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3,5-Dioxopimelates as new synthetic building blocks. Cyclocondensation with 1,2-, 1,3- and 1,4-dinucleophiles

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ABSTRACT

Cyclocondensation reactions of 3,5-dioxopimelates, new and versatile synthetic building blocks, with hydrazines, urea, thiourea and phenylene-1,2-diamines allow for a convenient synthesis of various heterocycles containing two ester-substituted side-chains.

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1. Introduction

1,3-Dicarbonyl compounds represent important dielectrophilic building blocks in organic chemistry. For example, pyrazoles are available by cyclization of 1,3-diketones with hydrazines.[1] Cyclocondensations with urea[2] and phenylene-1,2-diamine have also been reported.[3] The synthesis of 1,3,5-tricarbonyl compounds requires the reaction of moisture and air sensitive 1,3-dicarbonyl dianions[4] or 1,3-bis(silyloxy)-1,3-butadienes[5] with carboxylic acid derivatives. Therefore, synthetic applications of 1,3,5-tricarbonyl compounds are more rare. Examples include the cyclocondensation of methyl 3,5-dioxohexanoate with methylhydrazine.[6] In addition, the synthesis of 1,5-benzodiazepines by cyclization of phenylene-1,2-diamine with heptane-2,4,6-triones[7a] and with perfluorinated 1,2,5-triketones have been reported.[7b] 6-Chloro-3,5-dioxoalkanoates undergo base mediated cyclizations to give 3(2*H*)furanones.[8] 3,5-Dioxoalkanoates have been also used as building blocks during the synthesis of open-chained fragments of natural products.[9]

1,3,5,7-Tetracarbonyl compounds, such as 3,5,7-trioxoalkanoates and 1,3,5,7-tetraketones, and their higher homologues are unstable because they rapidly undergo intramolecular aldol condensations under the conditions of their formation. In fact, such reactions play an important role in the biosynthesis of phenolic natural products via the polyketide pathway.[10] Harris and co-workers reported the in situ generation of polycarbonyl compounds based on the reaction of 1,3-dicarbonyl dianions or 1,3,5-tricarbonyl trianions with carboxylic acid derivatives.[11]

In 2000, Jurczak and co-workers reported the first synthesis of dimethyl 3,5-dioxopimelate, which represents a stable 1,3,5,7-tetracarbonyl derivative, by reaction of ketene with malonyl dichloride.[12] Due to the lower electrophilicity of ester compared to keto groups, 3,5-dioxopimelates do not undergo intramolecular aldol reactions under the conditions of their formation. Recently, we have reported a new and convenient synthesis of a broad range of 3,5-dioxopimelates and a detailed analysis of their keto–enol tautomerism.[13a,b] We also reported the alkylation of the products.[13c] The synthesis of various heterocycles by cyclocondensation of 1,3-diketones with various dinucleophiles, such as hydrazines or thioureas, is known for many years and is present in many textbooks related to heterocyclic chemistry. However, similar cyclocondensations with more complex tetracarbonyl compounds have, to the best of our knowledge, not been reported to date. These reactions are more difficult to be carried out, because the tetracarbonyl compounds contain more than two electrophilic sites and several side reactions are, in principle, possible. Herein, we report, for the first time, a study related to cyclocondensation reactions of 3,5-dioxopimelates. These reactions allow for the synthesis of various heterocycles containing functionalized side-chains, which are not readily available by other methods.

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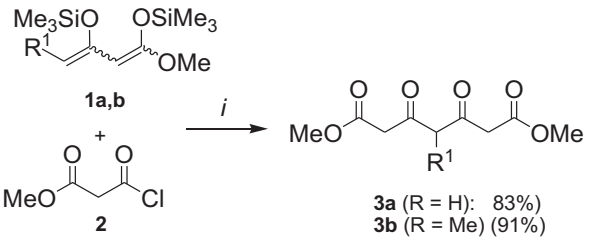
2. Results and discussion

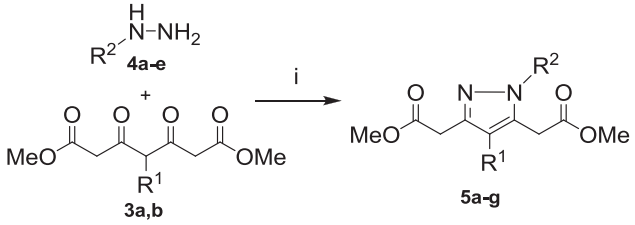
The reaction of 1,3-bis(silyloxy)-1,3-butadienes **1a**,**b** with acid chloride **2**, following our recently reported procedure,[13] afforded the 3,5-dioxopimelates **3a**,**b** in very good yields (Scheme 1).



Scheme 1. Synthesis of 3,5-dioxopimelates **3a**,**b**: (i) (1) CH_2Cl_2, TMSOTf, −78→22 °C, 14 h; (2) $NaHCO_3$.

2.1. Cyclization with hydrazines

Pyrazoles are of considerable pharmacological relevance. Fomepizol is an antidote to ethyleneglycol by inhibition of alcoholdehydrogenase (ADH).[14] Fipronil is used as an insecticide in crop protection.[15] The reaction of 3,5-dioxopimelates **3a**,**b** with hydrazines **4a**–**e** afforded the pyrazoles **5a**–**f** in 50–99% yields (Scheme 2, Table 1). The synthesis of **5a** has been previously reported.[16] While very good yields were obtained for products derived from parent hydrazine and from aromatic hydrazines, moderate yields were obtained for methylhydrazine. The cyclizations proceed via the two keto groups of **3a**,**b**, which are more electrophilic than the ester groups. The products thus contain two ester-substituted sidechains. The yields of the products derived from unsubstituted 3,5-dioxopimelate **3a** were generally slightly better than the yields of the pyrazoles derived from **3b**.



Scheme 2. Synthesis of pyrazoles **5a**–**f**. Conditions: (i) EtOH, 22 °C, 4–12 h.

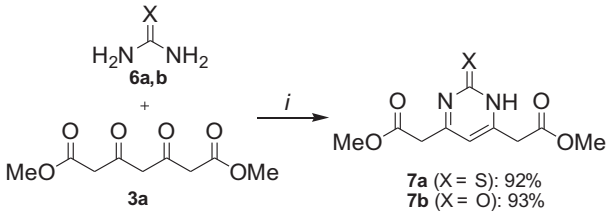
Table 1
Synthesis of pyrazoles **5a**–**f**

5	R^1	R^2	5 (%)[a]
a	H	H	80
b	H	Ph	90
c	H	Me	59
d	H	4-MeC_6H_4	99
e	Me	Me	50
f	Me	4-MeC_6H_4	90
g	Me	Ph	83

[a] Isolated yields.

2.2. Cyclization with urea and thiourea

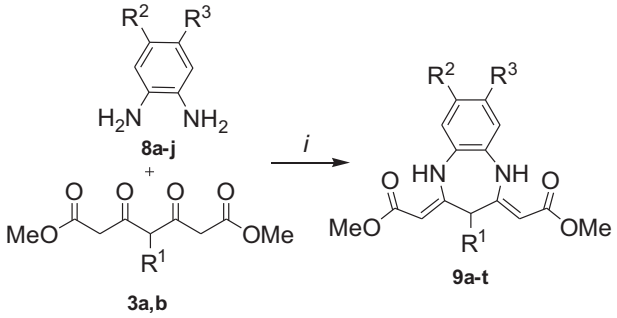
Pyrimidines and pyrimidinethiones are also of considerable pharmacological relevance. For example, propylthiouracil is used as a thyreostatic.[17] Trimethoprim is an antibiotic used for urinary tract infections.[18] The reaction of 3,5-dioxopimelates **3a**,**b** with thiourea (**6a**) and urea (**6b**) afforded pyrimidinone **7a** and pyrimidinethione **7b**, respectively (Scheme 3). In the ^{1}H NMR spectra of compounds **7a** and **7b** a broad NH signal with an intensity of one proton is observed in the range of 14–15 ppm. In the ^{13}C NMR spectra the signals for both C*C*N atoms did not appear due to a fast proton exchange. This indicates that both nitrogen atoms are involved in the dynamic process. But, it cannot be confirmed, to what extent the C=S and C=O groups are taking part in this process.



Scheme 3. Synthesis of **7a**,**b**. Conditions: (i) EtOH, 22 °C, 4 h.

2.3. Cyclization with 1,2-diaminobenzenes

Benzodiazepines are of considerable pharmacological relevance. For example, valium **A** und clobazam **B** are used in the clinic for the treatment of psychological and neurological disorders, respectively.[19] The reaction of 3,5-dioxopimelates **3a**,**b** with 1,2-diaminobenzenes **8a**–**j** afforded heterocycles **9a**–**t** (Scheme 4, Table 2). Most of the products were isolated in good to excellent yields (50–99%).

