# Towards Metformin Prodrugs

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**Abstract:** The first examples of possible metformin prodrugs have been synthesized and characterized by spectroscopic methods. These five different types of chemically stable prodrugs were prepared from metformin and the corresponding halogenated promoieties. The products from unstable derivatives were also identified and reasons for the rearrangements are discussed.

**Key words:** metformin, prodrug, heterocycle, self-immolative spacer group, urethane

Metformin (**1**, Met, *N*,*N*-dimethylimidodicarbonimidic diamide) is a synthetic antidiabetic drug widely used to treat type 2 diabetes. Its precursor, galegine (isoamylene guanidine), was isolated in the late 1920's from Goat's rue (*Galega officinalis*), a plant which was used in medieval times as a prescription for intense urination that can accompany the disease nowadays called diabetes.[1,2] Metformin was clinically used for the first time in Europe in the 1950's together with two other structurally analogous antidiabetic drugs, phenformin and buformin. However, phenformin was withdrawn from the market in the 1970's due to its side effect of frequent lactic acidosis and increased cardiac mortality while a less lipophilic metformin with a short plasma half-life, unsubstantial metabolism, and protein binding proved to be safer. Metformin was finally approved for the treatment of diabetes by FDA (United States Food and Drug Administration) in the mid 1990s. At the moment, metformin is the most popular antidiabetic drug in both the United States and Europe with ca. 35 million prescriptions filled in the US only in 2006.

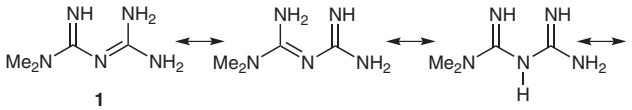


**Figure 1** Tautomeric stabilization of protonated metformin

Metformin is fully protonated under physiological conditions (Figure 1), and therefore slowly and incompletely absorbed from the upper intestine after oral administration. Together with a rapid kidney excretion, metformin suffers from the poor bioavailability and causes uncomfortable gastrointestinal side effects at effective doses.[3–5]

A typical solution for the above mentioned problems is to use the prodrug approach, in which an applicable bioreversible promoiety is attached to a parent drug. These pharmacologically inactive derivatives require a chemical and/or enzymatic degradation after the delivery to release the parent drug.

To our knowledge, prodrugs of metformin have not been reported, which is rather surprising, since typical requirements for prodrug derivatives of metformin are fulfilled: 1) widely used generic drug, 2) pharmacokinetic properties are far from perfect, and 3) there is functionality (here the $NH_2$ group) to attach promoieties. Most probably this is due to the complex chemistry of metformin with several nucleophilic electron pairs leading to susceptible formation of heteroaromatic rings after formation of classical N-substituted prodrugs, like *N*-acyls, *N*-alkoxycarbonyls or *N*-acyloxymethylcarbonyls.[6–10] Also characterization by NMR techniques is challenging, since metformin itself lacks protons bound to carbon atoms and protons at nitrogen atoms are to some extent pH dependent broad signals without any coupling information. Moreover, measuring of $^{13}C$ and $^{15}N$ NMR spectra is time consuming due to long relaxation times and $^{15}N$ also suffers from low natural abundance.

In this paper, we report for the first time chemically stable metformin derivatives to be used as prodrugs of metformin. Our strategy here was to demonstrate which kinds of metformin prodrug structures are stable, and not to prepare a series of compounds in which only one substituent is varied. The prepared compounds, collected in Scheme 1, are synthesized from metformin and the corresponding halogenated promoieties under basic conditions. According to our previous studies (described later in this paper) we realized that rigid spacer groups, like in the compounds **2** and **3**, or enough long alkyl chain, as in the compound **4**, are needed to avoid the above mentioned cyclization reactions. However, we were quite surprised when we found that the derivatives **5** and **6** were also stable crystalline compounds.

Nowadays, the most prominent rigid self-immolative spacer groups are based on an 1,6-elimination reaction. These spacer prodrugs release after the enzymatic hydrolysis of the amide or ester bond an intermediate that becomes electron-donating and initiates an electronic cascade, which leads to an elimination of either *p*-amino- or *p*-hydroxybenzylic leaving group, respectively, and the parent drug.[11–15] We used this prodrug method to prepare

