromatography (silica gel, 100% CH_2Cl_2).

4.1.1. 5-Chloro-6-methyl-1,3-diphenyl-2(1*H*)-pyrazinone 7a. Yield: 87%; solid, mp: 165 °C; IR (KBr) cm^{-1}: 1665 (s, CO), 1600 (s, C=N); ^{1}H NMR ($CDCl_3$, 300 MHz): 8.50–7.25 (m, 10H, ArH), 2.20 (s, 3H, CH_3); EIMS *m/z* (%): 296 (M^+, 95), 77 ($C_6H_5^+$, 100); HRMS: $C_{17}H_{13}ClN_2O$, calculated: 296.0716, found: 296.0722.

4.1.2. 5-(4-Benzyl-6-chloro-3-oxo-5-phenyl-3,4-dihydro-2-pyrazinyl)-2-methoxy-benzaldehyde 7b. Yield: 65%; solid, mp: 170 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 10.48 (s, 1H, CHO), 8.99 (d, $J=2.2$ Hz, 1H, H6′), 8.79 (dd, $J=2.6$, 9.1 Hz, 1H, H4′), 7.49–6.85 (m, 11H, ArH), 5.14 (s, 2H, CH_2Ph), 4.00 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 189.8 (CHO), 163.4 (*C*-OCH_3), 155.3 (C3), 149.5 (C2), 137.7 (C5), 135.8, 131.3, 127.1 (ArC-*ipso*), 137.2, 131.2, 130.5, 129.8, 129.2, 128.9, 128.1, 127.6, 111.7 (ArCH), 128.3 (C6), 124.9 (*C*-CHO), 56.3 (OCH_3), 50.6 (CH_2Ph); EIMS *m/z* (%): 430 (M^+, 77), 91 ($C_7H_7^+$, 100); HRMS: $C_{25}H_{19}ClN_2O_3$, calculated: 430.1084, found: 430.1063.

4.1.3. 1-Benzyl-5-chloro-6-phenyl-3-(3-thienyl)-2(1*H*)-pyrazinone 7c. Yield: 70%; solid, mp: 164.2 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 8.94 (dd, $J=1.1$, 2.9 Hz, 1H, H2′), 8.00 (dd, $J=1.1$, 5.1 Hz, 1H, H4′), 7.50–6.83 (m, 11H, ArH), 5.14 (s, 2H, CH_2Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): 154.9 (C2), 147.3 (C3), 137.4 (C6), 136.6, 135.9, 131.5 (ArC-*ipso*), 131.4, 130.4, 129.8, 129.2, 128.9, 128.3, 128.1, 127.4, 125.3 (ArCH), 126.9 (C6), 50.5 (CH_2Ph); EIMS *m/z* (%): 378 (M^+, 91), 91 ($C_7H_7^+$, 100); HRMS: $C_{21}H_{15}ClN_2OS$, calculated: 378.0593, found: 378.0589.

4.1.4. 5-Chloro-6-methyl-1-phenyl-3-[(*E*)-2-phenylethenyl]-2(1*H*)-pyrazinone 7d. Yield: 87%; solid, mp: 178.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 8.15 (d, $J=16$ Hz, 1H, HC=), 7.45 (d, $J=16$ Hz, 1H, HC=), 7.63–7.21 (m, 10H, ArH), 2.14 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 156.0 (C2), 149.6 (C3), 137.9 (C6), 138.5 (HC=), 136.9, 133.7 (ArC-*ipso*), 130.6, 130.0, 129.5, 129.2, 128.1, 127.5 (ArCH), 126.9 (C5), 122.9 (HC=), 18.7 (CH_3); EIMS *m/z* (%): 322 (M^+, 100), 293 (–CO, 81); HRMS: $C_{19}H_{15}ClN_2O$, calculated: 322.0873, found: 322.0866.

4.1.5. 1-Benzyl-5-chloro-6-phenyl-3-[(*E*)-2-phenylethenyl]-2(1*H*)-pyrazinone 7e. Yield: 98%; solid, mp: 182.2 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 8.12 (d, $J=16$ Hz, 1H, HC=), 7.66–6.84 (m, 16H, ArH), 5.10 (s, 2H, CH_2Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): 155.7 (C2), 151.0 (C3), 137.8 (C6), 138.8 (HC=), 136.6, 135.8, 130.4 (ArC-*ipso*), 131.5, 129.9, 129.7, 129.23, 129.2, 128.9, 128.3, 128.1, 127.6 (ArCH), 127.5 (C5), 122.2 (HC=), 50.4 (CH_2Ph); EIMS *m/z* (%): 398 (M^+, 100), 307 (–C_7H_7, 79), 91 ($C_7H_7^+$, 90); HRMS: $C_{25}H_{19}ClN_2O$, calculated: 398.1186, found: 398.1179.

4.2. Synthesis of 3-alkyl-2(1*H*)-pyrazinones 8a–d using alkyl-9-BBN reagents

General procedure. A dry flask equipped with magnetic stirring bar, septum inlet, and condenser was flushed with nitrogen. To the flask was added an alkene (1.1 mmol) and 1 mL of dry THF and then 2.2 mL of a solution of 9-BBN (0.5 M solution in THF, 1.1 mmol) at 0 °C. The mixture was warmed up slowly to RT and then stirred for 4–6 h to give a solution of alkyl-9-BBN. To this solution were added 24 mg of $Pd(dppf)Cl_2$ (0.03 mmol, 3 mol %), 330 mg of pyrazinone **6b** (1 mmol), additional 5 mL of THF, 1 mL of aqueous NaOH (3 M solution) at RT. The mixture was stirred at RT for 14–16 h. After the reaction was completed, the reaction mixture was diluted with 50 mL of toluene and water. The mixture was extracted with toluene, washed with brine and dried over $MgSO_4$, followed by purification using column chromatography (silica gel, 50% heptane/CH_2Cl_2 → 20% heptane/CH_2Cl_2).