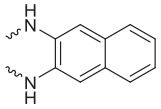
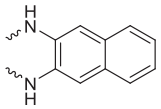


Scheme 4. Synthesis of **9a**–**t**. Conditions: (i) EtOH, 22 °C, 12 h.

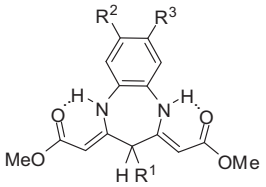
In general, benzodiazepines exclusively contain sp^2 hybridized carbon atoms and are completely conjugated. In contrast, derivatives **9a**–**t** contain an sp^3 hybridized carbon atom and two exocyclic double bonds. The conjugation is interrupted. This might be explained by the formation of two stable intramolecular hydrogen bonds in the 3-aminoacrylate substructures (Scheme 5). In addition, it is known from more simple benzodiazepines of this substitution pattern that they are not conjugated in order to minimize antiaromatic contributions. Protonation is known to lead to a benzodiazepinium salt containing two electronically decoupled π-systems, i.e., the benzene ring and the vinamidinium salt moiety.

In the ^{1}H NMR spectra of compounds **9a**–**t**, one or two signals in the region of 10–11 ppm are displayed for NH with a total intensity of 2H. Additionally, in the ^{1}H and ^{13}C NMR spectra of the Me substituted compounds **9k**–**t** some signals appear as broadened or doubled, which refer to a dynamic process. Therefore, we have measured **9t** in chloroform solution at different temperatures from 223 to 323 K. At 298 K two broad signals for C*H*Me and one broad signal for CH*Me* were observed in the 300 MHz ^{1}H NMR spectrum. At lowering the temperature to 223 K, in the ^{1}H NMR spectrum all signals were doubled in the ratio of 1:0.6. Likewise, in the ^{13}C NMR

Table 2
Synthesis of **9a**–**t**

9	8	R^1	R^2	R^3	**9** (%)[a]
a	**a**	H	H	H	65
b	**b**	H	H	Me	85
c	**c**	H	H	Cl	75
d	**d**	H	H	$C(O)C_6H_5$	87
e	**e**	H	Me	Me	85
f	**f**	H	Cl	Cl	89
g	**g**	H	H	Br	62
h	**h**	H	H	COOMe	65
i	**i**	H	H	CN	50
j	**j**	H			80
k	**g**	Me	H	Br	82
l	**h**	Me	H	COOMe	59
m	**i**	Me	H	CN	65
n	**j**	Me			51
o	**a**	Me	H	H	99
p	**b**	Me	H	Me	20
q	**c**	Me	H	Cl	65
r	**d**	Me	H	$C(O)C_6H_5$	30
s	**e**	Me	Me	Me	70
t	**f**	Me	Cl	Cl	62

[a] Isolated yields.



Scheme 5. Intramolecular hydrogen bonds in **9a**–**t**.

spectrum (75 MHz) of **9t** recorded at 298 K, all carbon atoms (except C=O and MeO) gave doubled signals in the ratio of 1:0.6, which coalescence at higher temperatures. Therefore, in the ^{13}C NMR spectrum recorded at 323 K only one set of signals was observed for the carbon atoms. In the whole temperature range, the signal for the NH protons at δ=10.63 remains nearly constant with respect to position and intensity (for two H), which proves the presence of the two intramolecular hydrogen bonds in all compounds (Scheme 3). Therefore, the presence of two isomeric species for **9k**–**t**, depending on the temperature, can *not* be explained by tautomerism, but more likely by a change in the conformation of the seven-membered ring system of the 1,4-diazepines.

3. Conclusions

We reported the first cyclocondensation reactions of 3,5-dioxopimelates with 1,2-, 1,3-, and 1,4-dinucleophiles. With regard to the dinucleophile, the reactions follow the pattern of regioselectivity, which was earlier reported for reactions of simple 1,3-diketones. With regard to the 3,5-dioxopimelate, all cyclizations regioselectively involve the two keto groups and not the (less electrophilic) ester groups. Due to the polyfunctional character of the 3,5-dioxopimelates and due to the regioselective character of the cyclizations, the reactions reported herein allow for the synthesis of a variety of functionalized heterocycles, which are not readily available by other methods.

4. Experimental section

4.1. General

^1H NMR spectra (250.13 and 300.13 MHz, respectively) and ^{13}C NMR spectra (62.9 and 75.5 MHz, respectively) of compounds **9a**–**t** were recorded on Bruker spectrometers AVANCE 250 and AVANCE 300 in $CDCl_3$ solution at 298 K. Compound **9t** was measured at temperatures from 223 to 323 K. The chemical shifts are referenced to solvent signals (δ ^1H=7.26, δ ^{13}C=77.0).

4.2. Synthesis of pyrazoles 5a–f, pyrimidinthione 7a and pyrimidinone 7b

To a solution of dimethyl 3,5-dioxopimelate **31a**,**b** (1.0 equiv) in ethanol (15 mL/mmol) is added the hydrazine compound **4a**–**e** or urea or thiourea **6a**,**b** (1.1 equiv) at a temperature of 22 °C. After 4–12 h of stirring the solvent is removed under reduced pressure and after column chromatography on silica (heptane/ethylacetate) the pure products **5a**–**f**, **7a**,**b** are obtained.

*4.2.1. Dimethyl 2,2′-(1H-pyrazole-3,5-diyl)diacetate (**5a**).* Yield 102 mg, 80%, yellow solid, mp 138–140 °C; ^1H NMR (300.13 MHz, $CDCl_3$): δ=3.72 (s, 4H, CH_2); 3.74 (s, 6H, OMe); 6.14 (s, 1H, CH); 6.95 (s, 1H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=32.6 (CH_2); 52.1 (OMe); 104.8 (CH); 140.6 (br, C_q); 170.7 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3289(w), 3188 (w), 3131 (w), 3104 (w), 3031 (w), 2992 (w), 2952 (w), 2877 (w), 2794 (w), 1734 (br s), 1642 (s), 1586 (w), 1533 (m), 1463 (w), 1435 (w), 1417 (w), 1402 (w), 1369 (w), 1336 (w), 1316 (w), 1265 (w), 1198 (w), 1170 (w), 1030 (w), 1012 (w). MS (EI, 70 eV): *m*/*z* (%)=212 ([M^+], 29), 180 (15), 154 (39), 153 (100), 152 (6), 121 (18), 93 (14), 84 (14). HRMS (EI, 70 eV): calcd for $C_9H_{12}N_2O_4$ ([M^+]) 212.07916, found 212.079032.

*4.2.2. Dimethyl 2,2′-(1-phenyl-1H-pyrazole-3,5-diyl)diacetate (**5b**).* Yield 156 mg, 90%, brown oil; ^1H NMR (300.13 MHz, $CDCl_3$): δ=3.66 (s, 3H, OMe); 3.69 (s, 2H, CH_2); 3.73 (s, 3H, OMe); 3.75 (s, 2H, CH_2); 6.40 (s, 1H, CH); 7.35–7.50 (m, 5H, Ph). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=32.1, 34.1 (CH_2); 52.1, 52.3 (OMe); 107.7 (CH); 125.5, 128.3, 129.2 (CH_{Ph}); 136.3, 139.1, 145.9 (C_q); 169.6, 171.6 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3063(w), 2998 (w), 2952 (w), 2844 (w), 1734 (br s), 1597 (m), 1551 (m), 1502 (s), 1453 (w), 1435 (m), 1408 (w), 1387 (w), 1336 (w), 1256 (w), 1199 (w), 1161 (w), 1073 (w), 1040 (w), 1009 (w). MS (EI, 70 eV): *m*/*z* (%)=288 ([M^+], 64), 230 (38), 229 (100), 170 (11), 142 (4), 169 (57), 141 (10). HRMS (EI, 70 eV): calcd for $C_{15}H_{16}N_2O_4$ ([M^+]) 288.11046, found 288.110474.

*4.2.3. Dimethyl 2,2′-(1-methyl-1H-pyrazole-3,5-diyl)diacetate (**5c**).* Yield 66 mg, 59%, colourless oil; ^1H NMR (250.13 MHz, $CDCl_3$) δ=3.61 (s, 2H, CH_2); 3.63 (s, 2H, CH_2); 3.67 (s, 3H, Me); 3.69 (s, 3H, Me); 3.75 (s, 3H, Me); 6.12 (s, 1H, CH). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ=31.5, 34.0 (CH_2); 36.3 (NMe); 51.9, 52.3 (OMe); 106.4 (CH); 135.6, 143.9 (CN); 169.2, 171.2 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3129(w), 2998 (w), 2953 (m), 2846 (w), 1732 (s), 1616 (w), 1549 (m). MS (EI, 70 eV): *m*/*z*=226 (M^+, 24), 225 (38), 193 (4), 168 (17), 167 (100), 108 (12). Anal. Calcd for $C_{10}H_{14}N_2O_4$ (226.229): C, 53.09; H, 6.24; N, 12.38. Found: C, 53.080; H, 6.153; N, 12,186.

