SUPPORTING INFORMATION

Diphenyl phosphonate inhibitors for the urokinase-type plasminogen activator: optimisation of the P4 position
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Table of Contents

✓ Synthetic procedures and spectroscopic data for intermediates 8 and 9. S2-S6
✓ Figures used to determine the inhibition type of compound 4 S7-S8
✓ Figures of compound 3a in the active pockets of uPA, plasmin, FXa, thrombin, trypsin and tPA. S9-S11
✓ Purity data for target compounds S12
Solid phase synthesis of the capped dipeptide 8

Attachment of carboxylic acids to the 2-chlorotrityl resin (1g, 1.2-1.4 mmol):

Fmoc-Ala-OH (1.5 eq.) and dry DIPEA (4 eq.) were added in dry DCM (10ml). This mixture was shaken for 2 hours at room temperature. Then the resin was washed 3 times with DCM/MeOH/DIPEA (17:2:1), 3 times with DCM, 2 times with DMF and 2 times with ether.

Removal of the Fmoc protecting group:
Piperidine (8 ml/20%) in DMF was added to the resin. The mixture was shaken for 30 min. The solvent was removed and the deprotection reaction was repeated for 30 min. The solvent was removed and the resin was washed with DMF (3x) and DCM (2x).

Coupling of Fmoc-D-Ser(OtBu)-OH:
Amino acid (1.5 eq.), TBTU (2 eq.) and triethylamine (4 eq.) in 10 ml DMF were added to the resin. The resin was shaken for 2 hours. Then the resin was washed with DMF (3x) and DCM (2x). For the synthesis of 3a Z-D-Ser(OtBu)-OH was used.

Coupling of different sulfonyl chlorides and acids:
Sulfonyl chloride (1.5 eq.), collidine (2 eq.) and 10 ml dry DCM were added to the resin. The resin was shaken for 2 hours. Then the resin was washed with DMF (3x) and DCM (2x).

For the acids the same procedure was used as the coupling described for Fmoc-D-Ser(OtBu)-OH.

Removal of the dipeptide from the resin:
The peptidyl resin was treated at room temperature with AcOH/MeOH/DCM (2:2:6) for 2 hours. The resin was removed by filtration and washed 3 times with the cleaving mixture and 2 times with hexane.

The solvent was evaporated to obtain the crude product. All the products were purified by flash chromatography.

[(N-Benzoylcarbonyl-O-tert-butyl)-D-seryl]-L-alanine (8a)
Yield: 63%. 1H NMR (CD2OD) δ 1.2 (s, 9H), 1.4 (d, 3H), 3.6 (m, 2H), 4.2 (m, 1H), 4.4 (m, 1H), 5.1 (s, 2H), 7.2-7.4 (m, 5H), 8.0 (s, 1H). MS (ESI): m/z = 389 (M^+Na).

[(N-Benzenesulfonyl-O-tert-butyl)-D-seryl]-alanine (8b)
Yield: 47%. 1H NMR (CDCl3) δ 1.1 (s, 9H), 1.3 (d, 3H), 3.2 (m, 1H), 3.6 (m, 2H), 4.3 (m, 2H), 7.4 (m, 2H), 7.5 (m, 1H), 7.8 (m, 2H). MS (ESI): m/z = 373 (M^+).

[(N-a-Toluenesulfonyl-O-tert-butyl)-D-seryl]-alanine (8c)
Yield: 49%. 1H NMR (CDCl3) δ 1.1 (s, 9H), 1.4 (d, 3H), 3.45 (dd, J = 6.4 Hz and J = 22 Hz, 1H), 3.55 (dd, J = 6.4 Hz and J = 22 Hz, 1H), 3.9 (m, 1H), 4.3 (s, 2H), 4.5 (q, 1H), 7.3-7.4 (m, 5H).

MS (ESI): m/z = 387 (M^+).

[(N-Benzylcarbonyl-O-tert-butyl)-D-seryl]-L-alanine (8d)
Yield: 28%. 1H NMR (MeOD) δ 1.2 (s, 9H), 1.4 (d, 3H), 3.7-3.8 (m, 2H), 4.5 (m, 1H), 4.8 (m, 1H), 7.5 (m, 2H), 7.6 (m, 1H), 7.9 (d, 2H). MS (ESI): m/z = 335 (M^+).

[(N-1-Naphtalenesulfonyl-O-tert-butyl)-D-seryl]-L-alanine (8e)
Yield: 33%. 1H NMR (CD2OD) δ 1.1 (s, 9H), 1.4 (m, 3H), 3.2 (dd, J = 5.6 Hz and J = 9.2 Hz, 1H), 4.1 (t, 1H), 4.4 (m, 1H), 7.7-7.9 (m, 3H), 8.1 (m, 1H), 8.3 (m, 1H), 8.4 (m, 1H), 9.0 (m, 1H). MS (ESI): m/z = 423 (M^+).
[(N-2-Thiophenesulfonyl-O-tert-butyl)-D-seryl]-L-alanine (8f)
Yield: 11%. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.1 (s, 9H), 1.3 (d, 3H), 3.3 (dd \(J = 6.0\) Hz and 9.2 Hz, 1H), 3.5 (dd \(J = 6.0\) Hz and 9.2 Hz, 1H), 3.9 (t, 1H), 4.3 (m, 1H), 7.1 (dd \(J = 4.8\) Hz and 3.6 Hz), 7.58 (dd \(J = 1.3\) and 3.7, 1H), 7.7 (dd \(J = 1.6\) and 4.8, 1H). MS (ESI): \(m/z = 379 (M^+1)\).

