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Combinatorial synthesis of 4-oxo-4*H*-imidazo[1,5-*a*]quinoxalines and 4-oxo-4*H*-pyrazolo[1,5-*a*]quinoxalines

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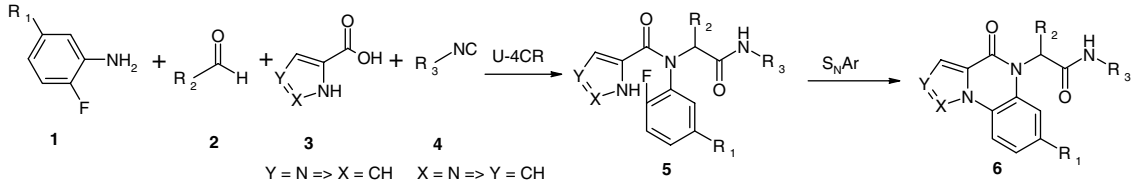
Abstract—A combinatorial synthetic route yielding imidazo[1,5-*a*]quinoxalines and pyrazolo[1,5-*a*]quinoxalines is described. The use of 2-fluoroaniline and 1*H*-imidazole-4-carboxylic acid, respectively, 1*H*-pyrazole-3-carboxylic acid in the Ugi-reaction (U-4CR) followed by a nucleophilic aromatic substitution (S_NAr) affords the imidazo- as well as the pyrazolo-[1,5-*a*]quinoxaline moiety in good yield and high diversity.

Imidazoquinoxalines belong to an important class of heterocycles that are often found in biologically active and pharmacologically useful agents.[1] Synthetic sequences that enable the preparation of polysubstituted heterocycles have attracted considerable attention in recent years.[2,3] The combinatorial synthesis of 'drug-like' compounds permits the fast preparation of compound libraries suitable for lead discovery and optimization.[4,5] Multi-component reactions (MCRs) are a powerful tool for the high-throughput screening strategy.[6,7] One of the most important MCRs is the Ugi-reaction.[8] In the Ugi four component reaction (U-4CR) an amine, an aldehyde, a carboxylic acid and an isocyanide react simultaneously to afford peptide-like structures in high diversity. This classical MCR followed by a post-condensation cyclization via nucleophilic aromatic substitution (S_NAr) leads to a new and versatile two-step synthesis of imidazo- and pyrazolo[1,5-*a*]quinoxalines. The first step of the synthesis is U-4CR[13] yielding products **5** (Scheme 1) as intermediates for the following cyclisation. The use of 2-fluoroaniline **1** and heterocyclic carboxylic acids **3** as bifunctional starting materials enables a subsequent nucleophilic aromatic substitution reaction in which the hydrogen-bearing nitrogen N1 of the heterocyclic carboxylic acid component acts as a nucleophile, and fluorine as a leaving group.[9–14] We used two different carboxylic acids, 1*H*-imidazole-4-carboxylic acid and 1*H*-pyrazole-3-carboxylic acid leading to two different tricyclic title scaffolds **6**.

The Ugi-reaction is generally initiated by the condensation of amine **1** with aldehyde **2** leading to an intermediate imine, which subsequently reacts with carboxylic acid **3** and isocyanide **4** to afford the desired product



Scheme 1. Combinatorial synthesis of 4-oxo-4*H*-imidazo[1,5-*a*]quinoxalines and 4-oxo-4*H*-pyrazolo[1,5-*a*]quinoxalines via U-4CR/S_NAr strategy.

Keywords: Ugi-reaction; Multi-component reaction; Imidazo-quinoxaline; Pyrazolo-quinoxaline; Nucleophilic aromatic substitution.
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5. Here 2,2,2-trifluoroethanol (TFE) turned out to be the best solvent for the MCR step. After completion of the MCR the TFE was removed in vacuo. Since the MCR products (**4a**–**h** and **6a**–**h**) were generally obtained in high yields and high purities (determined by HPLC-MS)[15] they were used in the next step without further purification.[16]

The subsequent S_NAr cyclisation requires a suitable base to enhance the nucleophilicity of the heterocyclic nitrogen N1 by deprotonation and capture of the hydrogen fluoride released during the reaction. The optimization (test system: 1*H*-pyrazole-3-carboxylic acid, *p*-anisaldehyde and *t*-butylisocyanide) of the S_NAr conditions (solvents, bases, reaction time and temperatures) is shown in Table 1. Conversions (*Y*) were determined by HPLC-MS after 20 min of reaction time under microwave (mw) irradiation or alternatively in pressure tubes at 120 °C after 19 h. The results show that Cs_2CO_3 or K_2CO_3 as a base in combination with microwave irradiation at a reaction temperature of 150 °C in DMF is the ideal method. All compounds were purified by crystallization or by column chromatography on silica gel.[17]