*4.2.4. Dimethyl 2,2′-(1-p-tolyl-1H-pyrazole-3,5-diyl)diacetate (**5d**).* Yield 145 mg, 99%, colourless liquid; ^1H NMR (300.13 MHz, $CDCl_3$) δ=2.39 (s, 3H, Me); 3.66 (s, 2H, CH_2); 3.66 (s, 3H, OMe); 3.73 (s, 3H, OMe); 3.74 (s, 2H, CH_2); 6.39 (s, 1H, CH); 7.26 (m, 4H, Ar). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=21.1 (Me); 32.1, 34.1 (CH_2); 52.1, 52.4 (OMe); 107.5 (CH); 125.5, 129.8 (CH_{Ar}); 136.5, 136.5, 138.4, 145.6 (C_q); 169.6, 171.2 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3131(w), 2927 (w), 2952 (m), 2925 (w), 2846 (w), 1735 (s), 1613 (w), 1587 (w), 1549 (m), 1518 (s).

MS (EI, 70 eV): m/z=302 (M^+, 88); 243 (100), 183 (34), 169 (23), 91 (11). HRMS (ESI-TOF, 70 eV) calcd for $C_{16}H_{19}N_2O_4$ (303.13393, $[M+H]^+$): 303.13429.

*4.2.5. Dimethyl 2,2′-(1,4-dimethyl-1H-pyrazole-3,5-diyl)diacetate (**5e**).* Yield 60 mg, 50%, yellow solid, mp 63–65 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=1.94 (s, 3H, Me); 3.58 (s, 2H, CH_2); 3.60 (s, 2H, CH_2); 3.68 (s, 3H, OMe); 3.69 (s, 3H, OMe); 3.77 (s, 3H, Me). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=8.0 (Me); 30.3, 32.7 (CH_2); 36.5 (NMe); 52.0, 52.3 (OMe); 113.9, 132.9, 142.6 (C_q); 169.3, 171.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3442(w), 3003 (w), 2955 (w), 2867 (w), 2753 (w), 1721 (s), 1650 (w), 1622 (w), 1591 (w), 1576 (w), 1502 (w), 1470 (w), 1450 (w), 1435 (w), 1427 (w), 1408 (w), 1387 (m), 1340 (w), 1327 (m), 1307 (w), 1203 (br s), 1173 (w), 1147 (m), 1027 (w). MS (EI, 70 eV): m/z (%)=240 ([M^+], 59), 182 (17), 181 (100), 180 (45), 122 (15), 121 (44). HRMS (ESI-TOF/MS): calcd for $C_{11}H_{17}N_2O_4$ ($[M+H]^+$) 241.11828, found 241.11841.

*4.2.6. Dimethyl 2,2′-(4-methyl-1-p-tolyl-1H-pyrazole-3,5-diyl)diacetate (**5f**).* Yield 142 mg, yellow oil; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=2.02 (s, 3H, Me); 2.38 (s, 3H, Me); 3.61 (s, 2H, CH_2); 3.66 (s, 3H, OMe); 3.71 (s, 2H, CH_2); 3.71 (s, 3H, OMe); 7.25 (m, 4H, Ar). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=8.1 (Me); 21.3 (Me); 30.8, 32.8 (CH_2); 52.0, 52.2 (OMe); 115.1 (C_q); 125.3, 129.6 (CH_{Ar}); 133.4, 136.8, 138.0, 144.5 (C_q); 169.3, 171.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3029(w), 2996 (w), 2952 (w), 2923 (w), 2864 (w), 2746 (w), 1734 (s), 1659 (w), 1651 (w), 1640 (w), 1612 (w), 1589 (w), 1574 (w), 1518 (s), 1493 (w), 1434 (m), 1414 (w), 1382 (m), 1333 (w), 1316 (w), 1295 (w), 1257 (m), 1196 (w), 1159 (br s), 1121 (w), 1109 (w), 1084 (w), 1040 (w), 1005 (s). MS (EI, 70 eV): m/z (%)=316 ([M^+], 100), 315 (44), 257 (98), 225 (15), 197 (36), 183 (34), 91 (13). HRMS (EI, 70 eV): calcd for $C_{17}H_{20}N_2O_4$ ([M^+]) 316.14176, found 316.141499.

*4.2.7. Dimethyl 2,2′-(3-methyl-1-phenyl-1H-pyrazole-3,5-diyl)diacetate (**5g**).* Yield 125 mg, 83%, yellow liquid; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ=2.03 (s, 3H, Me); 3.64 (s, 2H, CH_2); 3.67 (s, 3H, OMe); 3.73 (s, 2H, CH_2); 3.73 (s, 3H, OMe); 7.35–7.48 (m, 5H, Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=8.1 (Me); 30.8, 32.8 (CH_2); 52.0, 52.2 (OMe); 115.4 (C_q); 125.4, 127.9, 129.1 (CH_{Ph}); 133.4, 139.3, 144.8 (C_q); 169.6, 170.9 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3061(w), 2996 (w), 2952 (m), 2923 (w), 2846 (w), 1733 (s), 1597 (m), 1502 (s). MS (GC/MS, 70 eV): m/z=302 (M^+, 100), 301 (36), 243 (98), 211 (13), 183 (61), 77 (21). HRMS (EI, 70 eV) calcd for $C_{16}H_{18}O_4N_2$ (302.12611, $[M]^+$): 302.125894.

*4.2.8. Dimethyl 2,2′-(2-thioxo-1,2-dihydropyrimidine-4,6-diyl)diacetate (**7a**).* Yield 140 mg, 92%, yellow oil; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=3.37 (s, 4H, CH_2); 3.74 (s, 6H, OMe); 5.74 (s, 1H, CH); 14.80 (br s, 1H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=44.3 (CH_2); 52.5 (OMe); 101.0 (CH); 167.6 (C=O); 185.8 (CS); (CN signal is not displayed due to dynamical process). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3366(w), 3268 (w), 3154 (w), 3091 (w), 3008 (w), 2956 (w), 2850 (w), 2682 (w), 2352 (w), 2108 (w), 1736 (br s), 1602 (br s), 1456 (w), 1436 (w), 1405 (w), 1328 (w), 1256 (w), 1200 (w), 1151 (w), 1081 (w), 1012 (w). MS (EI, 70 eV): m/z (%)=256 ([M^+], 50), 241 (29), 240 (100), 225 (22), 224 (45), 212 (32), 198 (26), 184 (17), 171 (72), 153 (39), 143 (32), 111 (31), 69 (57). HRMS (ESI-TOF/MS): calcd for $C_{10}H_{11}N_2O_4S$ ($[M-H]^-$) 255.0445, found 255.04448.

*4.2.9. Dimethyl 2,2′-(2-oxo-1,2-dihydropyrimidine-4,6-diyl)diacetate (**7b**).* Yield 111 mg, 93%; white solid; ^{1}H NMR (250.13 MHz, $CDCl_3$) δ=3.34 (s, 4H, CH_2); 3.71 (s, 6H, OMe); 5.71 (s, 1H, CH); 14.75 (br s, 1H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ=44.2 (CH_2); 52.4 (OMe); 100.9 (CH); 167.6 (C=O); 185.8 (NCO); (CN signal is not displayed due to dynamical process). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3428(m), 3328 (m), 3251 (w), 3224 (w), 3108 (w), 2956 (w), 2849 (w), 1709 (m), 1673 (m), 1623 (w), 1591 (s), 1504 (w). MS (EI, 70 eV): m/z=240 (M^+, 100), 209 (60), 182 (64), 177 (51), 150 (40), 44 (88). HRMS (EI, 70 eV) calcd for $C_{10}H_{12}O_5N_2$ (240.07407, M^+): 240.074768.

4.3. Synthesis of benzo-1,5-diazepines 9a–t

To an ethanolic solution (15 mL/mmol) of dimethyl 3,5-dioxopimelates **31a**,**b** (1.0 equiv) are added the diamines **8a**–**j** (1.1 equiv) at 22 °C. After 4–12 h of stirring the solid, product compound can be separated and is washed with ethanol and dried. In case of some remaining impurities, column chromatography on silica (heptane/ethylacetate) is performed to afford the pure product.