4.2.1. 1-Benzyl-5-chloro-3-phenethyl-6-phenyl-2(1*H*)-pyrazinone 8a. Yield: 60%; oil; IR (KBr) cm^{-1}: 1651 (s, CO), 1560 (C=N); ^{1}H NMR ($CDCl_3$, 300 MHz): 7.49–6.77 (m, 15H, ArH), 5.03 (s, 2H, CH_2Ph), 3.28–3.09 (m, 4H, $2CH_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): 159.1 (C2), 155.9 (C3), 141.7 (C6), 136.7, 135.8, 130.4 (ArC-*ipso*), 131.3, 129.8, 129.2, 129.0, 128.9, 128.8, 128.1, 127.6, 126.4 (ArCH), 126.5 (C5), 50.2 (CH_2Ph), 35.7, 32.8 (CH_2); EIMS *m/z* (%): 400 (M^+, 33), 309 (–C_7H_7, 100), 91 ($C_7H_7^+$, 100); HRMS: $C_{25}H_{21}ClN_2O$, calculated: 400.1342, found: 400.1339.

4.2.2. 1-Benzyl-5-chloro-3-hexyl-6-phenyl-2(1*H*)-pyrazinone 8b. Yield: 30%; oil; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.45–6.83 (m, 10H, ArH), 5.10 (s, 2H, CH_2Ph), 2.90 (d, $J=$ 7.3 Hz, 2H, CH_2), 1.62–0.85 (m, 11H, $4CH_2+CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 159.9 (C2), 156.9 (C3), 136.3 (C6), 136.2, 130.5 (ArC-*ipso*), 130.4, 130.0, 129.5, 129.3, 128.7, 128.1 (ArCH), 126.9 (C5), 50.4 (CH_2Ph), 33.1, 29.5, 29.2, 28.5, 22.7 (CH_2), 14.0 (CH_3); EIMS *m/z* (%): 380 (M^+, 6), 287 (–C_7H_7, 15), 91 ($C_7H_7^+$, 100).

4.2.3. 1-Benzyl-5-chloro-3-cyclohexylmethyl-6-phenyl-2(1*H*)-pyrazinone 8c. Yield: 80%; oil; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.48–6.78 (m, 10H, ArH), 5.03 (s, 2H, CH_2Ph), 2.80 (d, $J=7.3$ Hz, 2H, CH_2), 2.05–1.05 (m, 11H, CH+

5CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): 159.7 (C2), 156.1 (C3), 136.3 (C6), 136.0, 131.4 (ArC-*ipso*), 130.3, 129.8, 129.2, 128.8, 128.0, 127.6 (ArCH), 126.2 (C5), 50.1 (CH_2Ph), 41.5 (CH_2), 36.7 (CH), 33.7, 26.8, 26.6 (CH_2); EIMS *m/z* (%): 392 (M^+, 8), 310 (–C_6H_{10}, 37), 301 (–C_7H_7, 100), 91 ($C_7H_7^+$, 65); HRMS: $C_{24}H_{25}ClN_2O$, calculated: 392.1655, found: 392.1653.

4.2.4. 1-Benzyl-5-chloro-6-phenyl-3-[3-(trimethylsilyl)-propyl]-2(1*H*)-pyrazinone 8d. Yield: 40%; oil; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.45–6.77 (m, 10H, ArH), 5.02 (s, 2H, CH_2Ph), 2.91 (d, J=7.6 Hz, 2H, CH_2), 1.83–1.72 (m, 2H, CH_2), 0.66–0.60 (m, 2H, CH_2), 0.01 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 161.5 (C2), 157.2 (C3), 137.6 (C6), 137.2, 132.6 (ArC-*ipso*), 131.6, 131.1, 130.4, 130.1, 129.3, 128.9 (ArCH), 127.6 (C5), 51.3 (CH_2Ph), 39.2, 23.2, 18.5 (CH_2), 0.01 (Si(CH_3)$_3$); EIMS *m/z* (%): 410 (M^+, 8), 319 (–C_7H_7, 100), 91 ($C_7H_7^+$, 88); HRMS: $C_{23}H_{27}ClN_2OSi$, calculated: 410.1581, found: 410.1568.

4.3. Synthesis of 3-alkenyl-2(1*H*)-pyrazinones via Heck-coupling reaction

General procedure. A mixture of 330 mg of pyrazinone **6b** (1 mmol), 7 mg of $Pd(OAc)_2$ (3 mol %) and 26 mg of P(*o*-tolyl)$_3$ (7 mol %) was stirred at room temperature under argon for 10 min. Add 1.5 mmol of alkene, 300 mg of dry Et_3N (3 mmol) and 1 mL DMF. The reaction mixture was heated at 100 °C in a capped heavy-walled glass tube in an oil bath for 18 h. After the completion of the reaction, the mixture was poured in water and extracted with 50 mL of CH_2Cl_2 three times. The organic layer was collected and dried over $MgSO_4$. After filtration and evaporation of CH_2Cl_2, the mixture was subjected to column chromatography (silica gel, A: 30% heptane/CH_2Cl_2 or B: 100% CH_2Cl_2→5% EtOAc/CH_2Cl_2).

Compound **7e** was isolated in 80% yield (solvent system A) using the present method.

4.3.1. Methyl (2*E*)-3-(4-benzyl-6-chloro-3-oxo-5-phenyl-3,4-dihydro-2-pyrazinyl)-2-propenoate 9a. Yield: 75%; solvent system B; solid, mp: 93.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.93 (d, J=16 Hz, 1H, HC=), 7.34 (d, J=16 Hz, 1H, HC=), 7.50–6.81 (m, 10H, ArH), 5.10 (s, 2H, CH_2Ph), 3.81 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 166.7 (COO), 155.0 (C3), 147.8 (C2), 139.7 (C5), 137.4 (HC=), 135.0, 130.6 (ArC-*ipso*), 130.3, 129.0, 128.9, 128.5, 127.9, 127.2 (ArCH), 127.3 (C6), 126.6 (HC=), 51.9 (OCH_3), 50.2 (CH_2Ph); EIMS *m/z* (%): 380 (M^+, 25), 321 (–$COOCH_3$, 13), 91 ($C_7H_7^+$, 100); HRMS: $C_{21}H_{17}ClN_2O_3$, calculated: 380.0928, found: 380.0927.

4.3.2. (2*E*)-3-(4-benzyl-6-chloro-3-oxo-5-phenyl-3,4-dihydro-2-pyrazinyl)-2-propenenitrile 9b. Yield: 70%; solvent system B; solid, mp: 117.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.63 (d, J=16 Hz, 1H, HC=), 7.02 (d, J=16 Hz, 1H, HC=), 7.55–6.80 (m, 10H, ArH), 5.11 (s, 2H, CH_2Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): 155.1 (C3), 146.1 (C2), 141.4 (C5), 143.9 (HC=), 135.0, 131.0 (ArC-*ipso*), 130.6, 129.4, 129.3, 129.0, 128.5, 127.6 (ArCH), 127.9 (C6), 118.1 (CN), 105.8 (HC=), 50.8 (CH_2Ph); EIMS *m/z* (%): 347 (M^+, 44), 91 ($C_7H_7^+$, 100); HRMS: $C_{20}H_{14}ClN_3O$, calculated: 347.0825, found: 347.0822.