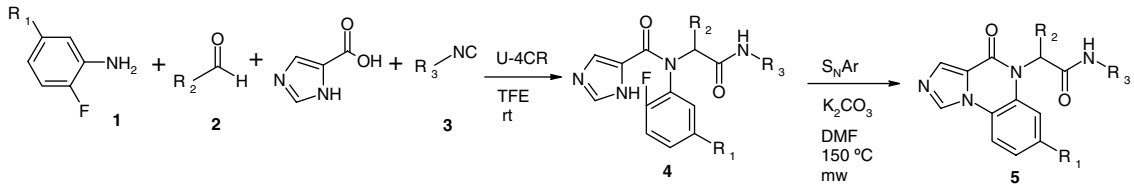
Tables 2 and 3 show the results for the synthesized compounds **5a**–**h** and **7a**–**h** with specific yields for each

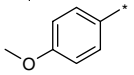
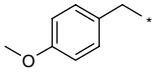
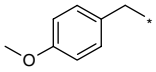
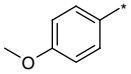
Table 1. S_NAr optimization

Base	Equiv	Solvent	reflux/mw	*T* (°C)	*Y* (%)
KOtBu	5	DMF	reflux 19 h	120	84
KOtBu	3	DMF	mw 40 min	150	0
K_2CO_3	5	DMF	mw 20 min	150	99
K_2CO_3	5	TFE	mw 40 min	100	0
Cs_2CO_3	1	DMF	reflux 40 h	105	40
Cs_2CO_3	5	DMF	mw 20 min	150	98

Y: crude product determined by HPLC-MS.

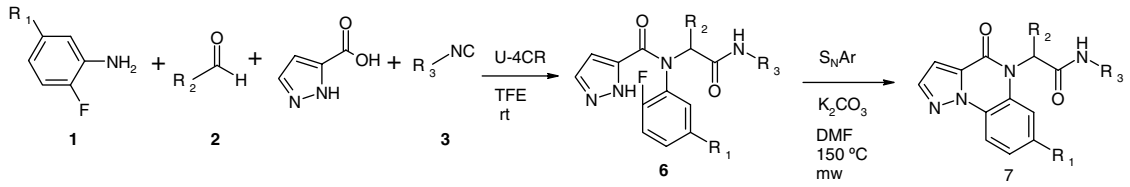
Table 2. Synthesized imidazo-[1,5-*a*]quinoxalines

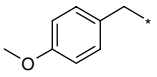
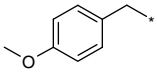
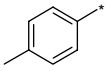
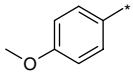
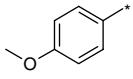


Entry	R_1	R_2	R_3	rt (h)	Y_1 (%) LC/(isol.)	MCR-product	Microwave (min)	Y_2 (%) LC/(isol.)	S_NAr-product
1	H			16	68 (61)	**4a**	20	99 (92)	**5a**
2	H			16	71	**4b**	20	68 (61)	**5b**
3	H			16	48	**4c**	40	65 (55)	**5c**
4	H			16	68	**4d**	20	59 (53)	**5d**
5	H	H		16	78	**4e**	20	86 (72)	**5e**
6	H	H		16	50	**4f**	20	57 (47)	**5f**
7	H			16	97	**4g**	20	74 (65)	**5g**
8	CF_3			16	65	**4h**	20	49 (37)	**5h**

Y_1: yield of MCR-product (equimolar: aniline, aldehyde, carboxylic acid and isocyanide, TFE, rt), crude product determined by HPLC-MS.
Y_2: yield of S_NAr-product (5 equiv K_2CO_3, 1 equiv MCR-product, DMF, 150 °C microwave) crude product determined by HPLC-MS (isolated).