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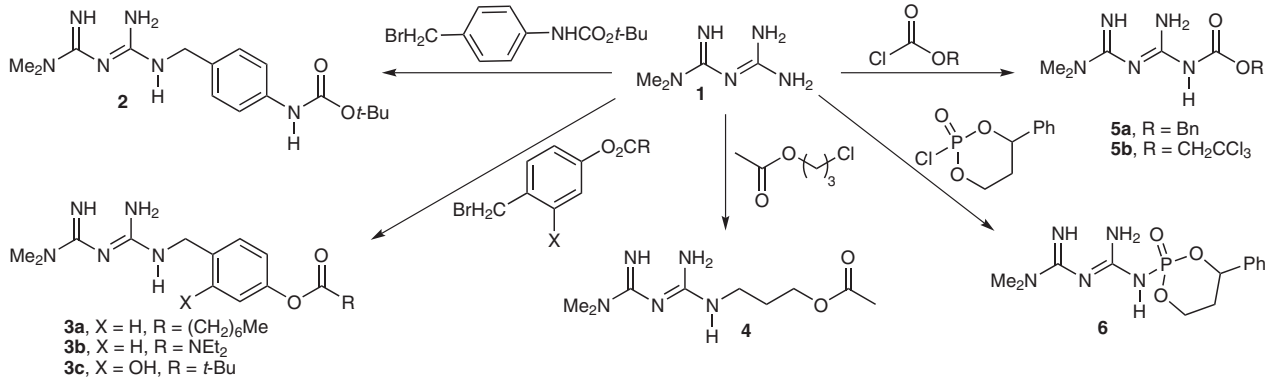
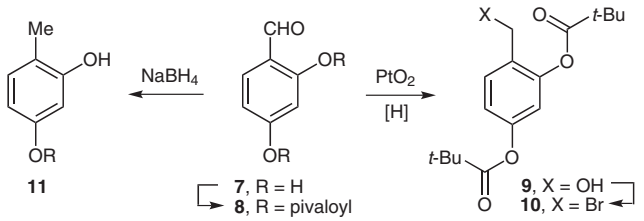



**Scheme 1** Designed and synthesized prodrugs of metformin (**1**)

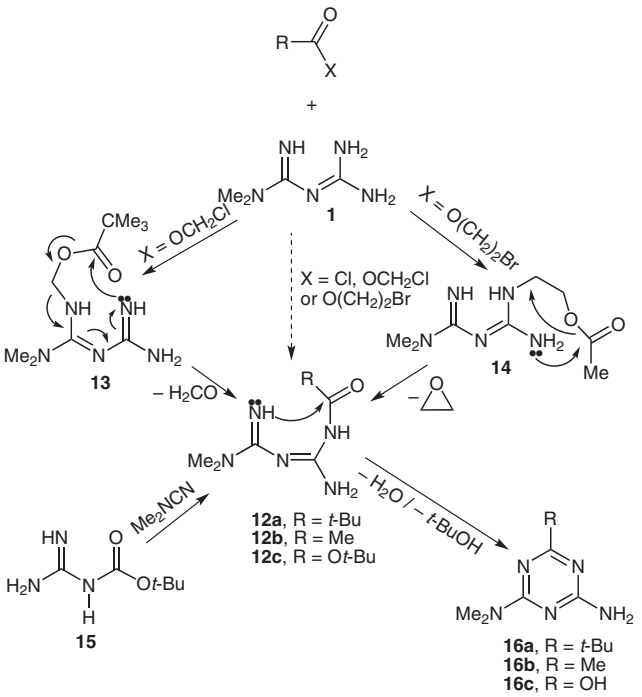
the aminocarbamic acid ester **2** and the esters **3a** and **3b** from selected halogenated benzyl derivatives and metformin in 20, 26 and 35% yield, respectively. In the case of the compound **3c**, the situation was more complex.

Surprisingly, the reduction of the aldehyde **8** to the alcohol **9** has not been previously described in the literature, not even with simple ester substituents, like acetyl and pivaloyl (Scheme 2). We realized the possible reason for that was probably the unexpected rearranged product **11** when we tried to reduce the aldehyde **8** with $NaBH_4$.[16] The correct product **9** was obtained by using Adam's catalyst ($PtO_2$) as the hydrogenation catalyst as shown in Scheme 2. Moreover, the coupling reaction of **10** to metformin afforded the monoester **3c**, possible due to anchimeric assistance of neighboring amino group of metformin.

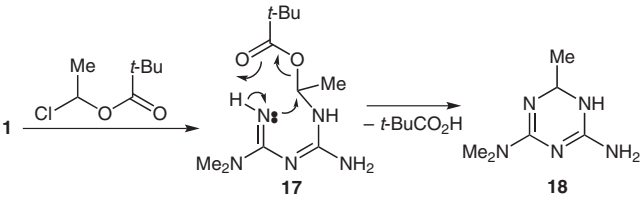



**Scheme 2** Reduction of 4-formylphenyl ester **8** with $NaBH_4$ yielded the compound **11** whereas desired compound **9** was obtained by hydrogenation with $PtO_2$ as catalyst

The prepared compound **4** is an uncommon choice for a prodrug due to poor leaving properties of the propyl chain. Actually, the propyl moiety was the first stable alkyl derivative in the series, which we managed to attach to metformin. This is because both acetyloxymethyl ester, which is a frequently used promoiety,[17] and acetyloxyethyl ester derivatives yielded in our hands aromatic 1,3,5-triazines **16a** and **16b**, respectively, as shown in Scheme 3. According to this and since compound **4** was stable, we expected that the corresponding methyl and ethyl intermediates **13** and **14** were formed first and rearranged further to the intermediate **12**, which was finally cyclized to the energetically favored aromatic end products **16a** and **16b**, respectively. On the other hand, direct attack of nucleophilic nitrogen of metformin to electrophilic carbonyl group of prodrug promoiety (route **1** → **12** in Scheme 3) is not favored, since the alkyloxy units are poor leaving groups. However, if the route **1** → **12** is predominant, the chloride or bromide anion must be the leaving group being formed after elimination of $H_2CO$ from $ClCH_2O$ group or an unusual ethyloxide from the corresponding ethyl derivative. Based on the result from the reaction with 1-chloroethyl pivalate (Scheme 4) the formation of the intermediate **12** via **13** or **14** is more liable.