4.3.3. 1-Benzyl-5-chloro-3-[(*E*)-2-ethoxyethenyl]-6-phenyl-2(1*H*)-pyrazinone 9c. Yield: 87%; solvent system B; oil. ^{1}H NMR ($CDCl_3$, 300 MHz): 8.24 (d, J=12 Hz, 1H, HC=), 7.46–6.80 (m, 10H, ArH), 6.27 (d, J=12 Hz, 1H, HC=), 5.04 (s, 2H, CH_2Ph), 4.03 (q, J=6.9 Hz, 2H, CH_2), 1.36 (t, J=6.9 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 159.2 (HC=), 155.0 (C2), 152.2 (C3), 136.0 (C6), 133.4, 131.7 (ArC-*ipso*), 130.2, 130.1, 129.1, 128.8, 127.9, 127.4 (ArCH), 127.2 (C5), 102.9 (HC=), 67.1 (CH_2CH_3), 50.2 (CH_2Ph), 15.1 (CH_2CH_3); EIMS *m/z* (%): 366 (M^+, 40), 338 (–C_2H_2, 50), 91 ($C_7H_7^+$, 100).

4.3.4. 1-Benzyl-5-chloro-3-(1-hexenyl)-6-phenyl-2(1*H*)-pyrazinone 9d. Yield: 53%; solvent system A; oil; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.47–6.81 (m, 12H, ArH), 5.05 (s, 2H, CH_2Ph), 1.56–0.90 (m, 9H, $3CH_2+CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 155.4 (C2), 151.2 (C3), 144.1 (HC=), 136.1 (C6), 135.9, 130.3 (ArC-*ipso*), 131.5, 129.9, 129.1, 128.8, 128.0, 127.6 (ArCH), 127.3 (C5), 124.5 (HC=), 50.3 (CH_2Ph), 33.6, 31.2, 22.7 (CH_2), 14.3 (CH_3); EIMS *m/z* (%): 378 (M^+, 3), 287 (–C_7H_7, 10), 91 ($C_7H_7^+$, 100); HRMS: $C_{23}H_{23}ClN_2O$, calculated: 378.1499, found: 378.1486.

4.3.5. 1-Benzyl-5-chloro-3-(1-cyclohexenyl)-6-phenyl-2(1*H*)-pyrazinone 9e. Yield: 50%; solvent system B; oil; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.86 (t, J=3.1 Hz, 1H, HC=), 7.44–6.81 (m, 10H, ArH), 5.06 (s, 2H, CH_2Ph), 2.57–2.54 (m, 2H, CH_2), 2.37–2.34 (m, 2H, CH_2), 1.78–1.75 (m, 2H, CH_2), 1.70–1.65 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): 154.8 (C2), 151.6 (C3), 138.3 (HC=), 135.2 (C6), 135.8, 131.3 (ArC-*ipso*), 134.6 (*C*=CH), 129.8, 129.4, 128.7, 128.4, 127.5, 127.0 (ArCH), 126.1 (C5), 49.9 (CH_2Ph), 26.6, 25.8, 22.6, 21.7 (CH_2); EIMS *m/z* (%): 376 (M^+, 5), 91 ($C_7H_7^+$, 100); HRMS: $C_{23}H_{21}ClN_2O$, calculated: 376.1342, found: 376.1338.

4.4. Synthesis of 2(1*H*)-pyrazinones 10a–f

The 3-methoxy-2(1*H*)-pyrazinones **10a–d** were prepared as described previously[22,26] The 3-methyl- and 3-phenyl-2(1*H*)-pyrazinones **10e–f** were prepared via Pd-catalysed reaction according to procedures described previously.[17,27]

4.5. Dechlorination of *C*-5 position of 2(1*H*)-pyrazinones 10a–f and 7a

General procedure. A mixture of 2(1*H*)-pyrazinone **10a–f** or **7a** (2 mmol) in 10 mL of MeOH and 280 mg (2 mmol) of K_2CO_3 was hydrogenated for 0.5–8 h in the presence of catalyst (10% Pd/C; 50 mg) under H_2 at atmospheric pressure. After removal of the catalyst by filtration, the filtrate was evaporated and the residue was dissolved in dichloromethane. The solution was washed twice with 20 mL of water, dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (silica gel, 10% EtOAc/CH_2Cl_2—100%CH_2Cl_2) to give the corresponding dechlorinated compounds **11a–g**. Compounds **11a**,**d**,**e**,**g** have been described previously.[26–28]

4.5.1. 1-Benzyl-3-methoxy-2(1*H*)-pyrazinone 11b. Yield: 92%; solid, mp: 78.5–79.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.34–7.28 (m, 5H, ArH), 6.78 (d, J=4.6 Hz, 1H, H5/H6), 6.73 (d, J=4.6 Hz, 1H, H6/H5), 5.1 (s, 2H, CH_2Ph), 3.96 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 157.2 (C3), 151.9 (C2), 135.6 (ArC-*ipso*), 129.3, 128.8, 128.7 (ArCH), 122.0 (C6), 119.7 (C5), 54.9 (OCH_3), 51.8 (CH_2Ph); EIMS *m/z* (%): 216 (M^+, 70), 91 ($C_7H_7^+$, 100); HRMS: $C_{12}H_{12}N_2O_2$, calculated: 216.0899, found: 216.0896.

4.5.2. 1-Benzyl-3-methoxy-6-phenyl-2(1*H*)-pyrazinone 11c. Yield: 30%; solid, mp: 116.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.42–6.85 (m, 10H, ArH), 6.73 (s, 1H, H5), 5.14 (s, 2H, CH_2Ph), 4.02 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 156.2 (C3), 152.3 (C2), 136.4 (C6), 135.2, 132.3 (ArC-*ipso*), 130.2, 129.7, 128.8, 128.7, 127.86, 127.82 (ArCH), 119.9 (C5), 54.8 (OCH_3), 48.8 (CH_2Ph); EIMS *m/z* (%): 292 (M^+, 90), 91 ($C_7H_7^+$, 100); HRMS: $C_{18}H_{16}N_2O_2$, calculated: 292.1212, found: 292.1203.