Table 3. Synthesized pyrazolo-[1,5-*a*]quinoxalines



Entry	R_1	R_2	R_3	rt (h)	Y_1 (%) LC/(isol.)	MCR-product	Microwave (min)	Y_2 (%) LC/(isol.)	S_NAr-product
1	H			16	80 (77)	**6a**	20	94 (89)	**7a**
2	H			16	83	**6b**	20	77 (61)	**7b**
3	H		—	16	77	**6c**	20	65 (51)	**7c**
4	H	H		16	89	**6d**	20	65 (51)	**7d**
5	H	H		16	54	**6e**	20	40 (37)	**7e**
6	H			16	90	**6f**	20	85 (79)	**7f**
7	3-CH_3			16	82	**6g**	40	61 (53)	**7g**
8	3-CF_3			16	74	**6h**	40	77 (75)	**7h**

Y_1: yield of MCR-product (equimolar: aniline, aldehyde, carboxylic acid and isocyanide, TFE, rt), crude product determined by HPLC-MS.
Y_2: yield of S_NAr-product (5 equiv K_2CO_3, 1 equiv MCR-product, DMF, 150 °C microwave), crude product determined by HPLC-MS (isolated).

step ($Y_1 =$ MCR, $Y_2 =$ S_NAr). Aliphatic, phenylic and benzylic isocyanides as well as aliphatic and aromatic aldehydes could be involved in the reaction successfully.

The reaction times (rt) for the S_NAr are generally short and the conversions are good for all compounds. Chromatographic methods allow the isolation of products with high purity (>95%). The protocol is quite robust and tolerates a broad range of starting materials.

MCR products **4a** and **6a** were isolated and analyzed by NMR as exemplary compounds. The spectra were compared with those of their cyclized analogs **5a** and **7a**. As expected the S_NAr cyclization leads to significant changes, the most prominent ones being the absence of the heterocyclic NH signals as well as the H–F coupling (aniline part) and a considerable downfield shift of the heterocyclic CH as well as the α-CH (previous aldehyde CH) signals.

In summary, a novel two-step synthesis procedure for the preparation of highly substituted 4-oxo-4*H*-imidazo-[1,5-*a*]quinoxalines and 4-oxo-4*H*-pyrazolo[1,5-*a*]quinoxalines has been described. Amines and carbonyls can be varied broadly, leading to compounds with three potential points of diversity.

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15. HPLC-MS/MS spectra (Varian 1200), Polaris, RP C18 column, 3 mm × 150 mm, 5 μm, ProStar 320 (254 nm), 1 mL/min, 3 min gradient from 90% H_2O to 10% H_2O (0.1% HCOOH) versus CH_3CN, coupled with a Quadrupol MS/MS mass spectrometer using electrospray ionisation (ESI).
16. *General procedure for the synthesis of MCR products* **4a**–**h** *and* **6a**–**h** (GP-MCR): Fluoroaniline **1** (1 mmol) and aldehyde **2** (1 mmol) were stirred in 3 mL TFE for 2 h. Then, carboxylic acid (1 mmol) and isocyanide 3 (1 mmol) were added and the reaction mixture was stirred for 16 h at room temperature. The solvent was removed in vacuo. The MCR products were generally obtained in high yields and high purities (determined by HPLC-MS) and they were used in the next step without further purification.
17. *General Procedure for the synthesis of 4-oxo-4H-imidazo*[1,5-*a*]*quinoxalines* **5a**–**h** *and 4-oxo-*4*H-pyrazolo*-[1,5-*a*]*quinoxalines* **7a**–**h** (*GP-cyclisation*): (1.0 mmol) of MCR-product **4a**–**h**, respectively, **6a**–**h** was dissolved in 4 mL DMF (dry) and 5 mmol K_2CO_3 was added. The reaction was stirred at 150 °C for 20–40 min under microwave irradiation (microwave system: Discover, BenchMate, CEM). Then, 10 mL water was added and the mixture was extracted with 3 × 15 mL of ethyl acetate. The organic layer was dried over $MgSO_4$ and the resulting crude product was purified by flash chromatography or crystallization.

Compound **4a** was prepared according to GP-MCR and the resulting crude product was purified by chromatography on silica gel with eluent ethyl acetate/hexane = 2/1 (219 mg, 61%). $m/z = 359$ $[M+H]^+$, $m/z = 381$ $[M+Na]^+$. ^1H NMR (DMSO-d_6, 250.13 MHz): 12.77 (bs, 1H), 7.97 (s, 1H), 7.61–7.19 (m, 6H), 4.08 (d, 1H, $J = 10.4$ Hz), 1.27 (s, 9H), 0.75 (s, 1H), 0.45–0.40 (m, 2H), 0.17 (m, 2H).