**Scheme 3** Proposed reaction mechanisms of rearrangement of metformin derivatives to 1,3,5-triazines **16a–c**



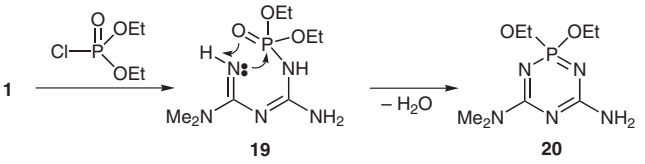

**Scheme 4** Proposed reaction mechanism of metformin and 1-chloroethyl pivalate to 1,3,5-triazine **18**

The cyclic products were also obtained with 1-chloroethyl pivalate (Scheme 4), which is currently the most ideal acyloxyalkyl promoiety due to its safe ethanal elimination product compared to formaldehyde obtained from the corresponding methyl derivative. In this case, the formed cyclic end product **18** was explained only by the expected alkylation product **17** synthesized from metformin and 1-chloroethyl pivalate.[18] However, the product **17** was not stable due to elimination of pivalic acid, which in this case was a good leaving group. The same elimination reaction was also observed in the reaction of the dimethylcyanamide and boc-guanidine **15** (Scheme 3) which led to the heteroaromatic product **16c**.[19]

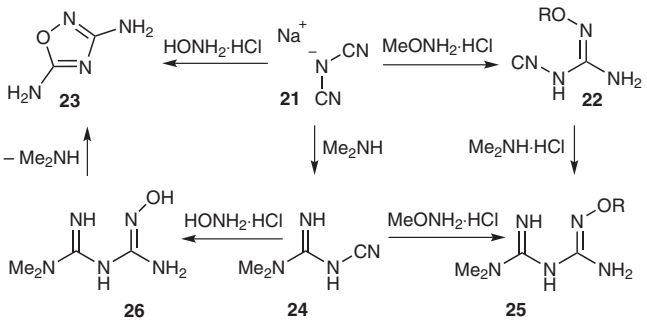
Unexpectedly, we were able to prepare also the traditional urethane prodrugs **5a**,**b** (Scheme 1) in 26 and 23% yields, respectively, while the amides **12** prepared from metformin and an acid derivative, for example, X = Cl, were unstable as shown in Scheme 3. In the case of urethanes **5a**,**b**, our first trials afforded also the heteroaromatic product **16** (R = OH) before we realized that cyclization occurred gradually during and after the chromatographic separation when the urethane derivative was in the base form. However, white crystalline products were obtained with reasonable yields when the crude product was first acidified with HCl gas and then purified using normal phase flash chromatography.

The last example, the compound **6** in the Scheme 1, belongs to the prodrug family of cyclic phosphates. The cyclic phosphates are cytochrome P450 (CYP)-selective prodrugs designed to be activated predominantly in the liver.[20,21] The cyclic phosphate **6** was synthesized from metformin and the corresponding cyclic chlorophosphate with 33% yield. Interestingly, it seems that only the cyclic phosphate derivatives, like the compound **6**, are stable since we tried to prepare also acyclic derivatives with poor success. As mentioned previously, the tendency for the stable, energetically favored heteroaromatic ring was strong since normally an extremely stable P=O bond from product **19** was broken up and the 1,3,5,2-triazaphosphinine **20** was formed after elimination of water (Scheme 5).

Prodrugs of metformin were also tried to prepare from selected nitriles as shown in Scheme 6 and previously in Scheme 3. In most cases we obtained either cyclic end products, a complicate mixture of products, or the starting materials did not react. Actually, the only prodrug candidate of metformin, which we managed to prepare by following this strategy, was the compound **25** (R = Me) either starting from sodium cyanamide (**21**) via $N^1$-cyano-$N^2$-methoxyguanidine (**22**) or $N^1$,$N^1$-dimethyl-$N^3$-cyanoguanidine (**24**) as shown in Scheme 6. In the case of *O*-pivaloylhydroxylamine (R = *t*-Bu) the reaction was extremely slow and with hydroxylamine, according to $^{13}C$ NMR (δ = 170.1, 168.5) and mass (*m*/*z* = 100.9, M + H$^+$) spectra results, the heteroaromatic 3,5-diamino-1,2,4-oxadiazole **23**[22,23] was obtained.