4.5.3. 1-Benzyl-3-phenyl-2(1*H*)-pyrazinone 11f. Yield: 84%; oil; ^{1}H NMR ($CDCl_3$, 300 MHz): 8.32–8.28 (m, 2H, ArH), 7.44–7.37 (m, 9H, ArH), 7.08 (d, J=4.3 Hz, 1H, H5/H6), 5.17 (s, 2H, CH_2Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): 155.9 (C2), 154.2 (C3), 136.3, 135.3 (ArC-*ipso*), 130.4, 129.5, 129.4, 128.97, 128.95, 128.4 (ArCH), 127.8 (C6), 123.8 (C5), 52.8 (CH_2Ph); EIMS *m/z* (%): 262 (M^+, 80), 91 ($C_7H_7^+$, 100); HRMS: $C_{17}H_{14}N_2O$, calculated: 262.1106, found: 262.1103.

4.6. Synthesis of 5-bromo and 5-iodo-2(1*H*)-pyrazinones 12a–g

General procedure. To a solution of pyrazinone **11a–g** (2 mmol) in DMF (2 mL) was added NBS or NIS (2.2 mmol). The reaction mixture was stirred in the dark under nitrogen atmosphere at RT for 1–2 h (NBS) or at 50–100 °C for 8–12 h (NIS). The mixture was poured into 50 mL of ice-water and extracted three times with CH_2Cl_2. After the usual work up, the residue was purified by column chromatography (silica gel, 100% CH_2Cl_2→5%EtOAc/CH_2Cl_2).

4.6.1. 1-Benzyl-5-bromo-3-methoxy-6-methyl-2(1*H*)-pyrazinone 12a. Yield: 90%; solid, mp: 85.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.35–7.15 (m, 5H, ArH), 5.34 (s, 2H, CH_2Ph), 4.01 (s, 3H, OCH_3), 2.34 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 153.5 (C3), 152.0 (C2), 135.3 (ArC-*ipso*), 129.2 (C6), 129.3, 128.3, 127.1 (ArCH), 112.1 (C5), 55.4 (OCH_3), 49.2 (CH_2Ph), 18.6 (CH_3); EIMS *m/z* (%): 308 (M^+, 100), 229 (–Br, 57); HRMS: $C_{13}H_{13}BrN_2O_2$, calculated: 308.0160, found: 308.0149.

4.6.2. 1-Benzyl-5-bromo-3-methoxy-2(1*H*)-pyrazinone 12b. Yield: 75%; solid, mp: 75 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.37–7.23 (m, 5H, ArH), 7.04 (s, 1H, H6), 5.04 (s, 2H, CH_2Ph), 3.92 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 156.2 (C3), 151.0 (C2), 135.0 (ArC-*ipso*), 129.2, 128.4, 128.1 (ArCH), 125.3 (C6), 115.2 (C5), 55.3 (OCH_3), 51.5 (CH_2Ph); EIMS *m/z* (%): 294 (M^+, 60), 215 (–Br, 20), 91 ($C_7H_7^+$, 100); HRMS: $C_{12}H_{11}BrN_2O_2$, calculated: 294.0004, found: 294.0001.

4.6.3. 1-Benzyl-5-iodo-3-methoxy-2(1*H*)-pyrazinone 12b′. Yield: 75%; oil; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.36–7.29 (m, 5H, ArH), 7.01 (s, 1H, H6), 5.02 (s, 2H, CH_2Ph), 3.95 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 155.5 (C3), 151.4 (C2), 134.7 (ArC-*ipso*), 129.0, 128.6, 128.4 (ArCH), 127.2 (C6), 78.6 (C5), 55.2 (OCH_3), 51.5 (CH_2Ph); EIMS *m/z* (%): 341 (M^+, 40), 215 (–I, 8), 91 ($C_7H_7^+$, 100); HRMS: $C_{12}H_{11}IN_2O_2$, calculated: 341.9865, found: 341.9860.

4.6.4. 1-Benzyl-5-bromo-3-methoxy-6-phenyl-2(1*H*)-pyrazinone 12c. Yield: 82%; solid, mp: 138.4–139.4 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.45–6.77 (m, 10H, ArH), 5.04 (s, 2H, CH_2Ph), 4.06 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 154.8 (C3), 151.6 (C2), 133.0 (C6), 135.9, 132.9 (ArC-*ipso*), 130.5, 130.1, 129.0, 128.7, 128.0, 127.8 (ArCH), 112.7 (C5), 55.6 (OCH_3), 50.3 (CH_2Ph); EIMS *m/z* (%): 370 (M^+, 40), 91 ($C_7H_7^+$, 100); HRMS: $C_{18}H_{15}BrN_2O_2$, calculated: 370.0317, found: 370.0300.

4.6.5. 5-Bromo-3-methoxy-6-methyl-1-phenyl-2(1*H*)-pyrazinone 12d. Yield: 73%; solid, mp: 141.1–141.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.57–7.15 (m, 5H, ArH), 4.00 (s, 3H, OCH_3), 2.00 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 154.2 (C3), 151.3 (C2), 135.9 (ArC-*ipso*), 129.8 (C6), 130.5, 129.8, 127.8 (ArCH), 115.6 (C5), 55.6 (OCH_3), 22.8 (CH_3); EIMS *m/z* (%): 294 (M^+, 100), 264 (–CO, 31), 77 ($C_6H_5^+$, 79); HRMS: $C_{12}H_{11}BrN_2O_2$, calculated: 294.0003, found: 293.9982.

4.6.6. 5-Iodo-3-methoxy-6-methyl-1-phenyl-2(1*H*)-pyrazinone 12d′. Yield: 78%; solid, mp: 128 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.53–7.13 (m, 5H, ArH), 3.97 (s, 3H, OCH_3), 2.07 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 153.3 (C3), 151.4 (C2), 138.0 (ArC-*ipso*),131.9 (C6), 130.0, 129.5, 127.3 (ArCH), 83.3 (C5), 54.9 (OCH_3), 23.2 (CH_3); EIMS *m/z* (%): 341 (M^+, 100), 312 (–CO, 12); HRMS: $C_{12}H_{11}IN_2O_2$, calculated: 341.9865, found: 341.9861.