*4.3.1. (2Z,2′Z)-Dimethyl 2,2′-(1H-benzo[b][1,4]diazepine-2,4(3H,5H)-diylidene)diacetate (**9a**).* Yield 113 mg, 65%, white solid, mp 200–202 °C; ^{1}H NMR (250.13 MHz, $CDCl_3$): δ=2.96 (br s, 2H, CH_2); 3.69 (s, 6H, OMe); 4.74 (s, 2H, CH); 7.06 (m, 4H, Ar); 10.37 (br s, 2H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=38.9 (CH_2); 50.6 (OMe); 84.3 (C-3); 122.6, 124.8 (CH_{Ar}); 131.1 (C-5); 157.1 (C-4); 170.7 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3257(w), 3201 (w), 3037 (w), 3011 (w), 2995 (w), 2948 (w), 2912 (w), 2831 (w), 1660 (w), 1645 (w), 1608 (br s), 1582 (w), 1502 (m), 1439 (m), 1372 (w), 1317 (m), 1271 (m), 1256 (w), 1234 (w), 1211 (w), 1186 (w), 1167 (m), 1145 (m), 1128 (w), 1040 (s). MS (EI, 70 eV): m/z (%)=288 ([M^+], 80), 257 (19), 256 (100), 225 (19), 224 (86), 169 (22), 168 (33), 112 (13). HRMS (EI, 70 eV): calcd for $C_{15}H_{16}N_2O_4$ ([M^+]) 288.11046, found 288.111233. Anal. Calcd for $C_{15}H_{16}N_2O_4$ (288.11): C, 62.49; H, 5.59; N, 9.72. Found: C, 62.434; H, 5.884; N, 9.533.

*4.3.2. (2Z,2′Z)-Dimethyl 2,2′-(7-methyl-1H-benzo[b][1,4]diazepine-2,4(3H,5H)-diylidene)diacetate (**9b**).* Yield 128 mg, 85%, yellow solid, mp 185 °C; ^{1}H NMR (250.13 MHz, $CDCl_3$): δ=2.30 (s, 3H, Me); 2.95 (s, 2H, CH_2); 3.68 (s, 3H, OMe); 3.69 (s, 3H, OMe); 4.72 (br s, 2H, CH); 6.85–6.95 (m, 3H, Ar); 10.32 (br s, 2H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=20.6 (Me); 38.9 (CH_2); 50.6, 50.6 (OMe); 83.6, 84.1 (C-3,3′); 122.5, 122.9, 125.7 (CH_{Ar}); 128.6 (C-5); 130.9 (C-10); 134.9 (C-8); 157.2, 157.3 (C-4,4′); 170.7, 170.8 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3270(w), 3205 (w), 3006 (w), 2947 (w), 2914 (w), 2855 (w), 1742 (w), 1660 (w), 1652 (w), 1604 (br s), 1582 (w), 1515 (m), 1493 (m), 1428 (m), 1365 (w), 1319 (m), 1271 (m), 1239 (m), 1218 (m), 1189 (w), 1168 (w), 1150 (w), 1139 (w), 1042 (s), 1014 (w). MS (EI, 70 eV): m/z (%)=302 ([M^+], 74), 271 (18), 270 (100), 238 (89), 183 (19), 182 (30), 119 (12). HRMS (EI, 70 eV): calcd for $C_{16}H_{18}N_2O_4$ ([M^+]) 302.12611, found 302.126202.

*4.3.3. (2Z,2′Z)-Dimethyl 2,2′-(7-chloro-1H-benzo[b][1,4]diazepine-2,4(3H,5H)-diylidene)diacetate (**9c**).* Yield 121 mg, 75%, grey-white solid, mp 204 °C; ^{1}H NMR (250.13 MHz, $CDCl_3$): δ=2.95 (s, 2H, CH_2); 3.69 (s, 6H, OMe); 4.76 (br s, 2H, CH); 6.94–7.05 (m, 3H, Ar); 10.37 (br s, 2H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=38.8 (CH_2); 50.7, 50.7 (OMe); 84.9, 85.4 (C-3,3′); 122.3, 123.6, 124.7 (CH_{Ar}); 129.7, 129.8 (C-5,8); 132.1 (C-10); 156.4, 156.6 (C-4,4′); 170.6, 170.7 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3269(w), 3210 (w), 3086 (w), 3056 (w), 3018 (w), 3002 (w), 2950 (w), 2904 (w), 2840 (w), 1672 (m), 1651 (w), 1620 (br s), 1615 (br s), 1579 (w), 1503 (m), 1485 (m), 1428 (s), 1359 (w), 1314 (m), 1282 (w), 1263 (w), 1239 (w), 1212 (m), 1174 (m), 1153 (m), 1133 (w), 1095 (m), 1041 (s). MS (EI, 70 eV): m/z (%)=324 ([M^+], [^{37}Cl], 17), 322 ([M^+], [^{35}Cl], 56), 292 (30), 291 (18), 290 (100), 260 (26), 258 (88), 202 (34), 129 (18). HRMS (EI, 70 eV): calcd for $C_{15}H_{15}ClN_2O_4$ ([M^+], [^{35}Cl]) 322.07149, found 322.071494.

*4.3.4. (2Z,2′Z)-Dimethyl 2,2′-(7-benzoyl-1H-benzo-[b][1,4]diazepine-2,4(3H,5H)-diylidene)diacetate (**9d**).* Yield 170 mg, 87%, orange solid, 169–172 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=3.01 (s, 2H, CH_2); 3.68 (s, 3H, OMe); 3.71 (s, 3H, OMe); 4.78 (s, 1H, CH); 4.84 (s, 1H, CH); 7.10

(d, 1H, ^3J=8.1 Hz, H-6); 7.46–7.62 (m, 5H, *m*-Ph, *p*-Ph, H-7,9); 7.74–7.77 (m, 2H, *o*-Ph); 10.41 (s, 1H, NH); 10.55 (s, 1H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=38.9 (CH_2); 50.7, 50.8 (OMe); 85.3, 86.4 (C-3,3′); 122.1, 124.7, 126.7 (CH_{Ar}); 128.4 (*m*-Ph); 129.8 (*o*-Ph); 130.6 (C-10); 132.4 (*p*-Ph); 133.7 (C-8); 134.8 (C-5); 137.5 (*i*-Ph); 156.0, 156.4 (C-4,4`); 170.6 (C=O); 194.8 (C=O_{Ph}). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3248(w), 3201 (w), 3076 (w), 3063 (w), 3030 (w), 2998 (w), 2949 (w), 2847 (w), 1742 (w), 1672 (w), 1650 (m), 1603 (w), 1574 (w), 1510 (w), 1495 (w), 1447 (w), 1432 (m), 1403 (w), 1323 (m), 1276 (w), 1269 (w), 1253 (w), 1233 (w), 1214 (m), 1189 (w), 1169 (m), 1153 (m), 1132 (w), 1075 (w), 1036 (s), 1010 (w). MS (EI, 70 eV): *m*/*z* (%)=392 ([M$^+$], 90), 361 (25), 360 (100), 328 (69), 195 (13), 105 (43). HRMS (ESI-TOF/MS): calcd for $C_{22}H_{21}N_2O_5$ ([M+H]$^+$) 393.1445, found 393.1441.

*4.3.5. (2Z,2′Z)-Dimethyl 2,2′-(7,8-dimethyl-1H-benzo-[b][1,4]diazepine-2,4(3H,5H)-diylidene)diacetate (**9e**).* Yield 134 mg, 85%, white solid, mp 224–226 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=2.20 (s, 6H, Me); 2.92 (s, 2H, CH_2); 3.68 (s, 6H, OMe); 4.69 (s, 2H, CH); 6.81 (s, 2H, Ar); 10.28 (br s, 2H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=19.0 (Me); 39.0 (CH_2); 50.5 (OMe); 83.7 (C-3); 123.4 (C-6); 128.6 (C-5); 133.5 (C-7); 157.3 (C-4); 170.8 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3268(w), 3203 (w), 2998 (w), 2951 (w), 2918 (w), 2863 (w), 1660 (s), 1621 (w), 1604 (s), 1581 (w), 1515 (w), 1500 (w), 1449 (w), 1430 (w), 1375 (w), 1328 (w), 1315 (w), 1286 (w), 1237 (s), 1237 (s), 1203 (w), 1187 (w), 1168 (w), 1150 (s), 1115 (m), 1036 (s), 1010 (w). MS (EI, 70 eV): *m*/*z* (%)=316 ([M$^+$], 73), 285 (20), 284 (100), 253 (19), 252 (93), 237 (11), 197 (21), 196 (34). HRMS (EI, 70 eV): calcd for $C_{17}H_{20}N_2O_4$ ([M$^+$]) 316.14176, found 316.142317. Anal. Calcd for $C_{17}H_{20}N_2O_4$ (316.35): C, 64.54; H, 6.37; N, 8.86. Found: C, 63.995; H, 6.279; N, 8.758.