**Scheme 5** Proposed reaction mechanism of metformin and diethyl chlorophosphate to 1,3,5,2-triazaphosphinine **20**




**Scheme 6** Proposed reaction mechanisms of the compounds **22** and **24**

In conclusion, the traditional methods to prepare more lipophilic prodrugs of metformin, like N-acetylation and N-alkoxycarbonylation, lead to rearrangement and internal cyclization of metformin derivatives producing five or six-membered heterocycles. To avoid the cyclization behavior of metformin derivatives, cyclic phosphate and urethane prodrugs were synthesized. Long and rigid spacer groups, like self-immolative 1,6-elimination spacer groups, were also used successfully in the syntheses of metformin prodrugs. Although prodrugs of metformin have not been described in literature previously, probably due to distinctive chemistry of metformin, novel approaches to enhance the bioavailability and to decrease variable adverse effects of this widely used antidiabetic drug are unquestionably needed.

Commercially available reagents and solvents were used without further purification. Reactions were monitored by using 60 $F_{245}$ TLC plates. Chromatographic separations were performed on Shimadzu preparative HPLC system (Shimadzu Corporation, Kyoto, Japan) attached to UV-VIS detector (wavelength 254 nm) by using a Kromasil® 100 Å column (C8, 150 × 20 mm, 5 μM), at a flow rate of 12 mL/min. $^1H$, $^{13}C$, and $^{31}P$ NMR spectra were recorded on a Bruker Avance 500 spectrometer (Bruker Biospin, Fällanden, Switzerland) operating at 500, 126, and 202 MHz, respectively. TMS was used as an internal standard. Elemental analyses (C, H, N) were performed on a ThermoQuest CE Instruments EA 1110-CHNSO elemental analyzer (CE Instruments, Milan, Italy). Mass spectra were obtained on a Finnigan LCQ quadropole ion trap mass spectrometer (Finnigan MAT, San Jose, CA, USA) equipped with an electrospray ionization source. The analytical and spectroscopical data for the known compounds **8**,[24] **15**,[25] **16a**,[26] **16b**, **18**,[27,28] and **24**[29] were not provided. The benzyl halides used in syntheses of the compounds **2** and **3a**,**b** were prepared in a similar manner to that of the benzyl bromide **10** given below.

**1,1-Dimethylimidodicarbonimidic Diamide (1)**

A mixture of 1,1-dimethylimidodicarbonimidic diamide hydrochloride (4.20 g, 25.5 mmol) in aq 1 M NaOH (30 mL) was stirred at r.t. for 30 min. $H_2O$ was evaporated in vacuo and the residue was dissolved in MeOH (50 mL). The solvent was evaporated and the residue was redissolved in MeOH (20 mL). NaCl formed was filtered out of the solution and the filtrate was evaporated to yield basic metformin as a white solid compound **1**; yield: 3.25 g (99%).

**Benzyl Derivatives of Metformin; General Procedure**

A solution of the bromo derivative in anhyd DMF or MeCN was added dropwise to a solution of metformin (**1**) in anhyd DMF at 0 °C under argon. The reaction mixture was stirred at r.t. for 2–18 h and the solvent was evaporated in vacuo. The residue was purified by flash chromatography eluting with MeOH–$CH_2Cl_2$ (1:10).

***tert*-Butyl 4-[(3-(*N*,*N*-Dimethylcarbamimidoyl)guanidino)methyl]phenyl Carbamate (2)**

Prepared from *tert*-butyl 4-(bromomethyl)phenylcarbamate (0.4 g, 1.4 mmol) in DMF (2 mL) and metformin (**1**; 0.27 g, 2.10 mmol) in DMF (8 mL) with an 18 h reaction time. Compound **2** was obtained as a yellowish oil; yield: 90 mg (20%).

$^1$H NMR (DMSO-$d_6$): δ = 1.47 (s, 3 H), 2.94 (s, 6 H), 4.24 (s, 2 H), 7.18–7.20 (m, 2 H), 7.39–7.41 (m, 2 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 28.09 (q, 3 C), 38.03 (q, 2 C), 45.21 (t), 78.83 (s), 117.94 (d), 127.62 (d), 132.21 (d), 138.40 (s), 152.71 (s), 156.48 (s), 159,65 (s).

ESI-MS: $m/z$ = 335.2 $(M + H)^+$.

Anal. Calcd for $C_{16}H_{26}N_6O_2$·4.8DMSO·2.8$H_2O$: C, 30.04; H, 5.61; N, 13.14. Found: C, 29.91; H, 6.06; N, 13.45.

**4-{[3-(*N*,*N*-Dimethylcarbamimidoyl)guanidino]methyl}phenyl Octanoate (3a)**

Prepared from 4-(bromomethyl)phenyl octanoate (0.3 g, 0.96 mmol) in MeCN (4 mL) and metformin (**1**; 0.19 g, 1.44 mmol) in MeCN (16 mL) with an 18 h reaction time. Compound **3a** was obtained as a yellowish oil; yield: 90 mg (26%).

$^1$H NMR (DMSO-$d_6$): δ = 0.87 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H), 1.21–1.38 (m, 8 H), 1.63 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H), 2.56 (t, $^3J_{H,H}$ = 7.4 Hz, 2 H), 2.92 (s, 6 H), 4.19 (s, 2 H), 7.09–7.13 (m, 2 H), 7.20–7.26 (m, 2 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 14.39 (q), 22.49 (t), 24.80 (t), 28.80 (t, 2 C), 31.56 (t), 37.93 (t), 38.49 (q), 45.76 (t), 115.45 (d), 122.04 (d), 129.10 (d), 129.96 (d), 156.93 (s), 160.16 (s).