4.6.7. 1-Benzyl-5-bromo-3-methyl-6-phenyl-2(1*H*)-pyrazinone 12e. Yield: 75%; solid, mp: 136.2–136.6 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.49–6.79 (m, 10H, ArH), 5.03 (s, 2H, CH_2Ph), 2.57 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 157.6 (C2), 156.3 (C3), 138.6 (C6), 135.8, 132.7 (ArC-*ipso*), 130.4, 129.8, 129.2, 128.8, 128.1, 127.7 (ArCH), 115.9 (C5), 50.5 (CH_2Ph), 21.4 (CH_3); EIMS *m/z* (%): 354 (M^+, 60), 275 (–Br, 6), 91 ($C_7H_7^+$, 100); HRMS: $C_{18}H_{15}BrN_2O$, calculated: 354.0368, found: 354.0362.

4.6.8. 1-Benzyl-5-iodo-3-phenyl-2(1*H*)-pyrazinone 12f. Yield: 72%; solid, mp: 140.3–141 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.34–8.31 (m, 2H, ArH), 7.42–7.33 (m, 8H, ArH), 5.09 (s, 2H, CH_2Ph); ^{13}C NMR ($CDCl_3$, 100 MHz): 154.4 (C2), 154.1 (C3), 134.9, 134.5 (ArC-*ipso*), 133.2 (C6), 130.5, 129.2, 129.1, 128.7, 128.6, 128.0 (ArCH), 83.2 (C5), 52.4 (CH_2Ph); EIMS *m/z* (%): 388 (M^+, 30), 91 ($C_7H_7^+$, 100); HRMS: $C_{17}H_{13}IN_2O$, calculated: 388.0073, found: 388.0069.

4.6.9. 5-Iodo-1,3-diphenyl-6-methyl-2(1*H*)-pyrazinone 12g. Yield: 66%; solid, mp: 184.8 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 8.38–8.34 (m, 2H, ArH), 7.60–7.18 (m, 8H, ArH), 2.22 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 155.8

(C2), 150.9 (C3), 139.5 (C6), 138.7, 135.3 (ArC-*ipso*), 130.6, 130.5, 129.9, 129.3, 128.4, 127.4 (ArCH), 89.7 (C5), 24.6 (CH_3); EIMS *m/z* (%): 388 (M^+, 100), 360 (–CO, 36), 77 ($C_6H_5^+$, 50); HRMS: $C_{17}H_{13}IN_2O$, calculated: 388.0073, found: 388.0051.

4.7. Synthesis of 5-(hetero)aryl and 5-alkenyl-2(1*H*)-pyrazinones 13a–j by Suzuki coupling of 5-bromo or 5-iodo-2(1*H*)-pyrazinones

General procedure. A mixture of pyrazinone **12a**,**b′**,**d**, **d′**, **e** and **f** (1 mmol) and 28 mg of tetrakis $Pd(PPh_3)_4$ (2.5 mol %) in dry toluene or DME (for the synthesis of 3-alkenyl-2(1*H*)-pyrazinones) was stirred under nitrogen for 10 min. Following addition of (hetero)aryl boronic acid (1.5 mmol), the mixture was stirred further for 10 min whereupon 2 M aqueous sodium carbonate (3 mL) was added. The reaction mixture was then heated at reflux for 18 h (1.5 h for the synthesis of 3-alkenyl-2(1*H*)-pyrazinones) and cooled to RT. The mixture was distributed between 50 mL of water and CH_2Cl_2 (50 mL) and the aqueous phase further extracted with CH_2Cl_2 two times (50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to afford a pale residue, which was subjected to column chromatography (silica gel, 100% CH_2Cl_2).

4.7.1. 1-Benzyl-3-methoxy-6-methyl-5-phenyl-2(1*H*)-pyrazinone 13a. Yield: 92%; solid, mp: 115 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.44–7.20 (m, 10H, ArH), 5.39 (s, 2H, CH_2Ph), 4.00 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 153.8 (C3), 152.2 (C2), 138.8, 136.0 (ArC-*ipso*), 129.4 (C6/C5), 127.8 (C5/C6), 129.9, 129.2, 128.5, 128.0, 127.9, 127.1 (ArCH), 54.7 (OCH_3), 48.3 (CH_2Ph), 16.9 (CH_3); EIMS *m/z* (%): 306 (M^+, 100), 215 (–C_7H_7, 65), 91 ($C_7H_7^+$, 90); HRMS: $C_{19}H_{18}N_2O$, calculated: 306.1368, found: 306.1366.

4.7.2. 5-(4-Benzyl-6-methoxy-3-methyl-5-oxo-4,5-dihydro-2-pyrazinyl)-2-methoxy-benzaldehyde 13b. Yield: 90%; solid, mp: 68 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 10.48 (s, 1H, CHO), 7.85 (d, J=2.5 Hz, 1H, H6′), 7.67 (dd, J=2.6,8.8 Hz, 1H, H4′), 7.33–7.19 (m, 5H, ArH), 7.05 (d, J=8.8 Hz, 1H, H3′), 5.39 (s, 2H, CH_2Ph), 3.99 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 189.9 (CHO), 161.6 (*C*–OCH_3), 153.9 (C6), 152.1 (C5), 135.8, 131.4 (ArC-*ipso*), 137.4, 129.5, 129.3, 128.1, 127.1, 112.1 (ArCH), 128.1 (C2/C3), 127.8 (C3/C2), 124.9 (*C*–CHO), 56.2 (ArO*C*H_3), 54.7 (OCH_3), 48.3 (CH_2Ph), 16.9 (CH_3); EIMS *m/z* (%): 364 (M^+, 100), 273 (–C_7H_7, 37), 41 (–C_7H_7 + (–CO), 37), 91 ($C_7H_7^+$, 79); HRMS: $C_{21}H_{20}N_2O_4$, calculated: 364.1423, found: 364.1420.

4.7.3. 1-Benzyl-3-methoxy-6-methyl-5-(3-thienyl)-2(1*H*)-pyrazinone 13c. Yield: 95%; solid, mp: 112–112.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.34–7.18 (m, 8H, ArH), 5.38 (s, 2H, CH_2Ph), 4.00 (s, 3H, OCH_3), 2.32 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 153.6 (C3), 152.1 (C2), 139.7, 135.9 (ArC-*ipso*), 127.7 (C5/C6), 125.1 (C6/C5), 129.3, 129.1, 128.0, 127.1, 125.5, 124.2 (ArCH), 54.6 (OCH_3), 48.3 (CH_2Ph), 16.8 (CH_3); EIMS *m/z* (%): 312 (M^+, 100), 221 (–C_7H_7, 60), 91 ($C_7H_7^+$, 95); HRMS: $C_{17}H_{16}N_2O_2S$, calculated: 312.0933, found: 312.0930.