*4.3.6. (2Z,2′Z)-Dimethyl 2,2′-(7,8-dichloro-1H-benzo[b][1,4]diazepine-2,4(3H,5H)-diylidene)diacetate (**9f**).* Yield 158 mg, 89%, white solid, mp 236–238 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=2.95 (s, 2H, CH_2); 3.69 (s, 6H, OMe); 4.78 (s, 2H, CH); 7.13 (s, 2H, Ar); 10.36 (s, 2H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=38.7 (CH_2); 50.8 (OMe); 85.9 (C-3); 123.6 (C-6); 127.8 (C-7); 130.7 (C-5); 156.0 (C-4); 170.6 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3253(w), 3197 (w), 3115 (w), 3031 (w), 3001 (w), 2952 (w), 2907 (w), 2839 (w), 1661 (s), 1629 (w), 1608 (br s), 1570 (w), 1502 (m), 1472 (w), 1430 (m), 1309 (m), 1283 (m), 1243 (m), 1217 (m), 1185 (w), 1168 (m), 1149 (w), 1140 (w), 1037 (s). MS (EI, 70 eV): *m*/*z* (%)=360 ([M$^+$], [^{37}Cl] [^{37}Cl], 6), 358 ([M$^+$], [^{37}Cl] [^{35}Cl], 36), 356 ([M$^+$], [^{35}Cl] [^{35}Cl], 57), 326 (62), 324 (100), 294 (48), 292 (74), 236 (33), 69 (34). HRMS (EI, 70 eV): calcd for $C_{15}H_{14}Cl_2N_2O_4$ ([M$^+$], [^{35}Cl] [^{35}Cl]) 256.03251, found 256.031827. Anal. Calcd for $C_{15}H_{14}Cl_2N_2O_4$ (357.19): C, 50.44; H, 3.95; N, 7.84. Found: C, 49.985; H, 4.112; N, 7.986.

*4.3.7. (2Z,2′Z)-Dimethyl 2,2′-(7-bromo-1H-benzo-[b][1,4]diazepine-2,4(3H,5H)-diylidene)diacetate (**9g**).* White solid, mp 221–222 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ=2.95 (s, 2H, CH_2); 3.69 (s, 3H, OMe); 3.69 (s, 3H, OMe); 4.76 (br s, 2H, CH); 6.89 (d, $^3J_{6,7}$=8.4 Hz, 1H, H-6); 7.17 (dd, $^3J_{6,7}$=8.4 Hz, $^4J_{7,9}$=2.1 Hz, 1H, H-7); 7.20 (d, $^4J_{7,9}$=2.1 Hz, 1H, H-9); 10.36 (br s, 2H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=38.7 (CH_2); 50.7, 50.7 (OMe); 85.0, 85.5 (C-3,3′); 117.0 (C-8); 123.8, 125.2, 127.6 (CH_{Ar}); 130.3 (C-5); 132.3 (C-10); 156.4, 156.5 (C-4,4′); 170.6, 170.7 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3260(w), 3203 (w), 3089 (w), 2999 (w), 2947 (m), 2842 (w), 1672 (m), 1650 (m), 1614 (s), 1594 (w), 1579 (w), 1504 (s). MS (EI, 70 eV): *m*/*z*=368 (M$^+$, ^{81}Br, 58), 366 (M$^+$, ^{79}Br, 58), 336 (^{81}Br, 100), 334 (^{79}Br, 99), 304 (^{81}Br, 71), 302 (^{79}Br, 71), 248 (^{81}Br, 31), 246 (^{79}Br, 30), 168 (20). HRMS (EI, 70 eV) calcd for $C_{15}H_{15}O_4N_2^{79}Br$ (366.02097, M$^+$): 366.021437; calcd for $C_{15}H_{15}O_4N_2^{81}Br$ (368.01892, M$^+$): 368.019265. Anal. Calcd for $C_{15}H_{15}BrN_2O_4$ (367.195): C, 49.06; H, 4.12; N, 7.63. Found: C, 48.575; H, 4.189; N, 7.74.

*4.3.8. (2Z,2′Z)-Dimethyl 2,2′-(7-(methoxycarbonyl)-1H-benzo[b][1,4]diazepine-2,4(3H,5H)-diylidene)diacetate (**9h**).* Light-brown solid, mp 261 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ=2.99 (s, 2H, CH_2); 3.70 (s, 6H, $OMe_{1,1'}$); 3.90 (s, 3H, OMe); 4.77 (s, 1H, CH); 4.82 (s, 1H, CH); 7.06 (d, $^3J_{6,7}$=8.1 Hz, 1H, H-6); 7.73 (dd, $^3J_{6,7}$=8.1 Hz, $^4J_{7,9}$=2.0 Hz, 1H, H-7); 7.76 (d, $^4J_{7,9}$=2.0 Hz, 1H, H-9); 10.45 (s, 1H, NH); 10.52 (s, 1H, NH). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ=38.9 (CH_2); 50.7, 50.8 ($OMe_{1,1'}$); 52.2 (OMe); 85.2, 86.3 (C-3,3′); 122.2, 124.2, 125.9 (CH_{Ar}); 126.3 (C-8); 130.6 (C-10); 135.0 (C-5); 156.0, 156.4 (C-4,4′); 165.9 (C=O_{Ar}); 170.6, 170.6 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3407(w), 3259 (w), 3204 (w), 3086 (w), 2988 (w), 2949 (m), 2904 (w), 2845 (w), 1715 (s), 1662 (s), 1634 (m), 1613 (s), 1607 (w), 1579 (m), 1519 (m), 1511 (m), 1505 (m). MS (EI, 70 eV): *m*/*z*=346 (M$^+$, 85), 314 (100), 282 (81), 226 (20), 128 (25), 69 (28). HRMS (EI, 70 eV) calcd for $C_{15}H_{15}O_4N_2^{79}Br$ (366.02097, M$^+$): 366.021437.

*4.3.9. (2Z,2′Z)-Dimethyl 2,2′-(7-cyano-1H-benzo[b][1,4]diazepine-2,4(3H,5H)-diylidene)diacetate (**9i**).* Light-brown solid, mp 209–210 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ=2.99 (s, 2H, CH_2); 3.70 (s, 3H, OMe); 3.70 (s, 3H, OMe); 4.81(s, 1H, CH); 4.85 (s, 1H, CH); 7.07 (m, 1H), 7.30–7.34 (m, 2H), (Ar); 10.44 (s, 1H, NH); 10.55 (s, 1H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=38.7 (CH_2); 50.8, 50.9 (OMe); 86.3, 87.2 (C-3,3′); 107.6 (C-8); 118.0 (CN); 122.9, 126.2, 128.0 (CH_{Ar}); 131.3 (C-10); 135.0 (C-5); 155.3, 155.7 (C-4,4′); 170.5 (C=O).IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3260(s), 3204 (w), 3018 (w), 2951 (w), 2922 (w), 2851 (w), 2226 (m), 1738 (w), 1659 (m), 1614 (s), 1574 (s), 1514 (m). MS (EI, 70 eV): *m*/*z*=313 (M$^+$, 57), 281 (100), 249 (89), 194 (27), 193 (50), 67 (6). HRMS (EI, 70 eV) calcd for $C_{16}H_{15}O_4N_3$ (313.10571, M$^+$): 313.105712.

*4.3.10. (2Z,2′Z)-Dimethyl 2,2′-(1H-naphtho[2,3-b][1,4]diazepine-2,4(3H,5H)-diylidene)diacetate (**9j**).* White solid, mp 245 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ=3.04 (s, 2H, CH_2); 3.72 (s, 6H, OMe); 4.80 (s, 2H, CH); 7.40 (m, 2H), 7.49 (s, 2H), 7.70 (m, 2H), (Ar); 10.58 (s, 2H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=38.7 (CH_2); 50.7 (OMe); 85.2 (C-3); 119.3, 125.6, 126.7 (CH_{Ar}); 130.9, 131.0 (C_{Ar}); 157.1 (C-4); 170.6 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3274(m), 3205 (w), 3047 (w), 3013 (w), 2950 (m), 2836 (w), 1660 (m), 1653 (w), 1606 (s), 1518 (m). HRMS (ESI-TOF, 70 eV) calcd for $C_{19}H_{19}N_2O_2$ (339.13393, [M+H]$^+$): 339.13346.

*4.3.11. (2Z,2′Z)-Dimethyl 2,2′-(7-bromo-3-methyl-1H-benzo[b][1,4]diazepine-2,4(3H,5H)-diylidene)diacetate (**9k**).* Yield 157 mg, 87%, yellow solid, mp 195–198 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=1.18–1.33 (br m, 3H, CH*Me*); 2.96 (br), 3.16 (br), (ratio 0.6:1, 1H, *CH*Me); 3.69 (s, 3H, OMe); 3.70 (s, 3H, OMe); 4.74 (s, 1H, CH); 4.75 (s, 1H, CH); 6.90 (br d, 1H), 7.10–7.23 (br m, 2H), (Ar); 10.62 (s, 2H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=12.6, 15.0 (CH*Me*); 36.4, 46.9 (*CH*Me); 50.7, 50.8 (OMe); 81.7, 82.3, 85.1, 85.5 (C-3,3′); 116.2, 117.0 (C-8); 122.7, 123.7, 124.0, 125.1, 126.9, 127.7 (CH_{Ar}); 129.9, 130.1 (C-5); 132.0, 132.3 (C-10); 159.5, 160.6 (C-4,4′); 171.0, 171.1 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3247(w), 3188 (w), 3120 (w), 3014 (w), 2986 (w), 2948 (w), 2885 (w), 2841 (w), 1661 (s), 1624 (w), 1599 (br s), 1575 (w), 1503 (w), 1482 (w), 1451 (w), 1432 (m), 1377 (m), 1320 (w), 1273 (s), 1258 (w), 1214 (s), 1187 (w), 1162 (s), 1131 (w), 1083 (w), 1060 (w), 1015 (s). MS (EI, 70 eV): *m*/*z* (%)=382 ([M$^+$], [^{81}Br]), 380 ([M$^+$], [^{79}Br], 34), 350 (43), 348 (43), 318 (24), 316 (25), 262 (17), 231 (100), 69 (22), 57 (50). HRMS (ESI-TOF/MS): calcd for $C_{16}H_{17}BrN_2NaO_4$ ([M+Na]$^+$, [^{79}Br]) 403.02639, found 403.02656. Anal. Calcd for $C_{16}H_{17}BrN_2O_4$ (381.22): C, 50.41; H, 4.49; N, 7.35. Found: C, 49.982; H, 4.824; N, 7.169.