ESI-MS: $m/z$ = 362.2 $(M + H)^+$.

Anal. Calcd for $C_{19}H_{31}N_5O_2$·2.1DMSO: C, 43.42; H, 5.95; N, 13.03. Found: C, 42.83; H, 5.90; N, 13.03.

**4-{[3-(*N*,*N*-Dimethylcarbamimidoyl)guanidino]methyl}phenyl Diethylcarbamate (3b)**

Prepared from 4-(Bromomethyl)phenyl diethylcarbamate (0.87 g, 3.05 mmol) and metformin (**1**; 0.79 g, 6.10 mmol) in anhyd MeCN (20 mL) with a 2 h reaction time to obtain compound **3b**; yield: 295 mg (29%).

$^1$H NMR ($CDCl_3$–$CD_3OD$): δ = 0.97 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H), 1.03 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H), 2.81 (s, 6 H), 3.14 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H), 3.23 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H), 4.12 (s, 2 H), 6.81 (d, $^3J_{H,H}$ = 8.52 Hz, 2 H), 7.09 (m, 2 H).

$^{13}$C NMR ($CDCl_3$–$CD_3OD$): δ = 12.63, 13.49, 37.84, 41.61, 41.91, 45.65, 121.43, 128.27, 134.82, 150.15, 154.37, 155.65, 159.80.

ESI-MS: $m/z$ = 335.2 $(M + H)^+$.

**4-[(3-(*N*,*N*-Dimethylcarbamimidoyl)guanidino)methyl]-3-hydroxyphenyl Pivalate (3c)**

Prepared from 4-(bromomethyl)-1,3-phenylene bis(2,2-dimethylpropanoate) (**10**; 0.33 g, 0.89 mmol) in DMF (2 mL) and metformin (**1**; 0.14 g, 1.07 mmol) in DMF (8 mL) with an 18 h reaction time. After flash chromatography eluting with MeOH–$CH_2Cl_2$ (1:20), compound **3c** was obtained as a yellowish oil; yield: 30 mg (8%).

$^1$H NMR (DMSO-$d_6$): δ = 1.33 (s, 3 H), 3.02 (s, 6 H), 4.39 (s, 2 H), 6.48–6.53 (m, 2 H), 7.18–7.21 (m, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 27.43 (q, 3 C), 39.98 (q, 2 C), 41.42 (t), 43.33 (s), 109.78 (d), 113.20 (d), 123.09 (s), 131.10 (d), 152.81 (s), 157.34 (s), 158.47 (s), 161.49 (s), 178.63 (s).

ESI-MS: $m/z$ = 336.4 $(M + H)^+$.

Anal. Calcd for $C_{16}H_{25}N_5O_3$·1.0MeOH·1.5$CH_2Cl_2$·0.5$H_2O$: C, 44.10; H, 6.30; N, 13.90. Found: C, 44.08; H, 6.43; N, 14.19.

**3-[3-(*N*,*N*-Dimethylcarbamimidoyl)guanidino]propyl Acetate (4)**

A mixture of the plain metformin (**1**; 0.1 g, 0.77 mmol), NaI (0.23 g, 1.55 mmol), and 3-chloropropyl acetate (0.19 mL, 1.55 mmol) in anhyd acetone (10 mL) was refluxed for 6 h under argon. The solvent was removed under reduced pressure and the residue was purified by flash chromatography eluting with MeOH–$CH_2Cl_2$ (0.5:10) to afford the compound **4** as a yellowish oil; yield: 130 mg (73%).

$^1$H NMR (DMSO-$d_6$): δ = 1.89–1.99 (m, 2 H), 2.07 (s, 3 H), 3.13 (s, 6 H), 3.33–3.39 (m, 2 H), 4.13–4.18 (m, 2 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 21.19 (q), 29.18 (t), 37.35 (q, 2 C), 37.92 (t), 65.68 (t), 156.25 (s), 157.22 (s), 171.55 (s).

ESI-MS: $m/z$ = 230.1 $(M + H)^+$.

Anal. Calcd for $C_9H_{19}N_5O_2$·0.87MeOH·1.1$CH_2Cl_2$·0.81HCl: C, 31.19; H, 6.18; N, 18.42. Found: C, 31.19; H, 6.18; N, 18.42.

**[(*N*′,*N*′-Dimethylguanidino)iminomethyl]carbamic Acid Benzyl Ester (5a)**

Benzyl chloroformate (0.85 g, 5.0 mmol) was added dropwise to a solution of plain metformin (**1**; 1.13 g, 8.8 mmol) in anhyd MeCN (50 mL) at 0 °C under argon. The mixture was stirred at 0 °C for 2.5 h. The mixture was filtered and the half of the filtrate was treated with dry HCl gas for few min and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with MeOH–$CH_2Cl_2$ (1:10) to afford the compound **5a** as a white solid; yield: 195 mg (26%).