4.7.4. 1-Benzyl-3-methoxy-6-methyl-5-[(*E*)-2-phenylethenyl]-2(1*H*)-pyrazinone 13d. Yield: 80%; solid, mp: 194.4–195 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.48–7.14 (m, 11H, ArH), 7.01 (d, J=15 Hz, 1H, HC=), 5.34 (s, 2H, CH_2Ph), 4.09 (s, 3H, OCH_3), 2.30 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): 153.0 (C3), 151.8 (C2), 137.4, 135.4 (ArC-*ipso*), 129.8 (HC=), 128.8, 128.5, 127.6, 127.4, 126.5, 126.4 (ArCH), 127.2 (C5/C6), 125.4 (C6/C5), 122.2 (HC=), 54.8 (OCH_3), 50.4 (CH_2Ph), 14.2 (CH_3); EIMS *m/z* (%): 332 (M^+, 28), 241 (–C_7H_7, 16), 91 ($C_7H_7^+$, 100); HRMS: $C_{21}H_{20}N_2O_2$, calculated: 332.1525, found: 332.1522.

4.7.5. 1-Benzyl-3-methoxy-5-phenyl-2(1*H*)-pyrazinone 13e. Yield: 78%, oil; ^{1}H NMR ($CDCl_3$, 300 MHz): 8.05–7.32 (m, 11H, ArH), 5.05 (s, 2H, CH_2Ph); EIMS *m/z* (%): 292 (M^+, 100), 91 ($C_7H_7^+$, 60).

4.7.6. 3-Methoxy-6-methyl-1,5-diphenyl-2(1*H*)-pyrazinone 13f. Yield: 94%; solid, mp: 160 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.58–7.24 (m, 10H, ArH), 4.02 (s, 2H, CH_2Ph), 1.93 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 154.3 (C3), 151.9 (C2), 138.7, 138.1 (ArC-*ipso*), 128.8 (C6/C5), 127.9 (C5/C6), 130.3, 129.8, 129.6, 128.5, 128.1, 127.6 (ArCH), 54.7 (OCH_3), 18.5 (CH_3); EIMS *m/z* (%): 306 (M^+, 100), 215 (–C_7H_7, 65), 91 ($C_7H_7^+$, 90); HRMS: $C_{19}H_{18}N_2O$, calculated: 306.1368, found: 306.1366.

The same compound **13f** was isolated in 85% yield when applying Suzuki coupling of 5-iodo compound **12d′** with phenylboronic acid.

4.7.7. 3-Methoxy-6-methyl-1-phenyl-5-(3-thienyl)-2(1*H*)-pyrazinone 13g. Yield: 55%; solid, mp: 165.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.57–7.21 (m, 8H, ArH), 4.02 (s, 3H, OCH_3), 2.00 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 154.1 (C3), 151.8 (C2), 139.7, 138.0 (ArC-*ipso*), 127.5 (C5/C6), 124.6 (C6/C5), 130.3, 129.6, 129.0, 128.0, 125.5, 124.0 (ArCH), 54.6 (OCH_3), 18.4 (CH_3); EIMS *m/z* (%): 298 (M^+, 100); HRMS: $C_{16}H_{14}N_2O_2S$, calculated: 298.0776, found: 298.0770.

4.7.8. 3-Methoxy-6-methyl-1-phenyl-5-[(*E*)-2-phenylethenyl]-2(1*H*)-pyrazinone 13h. Yield: 95%; solid, mp: 186 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.58–7.17 (m, 11H, ArH), 7.05 (d, J=15 Hz, 1H, HC=), 4.11 (s, 3H, OCH_3), 2.01 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 153.9 (C3), 152.0 (C2), 137.9 2x(ArC-*ipso*), 129.7 (HC=), 130.4, 130.1, 129.1, 128.0, 127.9, 127.9 (ArCH), 127.6 (C5/C6), 125.4 (C5/C6), 122.7 (HC=), 54.6 (OCH_3), 16.1 (CH_3); EIMS *m/z* (%): 318 (M^+, 100); HRMS: $C_{20}H_{18}N_2O_2$, calculated: 318.1368, found: 318.1368.

4.7.9. 1-Benzyl-3-methyl-5,6-diphenyl-2(1*H*)-pyrazinone 13i. Yield: 87%; solid, mp: 123.7 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): 7.34–6.87 (m, 15H, ArH), 5.13 (s, 2H, CH_2Ph), 2.64 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 156.6 (C2), 156.2 (C3), 138.2 (C6), 136.8, 136.6, 132.4 (ArC-*ipso*), 133.1 (C5), 131.1, 129.7, 129.6, 128.8, 128.8, 128.1, 127.8,

127.6, 127.3 (ArCH), 49.3 (CH_2Ph), 21.7 (CH_3); EIMS *m/z* (%): 352 (M^+, 100), 91 ($C_7H_7^+$, 64); HRMS: $C_{24}H_{20}N_2O$, calculated: 352.1576, found: 352.1573.

4.7.10. 1-Benzyl-3,5-diphenyl-2(1*H*)-pyrazinone 13j. Yield: 70%, oil; ^1H NMR ($CDCl_3$, 300 MHz): 8.49–8.46 (m, 2H, ArH), 7.79–7.29 (m, 14H, ArH), 5.17 (s, 2H, CH_2Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): 155.1 (C2), 152.3 (C3), 136.6, 136.3, 135.6 (ArC-*ipso*), 133.2 (C5), 130.4 (C6), 129.7, 129.5, 129.2, 128.9, 128.8, 128.4, 128.3, 125.4, 124.0 (ArCH), 53.3 (CH_2Ph); EIMS *m/z* (%): 338 (M^+, 100), 91 ($C_7H_7^+$, 40).

4.8. Synthesis of 5-alkenyl-2(1*H*)-pyrazinones 14a–e via Heck-coupling reaction of 5-bromo-2(1*H*)-pyrazinones

General procedure. A mixture of pyrazinone **12c** or **12e** (1 mmol), 7 mg of $Pd(OAc)_2$ (3 mol %) and 26 mg of P(*o*-tolyl)$_3$ (7 mol %) was stirred at room temperature under argon for 10 min. Add 1.5 mmol of alkene, 300 mg of dry Et_3N (3 mmol) and 1 mL DMF. The reaction mixture was heated at 100 °C in a capped heavy-walled glass tube in an oil bath for 18 h. After the completion of the reaction, the mixture was poured in water and extracted with 50 mL of CH_2Cl_2 three times. The organic layer was collected and dried over $MgSO_4$. After filtration and evaporation of CH_2Cl_2, the mixture was subjected to column chromatography (silica gel, A: 30% heptane/CH_2Cl_2 or B: 100% $CH_2Cl_2 \rightarrow$ 5% EtOAc/CH_2Cl_2).