*4.3.12. (2Z,2′Z)-Dimethyl 2,2′-(3-methyl-7-methoxycarbonyl-1H-benzo[b][1,4]diazepine-2,4-(3H,5H)-diylidene)diacetate (**9l**).* Yield 107 mg, 59%, yellow solid, mp 208–209 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=1.17–1.33 (br m, 3H, CH*Me*); 2.99 (br), 3.31 (br), (ratio 0.6:1, 1H, *CH*Me); 3.70 (s, 6H, $OMe_{1,1'}$); 3.89 (s, 3H, OMe); 4.75 (s, 1H, CH); 4.80 (s, 1H, CH); 7.07 (br, 1H), 7.68–7.77 (br, 2H), (Ar); 10.70

(s, 1H, NH); 10.76 (s, 1H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=12.7, 15.2 (CH*Me*); 36.5, 46.9 (*C*HMe); 50.7, 50.8 ($OMe_{1,1'}$); 52.1 (OMe); 81.8, 83.2, 85.1, 86.4 (C-3,3′); 121.2, 122.0, 123.2, 124.1, 125.5, 126.0 (CH_{Ar}); 125.6, 126.2 (C-8); 130.2, 130.5 (C-10); 134.5, 134.8 (C-5); 159.0, 159.5, 160.1, 160.6 (C-4,4′); 166.0 (C=O_{Ar}); 171.0, 171.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3242(w), 3186 (w), 3120 (w), 3072 (w), 2992 (w), 2948 (w), 2842 (w), 1720 (s), 1660 (m), 1625 (w), 1599 (br s), 1579 (w), 1514 (w), 1490 (w), 1455 (w), 1433 (s), 1393 (m), 1340 (m), 1276 (s), 1249 (w), 1209 (s), 1187 (w), 1161 (m), 1104 (w), 1062 (w), 1016 (w). MS (EI, 70 eV): *m*/*z* (%)=360 ([M$^+$], 100), 329 (27), 228 (97), 301 (15), 296 (51), 269 (24), 241 (30), 240 (30), 148 (11). HRMS (ESI-TOF/MS): calcd for $C_{18}H_{20}N_2NaO_6$ ([M+Na]$^+$) 383.12136, found 383.12204. Anal. Calcd for $C_{18}H_{20}N_2O_6$ (360.36): C, 59.99; H, 5.59; N, 7.77. Found: C, 59.772; H, 5.998; N, 7.401.

*4.3.13. (2Z,2′Z)-Dimethyl 2,2′-(7-cyano-3-methyl-1H-benzo[b][1,4]diazepine-2,4(3H,5H)-diylidene)diacetate (**9m**).* Yield 106 mg, 65%, white solid, mp 197–199 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=1.20–1.33 (br m, 3H, CH*Me*); 3.08 (br, 1H, *CH*Me); 3.70 (s, 3H, OMe); 3.70 (s, 3H, OMe); 4.79 (s, 1H, CH); 4.84 (s, 1H, CH); 7.06 (br d, 1H), 7.30 (br s, 2H), (Ar); 10.70 (s, 1H, NH); 10.80 (s, 1H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=12.7, 15.3 (CH*Me*); 36.4, 46.9 (*C*HMe); 50.9, 50.9 (OMe); 83.1, 84.2, 86.2, 87.2 (C-3,3′); 107.3 (C-8); 118.1 (CN); 121.9, 122.7, 125.2, 126.1, 127.5, 128.5 (CH_{Ar}); 131.5 (C-10); 134.8 (C-5); 158.6, 159.6 (C-4,4′); 170.9 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3246(w), 3190 (w), 3120 (w), 3082 (w), 3013 (w), 2983 (w), 2955 (w), 2923 (w), 2850 (w), 2232 (w), 2223 (m), 1745 (br m), 1680 (w), 1657 (br m), 1623 (w), 1596 (br s), 1570 (w), 1513 (w), 1496 (w), 1485 (w), 1448 (w), 1433 (w), 1428 (w), 1388 (w), 1376 (w), 1330 (w), 1273 (br s), 1219 (br s), 1184 (w), 1171 (w), 1157 (w), 1142 (w), 1116 (w), 1063 (w), 1013 (br, s). MS (EI, 70 eV): *m*/*z* (%)=327 (M$^+$, 83), 295 (100), 268 (13), 264 (17), 263 (63), 236 (29), 208 (37), 207 (42), 84 (47). HRMS (EI, 70 eV): calcd for $C_{17}H_{17}N_2O_4$ ([M$^+$]) 327.12136, found 327.121290. Anal. Calcd for $C_{17}H_{17}N_3O_4$ (327.33): C, 62.38; H, 5.23; N, 12.84. Found: C, 62.228; H, 6.060.

*4.3.14. (2Z,2′Z)-Dimethyl 2,2′-(3-methyl-1H-naphtho[2,3-b][1,4]diazepine-2,4(3H,5H)-diylidene)diacetate (**9n**).* Yield 90 mg, 51%, yellow solid, mp 227–228 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=1.19–1.35 (br m, 3H, CH*Me*); 3.01 (br), 3.33 (br), (ratio 0.6:1, 1H, *CH*Me); 3.72 (s, 6H, OMe); 4.79 (s, 2H, CH); 7.39 (br, 2H), 7.47 (br, 2H), 7.70 (br, 2H), (Ar); 10.84 (s, 2H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=12.7, 15.4 (CH*Me*); 36.1, 46.9 (*C*HMe); 50.7 (OMe); 81.8, 85.2 (C-3); 117.9, 119.3 (C-6); 125.7, 126.6 (br), (CH_{Ar}); 130.5 (br, C-5); 131.0 (C_{Ar}); 160.1, 161.3 (C-4); 171.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3255(w), 3189 (w), 3120 (w), 3050 (w), 3019 (w), 2987 (w), 2948 (w), 2833 (w), 1662 (br s), 1605 (m), 1591 (w), 1537 (w), 1518 (w), 1490 (m), 1468 (w), 1436 (w), 1422 (w), 1380 (s), 1315 (w), 1291 (s), 1248 (w), 1233 (w), 1188 (m), 1158 (s), 1120 (w), 1091 (w), 1063 (w), 1016 (br s). MS (EI, 70 eV): *m*/*z* (%)=352 ([M$^+$], 100), 321 (21), 320 (89), 288 (51), 261 (22), 232 (37), 219 (17), 208 (11), 180 (10), 78 (30), 63 (35). HRMS (EI, 70 eV): calcd for $C_{20}H_{20}N_2O_4$ ([M$^+$]) 352.14176, found 352.141511.

*4.3.15. (2Z,2′Z)-Dimethyl 2,2′-(3-methyl-1H-benzo[b][1,4]diazepine-2,4(3H,5H)-diylidene)diacetate (**9o**).* Brown solid, mp 156–158 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ=1.16–1.32 (br, 3H, CH*Me*); 2.96 (br), 3.19 (br), (1H, *CH*Me); 3.69 (s, 6H, OMe); 4.72 (s, 2H, CH); 6.99–7.09 (br m, 4H, Ar); 10.62 (s, 2H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=12.6, 14.8 (CH*Me*); 36.4, 47.0 (*CH*Me); 50.6 (OMe); 81.0, 84.4 (C-3); 116.8, 120.3, 122.5, 124.8 (CH_{Ar}); 130.6, 131.0 (C_{Ar}); 160.0, 161.2 (C-4); 171.1 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3383(w), 3361 (w), 3248 (m), 3192 (m), 2983 (w), 2947 (m), 2834 (w), 1738 (w), 1659 (s), 1618 (w), 1591 (s), 1581 (s), 1501 (s). MS (EI, 70 eV): *m*/*z*=302 (M$^+$, 94), 270 (100), 238 (58), 211 (40), 183 (43), 182 (45). HRMS (EI, 70 eV) calcd for $C_{16}H_{18}O_4N_2$ (302.12611, [M]$^+$): 302.125515. Anal. Calcd for $C_{16}H_{18}N_2O_4$ (302.325): C, 63.57; H, 6.00. Found: C, 63.28; H, 6.16.