$^1$H NMR ($CD_3OD$): δ = 3.09 (s, 6 H), 5.23 (s, 2 H), 7.37 (m, 5 H).

$^{13}$C NMR ($CD_3OD$): δ = 38.32 (q), 39.09 (q), 68.94 (t), 129.33 (d), 129.54 (d), 129.57 (d), 136.56 (s), 153.72 (s), 155.42 (s), 160.30 (s).

ESI-MS: $m/z$ = 263.3 $(M)^+$.

Anal. Calcd for $C_{12}H_{17}N_5O_2$·1.0HCl·0.5$H_2O$: C, 46.68; H, 6.20; N, 22.68. Found: C, 46.86; H, 6.20; N, 22.30.

**[(*N*′,*N*′-Dimethylguanidino)iminomethyl]carbamic Acid 2,2,2-Trichloroethyl Ester (5b)**

2,2,2-Trichloroethyl chloroformate (1.63 g, 7.8 mmol) was added dropwise to a solution of plain metformin (**1**; 2.0 g, 15.5 mmol) in anhyd MeCN (50 mL) at 0 °C under argon. The mixture was stirred at 0 °C for 2 h. The mixture was filtered and the filtrate was treated with dry HCl gas for few min and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with MeOH–$CH_2Cl_2$ (1:10) to afford the compound **5b** as a white solid; yield: 610 mg (23%).

$^1$H NMR ($CD_3OD$): δ = 3.10 (s, 6 H), 4.94 (s, 2 H).

$^{13}$C NMR ($CD_3OD$): δ = 37.94 (q), 38.82 (q), 75.70 (t), 96.03 (s), 153.04 (s), 154.44 (s), 161.65 (s).

Anal. Calcd for $C_7H_{12}Cl_3N_5O_2 \cdot 1.0HCl \cdot 0.4MeOH$: C, 46.68; H, 6.20; N, 22.68. Found: C, 46.86; H, 6.20; N, 22.30.

**[($N^1$,$N^1$-Dimethylcarbamimidoyl)guanidino]-4-phenyl-1,3,2-dioxaphosphoramidate (6)**

Freshly distilled $POCl_3$ (0.12 mL, 1.31 mmol) in cold anhyd $Et_2O$ (15 mL) was added dropwise to a solution of 1-phenylpropane-1,3-diol (0.2 g, 1.31 mmol) and $Et_3N$ (0.36 mL, 2.60 mmol) in anhyd $Et_2O$ (5 mL) at 0 °C under argon. The mixture was stirred at r.t. for 2 h. The precipitate was filtered out of the mixture and washed thoroughly with $Et_2O$ (3 × 10 mL). The filtrate was concentrated in vacuo to obtain the cyclic phosphoryl chloride as a brownish oily mixture of diastereomers (55:45, 0.34 g). Due to partial decomposition, the product was not purified further.

$^1$H NMR ($CDCl_3$): δ (major diastereomer) = 2.04–2.13 (m, 1 H), 2.47–2.76 (m, 1 H), 4.52–4.77 (m, 2 H), 5.57 (td, $^3J_{H,H}$ = 11.9 Hz, $^3J_{H,P}$ = 2.3 Hz, 1 H), 7.34–7.50 (m, 5 H); δ (minor diastereomer) = 2.17–2.47 (m, 2 H), 4.52–4.77 (m, 2 H), 5.74–5.80 (m, 1 H), 7.34–7.50 (m, 5 H).

$^{31}$P NMR ($CDCl_3$): δ (major diastereomer) = –1.85; δ (minor diastereomer) = –2.37.

The plain metformin (**1**; 1.51 mmol) in anhyd MeCN (10 mL) was added dropwise to a solution of the above prepared cyclic phosphoryl chloride (0.36 g, 1.56 mmol) and 1-methylimidazole (0.1 mL, 1.25 mmol) in anhyd MeCN (10 mL) at 0 °C under argon. The mixture was stirred at r.t. overnight, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with MeOH–$CH_2Cl_2$ (1:10) solution to afford the compound **6** as a yellowish oil; yield: 165 mg (33%).

$^1$H NMR (DMSO-$d_6$): δ = 1.92–2.11 (m, 2 H), 2.96 (s, 6 H), 4.36–4.15 (m, 2 H), 5.28–5.33 (m, 1 H), 6.42 (s, 1 H), 6.89 (s, 1 H), 7.09 (s, 1 H), 7.31–7.42 (m, 5 H), 7.57 (s, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 34.45 (dt, $^3J_{C,P}$ = 4.5 Hz), 36.71 (q), 66.53 (dt, $^2J_{C,P}$ = 7.0 Hz), 79.25 (dt, $^2J_{C,P}$ = 7.0 Hz), 125.92 (d), 128.42 (d), 128.87 (d), 140.99 (s), 159.69 (s), 162.48 (s).

$^{31}$P NMR (DMSO-$d_6$): δ = 2.65.

ESI-MS: $m/z$ = 326.1 $(M + H)^+$.