4.8.1. 1-Benzyl-3-methyl-6-phenyl-5-[(*E*)-2-phenylethenyl]-2(1*H*)-pyrazinone 14a. Yield: 71%; oil; ^1H NMR ($CDCl_3$, 300 MHz): 7.50–6.81 (m, 16H, ArH), 6.35 (d, J= 16 Hz, 1H, HC=), 5.03 (s, 2H, CH_2Ph), 2.65 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 157.0 (C2), 156.3 (C3), 137.7, 136.4, 131.4 (ArC-*ipso*), 130.1 (C6), 129.6 (HC=), 130.6, 129.6, 129.1, 128.9, 128.8, 127.9, 12.8, 127.5, 126.9 (ArCH), 127.8 (C5), 123.6 (HC=), 49.3(CH_2Ph), 21.9 (CH_3); EIMS *m/z* (%): 378 (M^+, 100), 287 (–C_7H_7, 38), 91 ($C_7H_7^+$, 50); HRMS: $C_{26}H_{22}N_2O$, calculated: 378.1732, found: 378.1729.

4.8.2. Methyl (2*E*)-3-(4-benzyl-6-methyl-5-oxo-3-phenyl-4,5-dihydro-2-pyrazinyl)-2-propenoate 14b. Yield: 84%; solid, mp: 141.5–142.2 °C; ^1H NMR ($CDCl_3$, 300 MHz): 6.96 (d, J=15 Hz, 1H, HC=), 7.51–7.02 (m, 8H, ArH), 6.81–6.78 (m, 2H, ArH), 6.76 (d, J=15 Hz, 1H, HC=), 5.00 (s, 2H, CH_2Ph), 3.66 (s, 3H, OCH_3), 2.59 (CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 168.0 (*C*OO), 157.3 (C5), 156.4 (C6), 140.7 (C3), 139.7, 136.0 (ArC-*ipso*), 130.5 (HC=), 130.3, 130.2, 129.3, 128.8, 128.0, 127.5 (ArCH), 127.6 (C2), 118.6 (HC=), 51.8 (COO*C*H$_3$), 49.4 (CH_2Ph), 21.7 (CH_3); EIMS *m/z* (%): 360 (M^+, 65), 301 (–$COOCH_3$, 16), 91 ($C_7H_7^+$, 100); HRMS: $C_{22}H_{20}N_2O_3$, calculated: 360.1474, found: 360.1464.

4.8.3. 1-Benzyl-3-methoxy-6-phenyl-5-[(*E*)-2-phenylethenyl]-2(1*H*)-pyrazinone 14c. Yield: 71%; solid, mp: 148 °C; ^1H NMR ($CDCl_3$, 300 MHz): 7.46–6.80 (m, 16H, ArH), 6.34 (d, J=15 Hz, 1H, HC=), 5.05 (s, 2H, CH_2Ph), 4.16 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): 154.9 (C3), 151.9 (C2), 137.6, 136.3, 131.6 (ArC-*ipso*), 132.0 (C6), 129.6 (HC=), 131.2, 129.9, 129.0, 128.9, 128.7, 127.8, 127.7, 127.6, 126.9 (ArCH), 127.0 (C5), 123.7 (HC=), 54.8 (OCH_3), 49.3 (CH_2Ph); EIMS *m/z* (%): 394 (M^+, 100), 303 (–C_7H_7, 36), 91 ($C_7H_7^+$, 80); HRMS: $C_{26}H_{22}N_2O_2$, calculated: 394.1681, found: 394.1674.

4.8.4. Methyl (2*E*)-3-(4-benzyl-6-methoxy-5-oxo-3-phenyl-4,5-dihydro-2-pyrazinyl)-2-propenoate 14d. Yield: 66%; solid, mp: 173.7 °C; ^1H NMR ($CDCl_3$, 300 MHz): 6.94 (d, J=15 Hz, 1H, HC=), 7.50–7.02 (m, 8H, ArH), 6.80–6.77 (m, 2H, ArH), 6.66 (d, J=15 Hz, 1H, HC=), 5.03 (s, 2H, CH_2Ph), 4.09 (s, 3H, OCH_3), 3.67 (s, 3H, COO*C*H$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): 167.9 (*C*OO), 154.8 (C6), 152.1 (C5), 136.6 (C3), 139.8, 135.9 (ArC-*ipso*), 130.4 (HC=), 130.8, 130.5, 129.1, 128.7, 128.0, 127.7 (ArCH), 124.9 (C2), 118.5 (HC=), 55.0 (OCH_3), 51.8 (COO*C*H$_3$), 49.4 (CH_2Ph); EIMS *m/z* (%): 376 (M^+, 61), 317 (–$COOCH_3$, 11), 91 ($C_7H_7^+$, 100); HRMS: $C_{22}H_{20}N_2O_4$, calculated: 376.1423, found: 376.1422.

4.8.5. 1-Benzyl-5-cyclohexylidenemethyl-3-methoxy-6-phenyl-2(1*H*)-pyrazinone 14e. Yield: 60%; oil; ^1H NMR ($CDCl_3$, 400 MHz): 7.38–6.79 (m, 10H, ArH), 5.33 (s, 1H, *H*C=), 5.03 (s, 2H, CH_2Ph), 2.74 (t, J=6.1 Hz, 2H, CH_2), 1.94 (t, J=6.1 Hz, 2H, CH_2), 1.58–1.47 (m, 6H, $3CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): 153.8 (C2), 150.8 (C3), 145.5 (*C*=CH), 136.1, 131.2 (ArC-*ipso*), 131.5 (C6), 130.6, 129.0, 128.4, 128.1, 127.3, 127.2 (ArCH), 127.6 (C5), 116.4 (*C*H=), 54.3 (OCH_3), 48.7 (CH_2Ph), 38.4 (C2′), 29.9 (C6′), 28.8, 27.7, 26.5 (CH_2); EIMS *m/z* (%): 386 (M^+, 55), 295 (–C_7H_7, 50), 91 ($C_7H_7^+$, 100); HRMS: $C_{25}H_{26}N_2O_2$, calculated: 386.1994, found: 386.1993.