Compound **6a** was prepared according to GP-MCR and the resulting crude product was purified by flash chromatography on silica gel with eluent ethyl acetate/hexane = 2/1 (259 mg, 72%). $m/z = 359$ $[M+H]^+$, $m/z = 381$ $[M+Na]^+$. ^1H NMR (DMSO-d_6, 250.13 MHz): 13.30 (bs, 1H), 7.94 (s, 1H), 7.58–7.19 (m, 6H), 4.13 (d, 1H, $J = 10.1$ Hz), 1.51 (s, 9H), 0.79–0.74 (m, 1H), 0.49–0.38 (m, 2H), 0.21–0.08 (m, 2H).

Compound **5a** was prepared according to GP-cyclisation and purified by crystallization from diethyl ether (314 mg, 92%). $m/z = 339$ $[M+H]^+$, $m/z = 361$ $[M+Na]^+$. ^1H NMR (DMSO-d_6, 250.13 MHz): 9.15 (s, 1H), 8.32 (d, 1H, $J = 7.4$ Hz), 7.95 (s, 1H), 7.47–7.19 (m, 3H), 7.19 (s, 1H), 5.11 (d, 1H, $J = 9.5$ Hz), 1.27 (s, 9H), 1.85–1.78 (m, 1H), 0.86–0.64 (m, 2H), 0.40–0.24 (m, 2H).

Compound **5b** was prepared according to GP-cyclisation and purified by crystallization from diethyl ether (239 mg, 61%). $m/z = 389$ $[M+H]^+$, $m/z = 411$ $[M+Na]^+$. ^1H NMR (DMSO-d_6, 250.13 MHz): 9.52 (s, 1H), 9.19 (bs, 1H), 8.35 (d, 1H, $J = 7.7$ Hz), 7.99 (bs, 1H), 7.56–7.44 (m, 2H), 7.38 (d, 3H, $J = 9.0$ Hz), 6.88 (d, 2H, $J = 9.0$ Hz), 5.37 (d, 1H, $J = 8.7$ Hz), 3.73 (s, 3H), 1.91–1.88 (m, 1H), 0.90–0.73 (m, 2H), 0.39–0.26 (m, 2H).

Compound **5c** was prepared according to GP-cyclisation and purified by crystallization from diethyl ether (222 mg, 55%). $m/z = 403$ $[M+H]^+$; $m/z = 445$ $[M+Na]^+$. ^1H NMR (DMSO-d_6, 250.13 MHz): 9.12 (s, 1H), 8.44 (bs, 1H), 8.31–8.27 (m, 1H), 7.93 (s, 1 H), 7.36–7.34 (m, 3 H), 7.06 (d, 2H, 8.4 Hz), 6.79 (d, 2H, 8.5 Hz), 5.21 (m, 1H), 4.12 (d, 2H, $J = 5.9$ Hz), 3.710 (s, 3H), 1.90–1.70 (m, 1H), 0.84–0.65 (m, 2H), 0.36–0.15 (m, 2H).

Compound **5d** was prepared according to GP-cyclisation and purified by crystallization from diethyl ether (157 mg, 53%). $m/z = 297$ $[M+H]^+$, $m/z = 319$ $[M+Na]^+$. ^1H NMR (DMSO-d_6, 250.13 MHz): 9.16 (s, 1H), 8.33 (d, 1H, $J = 7.7$ Hz), 7.96–7.89 (m, 2H), 7.40 (m, 3H), 5.15 (bs, 1H), 2.61 (d, 3H, $J = 4.4$ Hz), 1.82–1.78 (m, 1H), 0.87–0.66 (m, 2H), 0.39–0.16 (m, 2H).

Compound **5e** was prepared according to GP-cyclisation and purified by crystallization from diethyl ether (261 mg, 72%). $m/z = 363$ $[M+H]^+$, $m/z = 385$ $[M+Na]^+$. ^1H NMR (DMSO-d_6, 250.13 MHz): 9.15 (s, 1H), 8.71 (t, 1H, $J = 5.8$ Hz), 8.31 (d, 1H, $J = 6.6$ Hz), 7.91 (s, 1H), 7.51–7.30 (m, 3H), 7.18 (d, 2H, $J = 8.7$ Hz), 6.89 (d, 2H, $J = 8.7$ Hz), 4.93 (s, 2H), 4.25 (d, 2H, $J = 5.7$ Hz), 3.76 (s, 3H).