Anal. Calcd for $C_{13}H_{20}N_5O_3P \cdot 1.0MeOH \cdot 0.5CH_2Cl_2 \cdot 0.2H_2O$: C, 43.17; H, 6.22; N, 17.36. Found: C, 43.53; H, 6.57; N, 17.00.

**4-(Hydroxymethyl)-1,3-phenylene Bis(2,2-dimethylpropanoate) (9)**

To a solution of **8**[24] (1.22 g, 4 mmol) in propan-2-ol (50 mL) was added 10% Pd/C (100 mg) and the mixture was hydrogenated at 1.0 bar pressure for 3 h. Catalyst was filtered off through Celite, washed with propan-2-ol (10 mL) and the filtrates were evaporated to dryness in vacuo to give **9** (1.03 g, 84%) as a colorless oil. This product was used without further purification in the next step.

$^1$H NMR ($CDCl_3$): δ = 1.34 (s, 9 H), 1.37 (s, 9 H), 4.54 (s, 2 H), 6.82 (d, $^4J_{H,H}$ = 2.1 Hz, 1 H), 6.98 (dd, $^4J_{H,H}$ = 2.1 Hz, 1 H), 7.47 (d, $^3J_{H,H}$ = 8.4 Hz, 1 H).

$^{13}$C NMR $CDCl_3$): δ = 27.14 (q), 27.20 (q), 39.17 (s), 39.36 (s), 60.12 (t), 115.88 (d), 119.39 (d), 129.9 (d), 149.09 (s), 151.18 (s), 176.72 (s), 177.30 (s).

**4-(Bromomethyl)-1,3-phenylene Bis(2,2-dimethylpropanoate) (10)**

The conversion of the alcohol **9** into the corresponding bromide **10** was performed using a modification of the method reported by Lee and Hwang.[30] A solution of $Ph_3P$ (0.31 g, 1.17 mmol) in anhyd $CH_2Cl_2$ (10 mL) was added to a solution of **9** (0.30 g, 0.97 mmol) in anhyd $CH_2Cl_2$ (10 mL) at –20 °C under argon followed by *N*-bromosuccinimide (0.21 g, 1.17 mmol) in anhyd $CH_2Cl_2$ (10 mL). The mixture was stirred at r.t. for 2 h and quenched by the addition of hexane (100 mL). The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc–hexane (1:5) to yield the compound **10** as a yellowish oil, yield: 0.35 (97%).

$^1$H NMR ($CDCl_3$): δ = 1.34 (s, 9 H), 1.41 (s, 9 H), 4.38 (s, 2 H), 6.92–6.96 (m, 2 H), 7.39 (d, $^3J_{H,H}$ = 8.3 Hz, 1 H).

$^{13}$C NMR ($CDCl_3$): δ = 27.18 (q), 27.27 (q), 29.46 (t), 39.26 (s), 39.55 (s), 116.72 (d), 119.34 (d), 127.11 (d), 131.24 (s), 149.83 (s), 151.82 (s), 176.18 (s), 176.58 (s).

**4-Amino-6-dimethylamino[1,3,5]triazin-2-ol (16c)**

Boc-guanidine **15**[25] (0.8 g, 5 mmol) and dimethylcyanamide (5 mL, 61.3 mmol) were heated at 90 °C for 6 h. The mixture was filtered and washed with EtOAc (2 × 10 mL) to give the white solid product **16c**; yield: 0.18 g (23%).

$^1$H NMR (DMSO-$d_6$): δ = 3.01 (s, 6 H), 7.06 (br s, 2 H), 10.53 (br s, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 36.15 (q), 156.60 (s), 159.10 (s), 165.08 (s).

ESI-MS: $m/z$ = 156.2 $(M + H)^+$.

**2,2-Diethoxy-$N^4$,$N^4$-dimethyl-[1,3,5,2]triazaphosphinine-4,6-diamine (20)**

Freshly distilled $POCl_3$ (0.52 mL, 3.61 mmol) in cold anhyd MeCN (5 mL) was added dropwise to a solution of plain metformin (**1**; 0.31 g, 2.39 mmol) and pyridine (0.29 mL, 3.59 mmol) in anhyd MeCN (20 mL) at –10 °C under argon. The mixture was stirred at r.t. for 1 h and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography eluting with MeOH–$CH_2Cl_2$ (0.5:10) to yield the compound **20** as a yellowish solid; yield: 0.30 g (47%).

$^1$H NMR ($CDCl_3$): δ = 1.35 (t, $^3J_{H,H}$ = 7.3 Hz, 6 H), 3.10 (s, 3 H), 3.34 (s, 3 H), 4.02 (q, $^2J_{H,H}$ = 15.0 Hz, $^3J_{H,H}$ = 7.3 Hz, 4 H).

$^{13}$C NMR ($CDCl_3$): δ = 15.78 dq ($^3J_{C,P}$ = 7.8 Hz), 37.76 (dq, $^4J_{C,P}$ = 3.8 Hz), 38.03 (dq, $^4J_{C,P}$ = 3.8 Hz), 64.25 (dt, $^2J_{C,P}$ = 5.9 Hz), 155.58 (s), 158.67 (ds, $^2J_{C,P}$ = 5.8 Hz).