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References and notes

1. Hopkins, C. R.; Neuenschwander, K.; Scotese, A.; Jackson, S.; Nieduzak, T.; Pauls, H.; Liang, G. Y.; Sides, K.; Cramer, D.; Cairns, J.; Maignan, S.; Mathieu, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4819–4823.
2. Nantermet, P. G.; Barrow, J. C.; Newton, C. L.; Pellicore, J. M.; Young, M. B.; Lewis, S. D.; Lucas, B. J.; Krueger, J. A.; McMasters, D. R.; Yan, Y. W.; Kuo, L. C.; Vacca, J. P.; Selnick, H. G. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2781–2784.
3. Chung, J. Y. L.; Cvetovich, R. J.; Tsay, F. R.; Dormer, P. G.; DiMichele, L.; Mathre, D. J.; Chilenski, J. R.; Mao, B.; Wenslow, R. *J. Org. Chem.* **2003**, *68*, 8838–8846.
4. Parlow, J. J.; Case, B. L.; Dice, T. A.; Fenton, R. L.; Hayes, M. J.; Jones, D. E.; Neumann, W. L.; Wood, R. S.; Lachance, R. M.; Girard, T. J.; Nicholson, N. S.; Clare, M.; Stegeman, R. A.; Stevens, A. M.; Stallings, W. C.; Kurumbail, R. G.; South, M. S. *J. Med. Chem.* **2003**, *46*, 4050–4062.

5. Young, M. B.; Barrow, J. C.; Glass, K. L.; Lundell, G. F.; Newton, C. L.; Pellicore, J. M.; Rittle, K. E.; Selnick, H. G.; Stauffer, K. J.; Vacca, J. P.; Williams, P. D.; Bohn, D.; Clayton, F. C.; Cook, J. J.; Krueger, J. A.; Kuo, L. C.; Lewis, S. D.; Lucas, B. J.; McMasters, D. R.; Miller-Stein, C.; Pietrak, B. L.; Wallace, A. A.; White, R. B.; Wong, B.; Yan, Y. W.; Nantermet, P. G. *J. Med. Chem.* **2004**, *47*, 2995–3008.
6. South, M. S.; Case, B. L.; Wood, R. S.; Jones, D. E.; Hayes, M. J.; Girard, T. J.; Lachance, R. M.; Nicholson, N. S.; Clare, M.; Stevens, A. M.; Stegeman, R. A.; Stallings, W. C.; Kurumbail, R. G.; Parlow *J. Bioorg. Med. Chem. Lett.* **2003**, *13*, 2319–2325.
7. Becker, J. W.; Rotonda, J.; Soisson, S. M.; Aspiotis, R.; Bayly, C.; Francoeur, S.; Gallant, M.; Garcia-Calvo, M.; Giroux, A.; Grimm, E.; Han, Y. X.; McKay, D.; Nicholson, D. W.; Peterson, E.; Renaud, J.; Roy, S.; Thornberry, N.; Zamboni, R. *J. Med. Chem.* **2004**, *47*, 2466–2474.
8. Miyazaki, A.; Tsuda, Y.; Tachibana, Y.; Yokoi, T.; Bryant, S. D.; Lazarus, L. H.; Keri, G.; Okada, Y. *Biopolymers* **2003**, *71*, 367.
9. Jinsmaa, Y.; Miyazaki, A.; Fujita, Y.; Li, T. Y.; Fujisawa, Y.; Shiotani, K.; Tsuda, Y.; Yokoi, T.; Ambo, A.; Sasaki, Y.; Bryant, S. D.; Lazarus, L. H.; Okada, Y. *J. Med. Chem.* **2004**, *47*, 2599–2610.
10. Jinsmaa, Y.; Okada, Y.; Tsuda, Y.; Sasaki, T. Y.; Ambo, A.; Bryant, S. D.; Lazarus, L. H. *Biopolymers* **2003**, *71*, 371.
11. Jinsmaa, Y.; Okada, Y.; Tsuda, Y.; Shiotani, K.; Sasaki, Y.; Ambo, A.; Bryant, S. D.; Lazarus, L. H. *J. Pharmacol. Exp. Ther.* **2004**, *309*, 432–438.
12. Azzam, R.; De Borggraeve, W.; Compernolle, F.; Hoornaert, G. J. *Tetrahedron Lett.* **2004**, *45*, 1885–1888.
13. Rogiers, J.; De Borggraeve, W. M.; Toppet, S. M.; Compernolle, F.; Hoornaert, G. J. *Tetrahedron* **2003**, *59*, 5047–5054.
14. Kaval, N.; Bisztray, K.; Dehaen, W.; Kappe, C. O.; Van der Eycken, E. *Mol. Divers.* **2003**, *7*, 125–134.
15. Achab, S.; Guyot, M.; Potier, P. *Tetrahedron Lett.* **1993**, *34*, 2127–2130.
16. Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866–867.
17. Vandenberghe, S. M.; Buysens, K. J.; Meerpoel, L.; Loosen, P. K.; Toppet, S. M.; Hoornaert, G. J. *J. Org. Chem.* **1996**, *61*, 304–308.
18. Loosen, P. K.; Tutonda, M. G.; Khorasani, M. F.; Compernolle, F.; Hoornaert, G. J. *Tetrahedron* **1991**, *47*, 9259–9268.
19. Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314–321.
20. Ishiyama, T.; Miyaura, N.; Suzuki, A. *Synlett* **1991**, 687–688.
21. Nomoto, Y.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 727–729.
22. Buysens, K. J.; Vandenberghe, D. M.; Toppet, S. M.; Hoornaert, G. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 231–237.
23. Vanchuyen, N.; Kurata, T.; Fujimaki, M. *Agr. Biol. Chem.* **1973**, *37*, 327–334.
24. Littke, A. F.; Dai, C. Y.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.
25. Aoyagi, Y.; Fujiwara, T.; Ohta, A. *Heterocycles* **1991**, *32*, 2407–2415.
26. Buysens, K. PhD Thesis, K. U. Leuven 1996.
27. Tutonda, M.; Vanderzande, D.; Hendrickx, M.; Hoornaert, G. *Tetrahedron* **1990**, *46*, 5715–5732.
28. Buysens, K. J.; Vandenberghe, D. M.; Hoornaert, G. J. *Tetrahedron* **1996**, *52*, 9161–9178.