Compound **5f** was prepared according to GP-cyclisation and purified by crystallization from diethyl ether (145 mg, 47%). $m/z = 299$ $[M+H]^+$, $m/z = 321$ $[M+Na]^+$. ^1H NMR (DMSO-d_6, 250.13 MHz): 9.16 (s, 1H), 8.31 (d, 1H, $J = 7$ Hz), 8.00 (s, 1H), 7.96 (bs, 1H) 7.27–7.49 (m, 3H), 4.84 (s, 2H), 1.30 (s, 9H).

Compound **5g** was prepared according to GP-cyclisation and purified by crystallization from diethyl ether (260 mg, 65%). $m/z = 405$ $[M+H]^+$, $m/z = 427$ $[M+Na]^+$. ^1H NMR (DMSO-d_6, 250.13 MHz): 9.16 (s, 1H,), 8.27 (d, 1H, $J = 7.1$ Hz), 8.01 (s, 1H), 7.75 (s, 1H), 7.35–7.24 (m, 5H), 6.92 (m, 3H), 3.75 (s, 3H), 1.28 (s, 9H).

Compound **5h** was prepared according to GP-cyclisation and purified by crystallization from diethyl ether (151 mg, 37%). $m/z = 407$ $[M+H]^+$, $m/z = 429$ $[M+Na]^+$. ^1H NMR (DMSO-d_6, 250.13 MHz): 9.21 (s, 1H), 8.51 (d, 1H, $J = 8.4$ Hz), 7.99 (s, 1H), 7.73 (d, 1H, $J = 8.6$ Hz), 7.68 (s, 1H), 7.32 (s, 1H), 5.18 (d, 1H, $J = 9.5$ Hz), 1.70–1.65 (m, 1H), 1.20 (s, 9H), 0.85–0.82 (m, 1H), 0.67–0.63 (m, 1H), 0.37–0.34 (m, 1H), 0.28–0.22 (m, 1H). ^{13}C NMR (DMSO-d_6, 62.89 MHz): 168.32, 155.78, 134.79, 133.19, 129.76, 127.80 (d, $^2J(C,F) = 23.7$ Hz), 125.13, 124.50 (d, $^1J(C,F) = 272.47$ Hz), 122.43, 120.95 (d, $^3J(C,F) = 3.6$ Hz), 118.57, 114.73 (d, $^3J(C,F) = 3.6$ Hz), 99.99, 60.09, 51.88, 28.98, 12.18, 7.60, 3.19.

Compound **7a** was prepared according to GP-cyclisation and purified by chromatography on silica gel with eluent chloroform/ethyl acetate = 1/1 (303 mg, 89%). $m/z = 339$ $[M+H]^+$, $m/z = 361$ $[M+Na]^+$. ^1H NMR (DMSO-d_6, 250.13 MHz): 8.32 (d, 1H, $J = 7.4$ Hz), 8.15 (s, 1H), 7.55–7.43 (m, 3H), 7.25 (s, 2H), 5.15 (d, 1H, $J = 9.5$ Hz) 1.87–1.83 (m, 1H), 1.27 (s, 9H), 0.86–0.68 (m, 2H), 0.37–0.24 (m, 2H).

Compound **7b** was prepared according to GP-cyclisation and purified by crystallization from diethyl ether (246 mg, 61%). $m/z = 403$ $[M+H]^+$, $m/z = 445.0$ $[M+Na]^+$. ^1H NMR (DMSO-d_6, 250.13 MHz): 8.49 (s, 1H), 8.34–8.16 (m, 1H), 8.15 (s, 1H), 7.42–7.46 (m, 3H), 7.25 (d, 1H, $J = 2.1$ Hz), 7.10 (d, 2H, $J = 8.4$ Hz), 6.83 (d, 2H, $J = 7.5$ Hz), 5.29 (bs, 1H), 4.24 (d, 2H; $J = 5.9$ Hz), 3.74 (s, 3H), 1.87–1.86 (m, 1H), 0.89–0.72 (m, 2H), 0.41–0.19 (m, 2H).