$^{31}$P NMR ($CDCl_3$): δ = 22.53.

ESI-MS: $m/z$ = 248.1 $(M + H)^+$.

**1-Cyano-2-methoxyguanidine (22)**

Sodium dicyanamide (1.1 g, 12.36 mmol) and methoxylamine hydrochloride (1.03 g, 12.36 mmol) in anhyd EtOH (20 mL) were stirred at r.t. overnight. NaCl was filtered out of the solution and the solvent was evaporated in vacuo. The product **22** (1.25 g, 98%) was recrystallized from $H_2O$.

$^1$H NMR (DMSO-$d_6$): δ = 3.48 (s, 3 H), 7.44 (br s, 2 H), 10.52 (br s, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 64.24 (q), 117.43 (s), 162.85 (s).

ESI-MS: $m/z$ = 113.4 $(M - H)^-$.

Anal. Calcd for $C_3H_6N_4O \cdot 0.38H_2O$: C, 29.79; H, 5.63; N, 46.32. Found: C, 30.16; H, 5.19; N, 45.90.

**[1,2,4]Oxadiazole-3,5-diamine (23)**

*Method A*: $N^1$,$N^1$-Dimethyl-$N^3$-cyanoguanidine (**24**;[29] 0.4 g, 3.57 mmol), $NH_2OH \cdot HCl$ (0.37 g, 5.35 mmol) and $Et_3N$ (0.75 mL, 5.35 mmol) were stirred in anhyd EtOH (10 mL) at r.t. overnight. The solution was filtered and the solvent was evaporated in vacuo. The residue was purified by preparative HPLC on reversed phase Kromasil® 100 Å (C8) column using MeCN–$H_2O$ (3:7) as eluent to obtain the white solid compound **23**; yield: 0.28 g (78%).

$^1$H NMR (DMSO-$d_6$): δ = 5.52 (br s, 2 H), 7.24 (br s, 2 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 168.46 (s), 170.08 (s).

ESI-MS: $m/z$ = 100.9 $(M + H)^+$.

Anal. Calcd for $C_2H_4N_4O{\cdot}1.85EtOH{\cdot}0.1Me_2NH$: C, 36.07; H, 8.02; N, 29.52. Found: C, 36.12; H, 7.61; N, 29.21.

*Method B*:[28,29] Sodium dicyanamide (**21**; 0.5 g, 5.62 mmol) and $NH_2OH{\cdot}HCl$ (0.39 g, 5.62 mmol) were stirred in anhyd EtOH (10 mL) at r.t. overnight. NaCl was filtered out of the solution and the solvent was evaporated under reduced pressure to obtain the product **23**; yield: 0.26 g (45%). The chemical shifts of the NMR spectra as well as the ESI-MS spectrum were identical to spectra of compound **23** obtained by the Method A.

Anal. Calcd for $C_2H_4N_4O{\cdot}0.27HCl$: C, 21.85; H, 3.92; N, 50.97. Found: C, 22.25; H, 4.02; N, 50.81.

**$N^1$,$N^1$-Dimethylcarbamimidoyl-$N^4$-methoxyguanidine (25)**

*Method A*: $N^1$,$N^1$-dimethyl-$N^3$-cyanoguanidine (**24**;[29] 0.5 g, 4.46 mmol), methoxyamine hydrochloride (0.74 g, 8.92 mmol), and pyridine (0.72 mL, 8.92 mmol) were refluxed in anhyd EtOH (10 mL) for 6 h. The solvent was evaporated under reduced pressure and the residue was purified by preparative HPLC on reversed phase Kromasil® 100 Å (C8) column using MeCN–$H_2O$ (3:7) as eluent to obtain **25** (0.47 g, 66%) as a light yellow oil.

$^1$H NMR (DMSO-$d_6$): δ = 2.95 (s, 6 H), 3.69 (s, 3 H), 7.52 (br s, 3 H), 8.41 (br s, 1 H).

$^{13}$C NMR (DMSO-$d_6$): δ = 38.32 (q), 64.40 (q), 157.17 (s), 157.61 (s).

ESI-MS: $m/z$ = 160.0 $(M + H)^+$.

Anal. Calcd for $C_5H_{13}N_5O{\cdot}1.0MeOH{\cdot}0.6$pyridine: C, 30.19; H, 7.18; N, 29.34. Found: C, 30.49; H, 7.13; N, 29.14.

*Method B*: $N^1$-Cyano-$N^2$-methoxyguanidine (**22**; 0.5 g, 4.38 mmol), dimethylamine hydrochloride (0.36 g, 4.38 mmol), and $Et_3N$ (0.61 mL, 4.38 mmol) were refluxed in anhyd EtOH (10 mL) overnight. The solvent was evaporated in vacuo and the residue was purified by preparative HPLC on reversed phase Kromasil® 100 Å (C8) column using MeCN–$H_2O$ (3:7) as eluent to obtain the impure compound **25** (0.32 g, 46%) as a light yellow oil. The chemical shifts of the NMR spectra as well as the ESI-MS spectrum were identical to the spectra of compound **25** obtained by Method A.

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