*4.3.16. (2Z,2′Z)-Dimethyl 2,2′-(3,7-dimethyl-1H-benzo-[b][1,4]diazepine-2,4(3H,5H)-diylidene)diacetate (**9p**).* White solid, mp 178 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ=1.17–1.31 (br m, 3H, CH*Me*); 2.30 (s, 3H, Me); 2.94 (br q, *J*=6.6 Hz), 3.18 (br q, *J*=6.6 Hz) (ratio 0.6:1, 1H, *CH*Me); 3.68 (s, 3H, OMe); 3.69 (s, 3H, OMe); 4.69 (s, 1H), 4.70 (s, 1H), (CH); 6.81–6.96 (m, 3H, Ar); 10.58 (br s, 2H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=12.6, 14.7 (CH*Me*); 20.6, 20.6 (Me); 36.5, 47.1 (*C*HMe); 50.6, 50.6 (OMe); 80.4, 80.9, 83.8, 84.3 (C-3,3′); 121.4, 121.9, 122.4, 122.8, 125.0, 125.7 (CH_{Ar}); 128.2, 128.5 (C-10); 130.4, 130.8 (C-5); 134.1, 132.9 (C-8); 160.1, 161.2 (C-4,4′); 171.1 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3248(m), 3192 (m), 3017 (w), 2986 (w), 2946 (m), 2917 (w), 2838 (w), 1660 (s), 1626 (m), 1596 (s), 1582 (w), 1515 (m). MS (EI, 70 eV): *m*/*z*=316 (M$^+$, 100), 284 (98), 252 (79), 225 (42), 196 (45), 126 (14). HRMS (EI, 70 eV) calcd for $C_{17}H_{20}O_4N_2$ (316.14176, [M]$^+$): 316.141626.

*4.3.17. (2Z,2′Z)-Dimethyl 2,2′-(7-chloro-3-methyl-1H-benzo[b][1,4]diazepine-2,4(3H,5H)-diylidene)diacetate (**9q**).* White solid, mp 195–196 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ=1.18–1.31 (br m, 3H, CH*Me*); 2.96 (br), 3.15 (br), (ratio 0.6:1, 1H, *CH*Me); 3.69 (s, 3H, OMe); 3.69 (s, 3H, OMe); 4.73 (s, 1H), 4.75 (s, 1H), (CH); 6.92–7.07 (m, 3H, Ar); 10.62 (br s, 2H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=12.6, 14.9 (CH*Me*); 36.4, 46.8 (*C*HMe); 50.7, 50.7 (OMe); 81.7, 82.2, 84.9, 85.5 (C-3,3′); 121.1, 122.2, 122.4, 123.5, 124.0, 124.5 (CH_{Ar}); 128.9, 129.4, 129.6 (C-5,8); 131.6, 132.0 (C-10); 159.5, 160.5, 160.7 (C-4,4′); 170.9, 171.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3246(w), 3191 (w), 3119 (w), 3015 (w), 2983 (w), 2949 (m), 2842 (w), 1661 (s), 1622 (w), 1598 (s), 1576 (w), 1501 (m). MS (EI, 70 eV): *m*/*z*=338 (M$^+$, ^{37}Cl, 31), 336 (M$^+$, ^{35}Cl, 93), 306 (^{37}Cl, 35), 304 (^{35}Cl, 100), 274 (22), 272 (76), 245 (23), 216 (39), 136 (14). HRMS (EI, 70 eV) calcd for $C_{16}H_{17}O_4N_2^{35}Cl$ (336.08714, [M]$^+$): 336.087080; calcd for $C_{16}H_{17}O_4N_2^{37}Cl$ (338.08419, [M]$^+$): 333.084983. Anal. Calcd for $C_{16}H_{17}ClN_2O_4$ (336.770): C, 57.06; H, 5.09; N, 8.32. Found: C, 57.122; H, 5.331; N, 8.050.

*4.3.18. (2Z,2′Z)-Dimethyl 2,2′-(7-benzoyl-3-methyl-1H-benzo[b][1,4]diazepine-2,4(3H,5H)-diylidene)diacetate (**9r**).* Brown solid, mp 187 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ=1.22–1.35 (br m, 3H, CH*Me*); 3.01 (br s), 3.22 (br s), (ratio 0.6:1, 1H, *CH*Me); 3.70 (s, 3H, OMe); 3.71 (s, 3H, OMe); 4.76 (s, 1H), 4.83 (s, 1H), (CH); 7.10 (br, 1H, H-6); 7.46–7.62 (m, 5H, H-7,9, *m*-Ph, *p*-Ph); 7.75–7.79 (m, 2H, *o*-Ph); 10.68 (s, 1H, NH); 10.81 (s, 1H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=12.7, 15.2 (CH*Me*); 36.5, 47.0 (*C*HMe); 50.7, 50.8 (OMe); 82.0, 83.3, 85.3, 86.6 (C-3,3′); 121.0, 122.0, 123.6, 124.7, 126.2, 126.8 (CH_{Ar}); 128.4, 129.7 (*o*-Ph, *m*-Ph); 130.1, 130.4 (C-10); 132.3 (*p*-Ph); 133.0, 133.7 (C-8); 134.4, 134.7 (C-5); 137.5 (*i*-Ph); 159.0, 159.3, 160.1, 160.5 (C-4,4′); 171.0 (C=O); 194.8 (C=O_{Ph}). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3247(w), 3191 (w), 3119 (w), 2991 (w), 2948 (w), 2844 (w), 1652 (s), 1622 (m), 1593 (s), 1572 (w), 1514 (w). MS (EI, 70 eV): *m*/*z*=406 (M$^+$, 100), 374 (88), 242 (45), 287 (17), 105 (59), 77 (17). HRMS (EI, 70 eV) calcd for $C_{23}H_{22}O_5N_2$ (406.15232, [M]$^+$): 406.152380.

*4.3.19. (2Z,2′Z)-Dimethyl 2,2′-(3,7,8-trimethyl-1H-benzo-[b][1,4]diazepine-2,4(3H,5H)-diylidene)diacetate (**9s**).* White solid, mp 224 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ=1.17–1.31 (br m, 3H, CH*Me*); 2.21 (s, 6H, Me); 2.95 (br), 3.18 (br), (ratio 0.6:1, 1H, *CH*Me); 3.69 (s, 6H, OMe); 4.68 (s, 2H, CH); 6.83 (br, 2H, Ar); 10.58 (br s, 2H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=12.6, 14.6 (CH*Me*); 19.0 (Me); 36.5, 47.0 (*CH*Me); 50.5 (OMe); 80.3, 83.7 (C-3); 122.4, 123.3 (CH_{Ar}); 128.1, 128.6 (C-5); 132.8, 133.6 (C-7); 160.2, 161.3 (C-4); 171.2 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3245(m), 3187 (m), 3015 (w), 2986 (w), 2949 (m), 2916 (w), 2882 (w), 2859 (w), 1659 (s), 1622 (m), 1597 (s), 1591 (w),

1514 (m). MS (EI, 70 eV): m/z=330 (M^+, 93), 298 (100), 266 (66), 251 (10), 239 (27), 210 (36). HRMS (ESI, 70 eV) calcd for $C_{18}H_{23}O_4N_2$ (331.16523, $[M+H]^+$): 331.16529. Anal. Calcd for $C_{18}H_{22}N_2O_4$ (330.378): C, 65.44; H, 6.71; N, 8.48. Found: C, 65.483; H, 6.922; N, 8.493.

*4.3.20. (2Z,2′Z)-Dimethyl 2,2′-(7,8-dichloro-3-methyl-1H-benzo[b][1, 4]diazepine-2,4(3H,5H)-diylidene)diacetate (**9t**).* Brown solid, mp 228–229 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$) δ=1.18–1.35 (br, 3H, CH*Me*); 2.97 (br), 3.15 (br), (1H, C*H*Me); 3.70 (s, 6H, OMe); 4.76 (s, 2H, CH); 7.13 (s, 2H, Ar); 10.63 (s, 2H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=12.5, 15.2 (CH*Me*); 36.4, 46.7 (*C*HMe); 50.8 (OMe); 82.7, 86.0 (C-3); 122.5, 123.5 (CH_{Ar}); 127.0, 127.8 (C-7); 130.4, 130.6 (C-5); 159.1, 160.2 (C-4); 171.0 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3246(w), 3189 (w), 3116 (w), 2991 (w), 2949 (m), 2837 (w), 1660 (s), 1621 (w), 1598 (s), 1569 (m), 1503 (m). MS (EI, 70 eV): m/z=374 (M^+, $^{37}Cl^{37}Cl$, 9), 372 (M^+, $^{35}Cl^{37}Cl$, 50), 370 (M^+, $^{35}Cl^{35}Cl$, 79), 342 ($^{37}Cl^{37}Cl$, 12), 340 ($^{35}Cl^{37}Cl$, 66), 338 ($^{35}Cl^{35}Cl$, 100), 310 ($^{37}Cl^{37}Cl$, 10), 308 ($^{35}Cl^{37}Cl$, 44), 306 ($^{35}Cl^{35}Cl$, 66), 250 (37), 231 (25). HRMS (ESI, 70 eV) calcd for $C_{16}H_{16}^{35}Cl_2O_4N_2$ (371.05599, M^+): 371.05652; calcd for $C_{16}H_{16}^{37}Cl_2O_4N_2$ (373.05335, M^+): 373.05362. Anal. Calcd for $C_{16}H_{16}Cl_2N_2O_4$ (371.215): C, 51.77; H, 4.34; N, 7.55. Found: C, 51.588; H, 4.525; N, 7.527.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi:10.1016/j.tet.2012.05.119.