Compound **7c** was prepared according to GP-cyclisation and purified by crystallization from diethyl ether (151 mg, 51%). $m/z = 297$ $[M+H]^+$, $m/z = 319$ $[M+Na]^+$. ^1H NMR (DMSO-d_6, 250.13 MHz): 8.30 (d, 1H, $J = 5.6$ Hz), 8.12 (d, 1H, $J = 2.0$ Hz), 7.89–7.88 (m, 1H), 7.46–7.38 (m, 3H), 7.22 (d, 2H, $J = 2.0$ Hz), 5.16 (m, 1H), 2.59 (d, 3H,

$J = 4.4$ Hz), 1.83–1.78 (m, 1H), 0.88–0.38 (m, 2H), 0.36–0.14 (m, 2H).

Compound **7d** was prepared according to GP-cyclisation and purified by crystallization from diethyl ether (190 mg, 51%). $m/z = 363$ $[M+H]^+$, $m/z = 385$ $[M+Na]^+$. ^1H NMR (DMSO-d_6, 250.13 MHz): 8.70 (t, 1H, $J = 4.4$ Hz), 8.30 (d, 1H, $J = 8.1$ Hz), 8.15 (d, 1H, $J = 2.1$ Hz), 7.49–7.41 (m, 3H), 7.25 (d, 1H, $J = 2.1$ Hz), 7.18 (d, 2H, $J = 8.7$ Hz), 6.90 (d, 2H,$J = 8.7$ Hz), 5.00 (s, 2H), 4.26 (d, 2H, $J = 5.7$ Hz), 3.76 (s, 3H); ^{13}C NMR (DMSO-d_6, 62.89 MHz): 167.28, 159.15, 155.04, 142.64, 132.65, 131.88, 130.01, 129.36, 127.98, 125.34, 124.74, 116.93, 116.11, 114.57, 108.14, 55.98, 45.30, 42.55.

Compound **7e** was prepared according to GP-cyclisation and purified by crystallization from dietyhl ether (124 mg, 37%). $m/z = 333[M+H]^+$, $m/z = 355$ $[M+Na]^+$. ^1H NMR (DMSO-d_6, 250.13 MHz): 10.34 (s, 1H), 8.29 (d, 1H, $J = 9.0$ Hz), 8.14 (d, 1H, $J = 1.9$ Hz), 7.57–7.39 (m, 5H), 7.24 (d, 1H, $J = 2.0$ Hz), 7.12 (d, 2H, $J = 8.2$ Hz), 5.15 (s, 2H), 2.25 (s, 3H).

Compound **7f** was prepared according to GP-cyclisation and the resulting crude product was purified by flash chromatography on silica gel with eluent chloroform (320 mg, 79%). $m/z = 405$ $[M+H]^+$, $m/z = 427$ $[M+Na]^+$. ^1H NMR (DMSO-d_6, 250.13 MHz): 8.29 (d, 1H, $J = 7.9$ Hz), 8.16 (d, 1H, $J = 2.1$ Hz), 7.78 (s, 1H), 7.44–7.28 (m, 6H), 6.93 (d, 2H, $J = 1.7$ Hz), 6.90 (s, 1H), 3.75 (s, 3H), 1.29 (s, 9H).

Compound **7g** was prepared according to GP-cyclisation and purified by crystallization from diethyl ether (222 mg, 53%). $m/z = 419$ $[M+H]^+$, $m/z = 441$ $[M+Na]^+$. ^1H NMR (DMSO-d_6, 250.13 MHz): 8.15 (d, 1H, $J = 8.2$ Hz), 8.10 (d, 1H, $J = 2.0$ Hz), 7.59 (s, 1H), 7.26–7.15 (m, 5H), 6.88 (d, 2H, $J = 8.7$ Hz), 6.80 (s, 1H), 3.72 (s, 3H), 2.24 (s, 3H), 1.23 (s, 9H).

Compound **7h** was prepared according to GP-cyclisation and purified by crystallization from diethyl ether (306 mg, 75%). $m/z = 407$ $[M+H]^+$, $m/z = 429$ $[M+Na]^+$. ^1H NMR (DMSO-d_6, 250.13 MHz): 8.48 (d, 1H, $J = 8.9$ Hz), 8.24 (d, 1H, $J = 1.7$ Hz), 7.79 (s, 2H), 7.41 (s, 1H), 7.34 (d, 1H, $J = 1.7$ Hz), 5.25 (d, 1H, $J = 9.5$ Hz), 1.76–1.72 (m, 1H), 1.24 (s, 9H), 0.87–0.85 (m, 1H), 0.74–070 (m, 1H), 0.40–0.26 (m, 2H).