References and notes

1. For recent applications, see: (a) Anandarajagopal, K.; Anbu Jeba Sunilson, J.; Illavarasu, A.; Thangavelpandian, A.; Kalirajan, N. *Int. J. Chem. Tech. Res.* **2010**, *2*, 46; (b) Han, Y.; Huynh, H. V. *Chem. Commun.* **2007**, 1089; (c) Sreekumar, R.; Padmakumar, R. *Synth. Commun.* **1998**, *28*, 1661.
2. For a recent application, see: Bhasin, K. K.; Arora, E.; Rishu, E.; Doomra; Nishima, Y.; Nagpal, Y.; Kumar, R.; Weigand, W.; Mehta, K. S. *Phosphorus, Sulfur, and Silicon* **2008**, *183*, 986.
3. For recent applications, see: (a) Goswami, P.; Das, B. *Synth. Commun.* **2010**, *40*, 1685; (b) Chen, X.; She, J.; Shang, Z.-C.; Wu, J.; Zhang, P. *Synth. Commun.* **2009**, *39*, 947; (c) Chen, X.; She, J.; Shang, Z.; Wu, J.; Wu, H.; Zhang, P. *Synthesis* **2008**, *21*, 3478.
4. Reviews of dianions: (a) Kaiser, E. M.; Petty, J. D.; Knutson, P. L. A. *Synthesis* **1977**, 509; (b) Thompson, C. M.; Green, D. *Tetrahedron* **1991**, *47*, 4223; (c) Thompson, C. M. *Dianion Chemistry in Organic Synthesis*; CRC: Boca Raton, FL, 1994; (d) Langer, P.; Freiberg, W. *Chem. Rev.* **2004**, *104*, 4125.
5. (a) Rahn, T.; Nguyen, V. T. H.; Dang, T. H. T.; Ahmed, Z.; Lalk, M.; Fischer, C.; Spannenberg, A.; Langer, P. *J. Org. Chem.* **2007**, *72*, 1957; (b) Rahn, T.; Dang, T. H. T.; Spannenberg, A.; Fischer, C.; Langer, P. *Org. Biomol. Chem.* **2008**, *6*, 3366; (c) Rahn, T.; Appel, B.; Baumann, W.; Jiao, H.; Fischer, C.; Börner, A.; Langer, P. *Org. Biomol. Chem.* **2009**, *7*, 1931.
6. (a) Vicentini, C. B.; Manfrini, M.; Mozzanti, M.; Manferdine, M.; Morelli, C. F.; Veronese, C. *Heterocycles* **2000**, *53*, 1285; See also: (b) Friedmann, H.; Hänsel, W. *Arch. Pharm. (Weinheim)* **1983**, *316*, 726.
7. (a) Furuhashi, A.; Aoki, K.; Sugimoto, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2157; (b) Yachevskii, D. S.; Chizhov, D. L.; Kodess, M. I.; Pashkevich, K. I. *Monatsh. Chem.* **2004**, *135*, 23.
8. Yamaguchi, M.; Shibato, K. *Tetrahedron* **1988**, *44*, 4767.
9. (a) Barrett, A. G. M.; Carr, R. A. E.; Finch, M. A. W.; Florent, J.-C.; Richardson, G.; Walshe, N. D. A. *J. Org. Chem.* **1986**, *51*, 4254; (b) Barrett, A. G. M.; Morris, T. M.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2272; for 5-aryl-3,5-dioxopentanoates, see for example: (c) Narasimhan, N. S.; Ammanamanchi, R. K. *J. Org. Chem.* **1983**, *48*, 3945; (d) Douglas, C. J.; Sklenicka, H. M.; Shen, H. C.; Mathias, D. S.; Degen, S. J.; Golding, G. M.; Morgan, C. D.; Shih, R. A.; Müller, K. L.; Seurer, L. M.; Johnson, E. W.; Hsung, R. P. *Tetrahedron* **1999**, *55*, 13683.
10. Poly(β-oxo)carboxylic acids (polyketides) occur in a variety of natural products and are of great pharmacological relevance: (a) Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380; (b) Koskinen, A. M. P.; Karisalmi, K. *Chem. Soc. Rev.* **2005**, *34*, 677; (c) *Römpp-Lexikon Naturstoffe*; Fugmann, B., Ed.; Georg Thieme: Stuttgart, New York, NY, 1997.
11. For a review, see: (a) Harris, T. M.; Harris, C. M. *Tetrahedron* **1977**, *33*, 2159; see also: (b) Murray, T. P.; Harris, T. M. *J. Am. Chem. Soc.* **1972**, *94*, 8253; (c) Harris, C. M.; Roberson, J. S.; Harris, T. M. *J. Am. Chem. Soc.* **1976**, *98*, 5380; (d) Harris, T. M.; Hay, J. V. *J. Am. Chem. Soc.* **1977**, *99*, 1631; (e) Hubbard, J. S.; Harris, T. M. *Tetrahedron Lett.* **1978**, *47*, 4601; (f) Sandifer, R. M.; Bhattacharya, A. K.; Harris, T. M. *J. Org. Chem.* **1981**, *46*, 2260; (g) Gilbreath, S. G.; Harris, C. M.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 6172; (h) Harris, T. M.; Boatman, S.; Hauser, C. R. *J. Am. Chem. Soc.* **1965**, *87*, 3186.
12. Kiegiel, J.; Jozwik, J.; Wozniak, K.; Jurczak, J. *Tetrahedron Lett.* **2000**, *41*, 4959.
13. (a) Reim, S.; Michalik, D.; Weisz, K.; Xiao, Z.; Langer, P. *Org. Biomol. Chem.* **2008**, *6*, 3079; (b) Erfle, S.; Reim, S.; Michalik, D.; Jiao, H.; Langer, P. *Eur. J. Org. Chem.* **2011**, 4367; (c) Erfle, S.; Rahn, T.; Bendrath, F.; Baumann, W.; Michalik, D.; Jiao, H.; Spannenberg, A.; Börner, A.; Langer, P. *Tetrahedron* **2011**, *67*, 8780.
14. (a) Bestic, M.; Blackford, M.; Reed, M. *J. Clin. Pharmacol.* **2009**, *49*, 130; (b) Martens, F. *Pharmakotherapie*; Springer: Hamburg, 2010; p 507.
15. (a) Ebert, T. A.; Taylor, R. A.; Downer, R. A.; Hall, F. R. *Pestic. Sci.* **1999**, *55*, 793; (b) Krieger, R. I. *Handbook of Pesticide Toxicology: Principles*, 2. Aufl.; Academic: San Diego, CA, 2001; 344ff.
16. Gondoh, A.; Koike, T.; Akita, M. *Inorg. Chim. Acta* **2011**, *374*, 489.
17. (a) Oppenheimer, J. H.; Schwartz, H. L.; Surks, M. I. *J. Clin. Invest.* **1972**, 2493; (b) Staudenherz, A.; Gessl, A.; Becherer, A. *Das kleine 1x1 der Thyreologie*, 2.Aufl.; Sandoz: Wien, 2004; 27f.
18. Oberdisse, E.; Hackenthal, E.; Kuschinsky, K. *Pharmakologie und Toxikologie*, 3. Aufl.; Springer: Berlin, 2002; 642ff; Darrell, J. H.; Garrod, L. P.; Waterworth, P. M. *J. Clin. Pathol.* **1968**, *21*, 202.
19. (a) Tinuper, P.; Aguglia, U.; Gastaut, H. *Epilepsia* **1986**, *27*, 518; (b) Poupaert, J. H.; Guiot, P.; Jacqmin, P.; Dumont, P. *Eur. J. Med. Chem.* **1989**, *23*, 417; (c) Meldrum, B. S. *J. Med. Chem.* **1981**, *24*, 644; (d) Gastaut, H. *Epilepsia* **1981**, *22*, 237; (e) Florence, K.; Manisha, L.; Kumar, B. A.; Ankur, K.; Kumar, M. A.; Ambikanandan, M. *J. Pharm. Sci.* **2011**, *100*, 2.