[(N-Thienyl-O-tert-butyl)-D-seryl]-L-alanine (8g)
Yield: 73%. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.1 (s, 9H), 1.3 (d, 3H), 3.5 (dd \(J = 6.0\) Hz and 9.2 Hz, 1H), 4.1 (dd \(J = 7.2\) Hz and 14.5 Hz, 1H), 4.4 (m, 1H), 4.7 (m, 1H), 7.1 (dd \(J = 4.0\) Hz and 4.8 Hz, 1H), 7.58 (dd \(J = 0.8\) and 4.8 Hz, 1H), 7.7 (dd \(J = 0.8\) and 3.6, 1H). MS (ESI): \(m/z = 365 (M^+Na)\).

[(N-1-Adamantoyl-O-tert-butyl)-D-seryl]-L-alanine (8h)
Yield: 24%. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.2 (s, 9H), 1.4 (d, 3H), 1.7 (m, 6H), 1.8 (m, 6H), 2.0 (m, 3H), 3.5 (dd \(J = 4.4\) Hz and 8.8 Hz), 4.5 (m, 2H), 6.7 (d, 1H), 7.4 (d, 1H). MS (ESI): \(m/z = 393 (M^+1)\).

[(N-p-Methoxybenzenesulfonyl-O-tert-butyl)-seryl]-L-alanine (8i)
Yield: 57%. \(^1\)H NMR (CD\(_3\)OD) \(\delta\) 1.0 (s, 9H), 1.1 (d, 3H), 3.33 (dd, \(J = 6\) Hz and \(J = 9.2\) Hz), 3.49 (dd, \(J = 6\) Hz and \(J = 9.2\) Hz), 3.8 (s, 3H), 4.0 (m, 1H), 4.2 (m, 1H), 7.0 (m, 2H), 7.8 (m, 2H). MS (ESI): \(m/z = 401 (M^+1)\).

[(N-p-Bromobenzene-1-sulfonyl-O-tert-butyl)-D-seryl]-alanine (8j)
Yield: 38%. \(^1\)H NMR (CD\(_3\)OD) \(\delta\) 1.1 (s, 9H), 1.3 (d, 3H), 3.42 (dd, \(J = 6\) Hz and \(J = 9.2\) Hz, 1H), 3.52 (dd, \(J = 6\) Hz and \(J = 9.2\) Hz, 1H), 3.9 (m, 1H), 4.2 (m, 1H), 7.6-7.9 (dm, 4H). MS (ESI): \(m/z = 451 (M^+1)\).

[(N-p-Cyanobenzene-1-sulfonyl-O-tert-butyl)-D-seryl]-alanine (8k)
Yield: 58%. \(^1\)H NMR (CD\(_3\)OD) \(\delta\) 1.0 (s, 9H), 1.3 (d, 3H), 3.4 (m, 1H), 3.6 (m, 1H), 4.0 (m, 1H), 4.2 (m, 1H), 7.6 (m, 2H), 7.9 (m, 2H). MS (ESI): \(m/z = 396 (M^+1)\).

[(N-o-Methylbenzoyl-O-tert-butyl)-D-seryl]-L-alanine (8l)
Yield: 42%. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.2 (s, 9H), 1.4 (d, 3H), 2.3 (s, 3H), 3.4 (dd \(J = 4.4\) Hz and 8.8 Hz, 1H), 3.8 (dd \(J = 4.4\) Hz and 8.8 Hz, 1H), 4.5 (m, 1H), 4.8 (m, 1H), 7.1 (d, 2H), 7.5 (d, 1H), 7.6 (d, 1H), 7.7 (d, 2H). MS (ESI): \(m/z = 351 (M^+1)\).

[(N-o-Methylbenzoyl-O-tert-butyl)-D-seryl]-L-alanine (8m)
Yield: 71%. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.2 (s, 9H), 1.4 (d, 3H), 2.3 (s, 3H), 3.4 (dd \(J = 4\) Hz and 8.4 Hz, 1H), 3.8 (dd \(J = 4\) Hz and 8.4 Hz, 1H), 4.5 (m, 1H), 4.8 (m, 1H), 7.2 (m, 2H), 7.3-7.6 (m, 4H). MS (ESI): \(m/z = 351 (M^+1)\).

Coupling of the peptide 8 to phosphonate 14
PS-carbodiimide (0.33 mmol, 172.5 mg, 2 eq.), peptide (0.25 mmol, 1.5 eq.) and HOBT (0.29 mmol, 37.6 mg, 1.7 eq.) in dry DCM were stirred for 10 min prior to addition of...
the phosphonate (1 eq., 0.16 mmol, 100 mg). The mixture was shaken at rt overnight. PS-Trisamine (5 eq.) was added for 2 h at rt prior to filtration. The solvent was evaporated and the crude product purified with flash chromatography.

**Diphenyl 1-[(N-benzyloxy carbonyl-O-tert-butyl-D-seryl)-L-alanyl]amino-2-(4-(N,N'-bis(tert-butyloxy carbonyl) guanidino) phenyl) ethane phosphonate. (9a)**

Yield: 52 %. $^1$H NMR (CDCl$_3$) $\delta$ 1.1 (m, 9H), 1.3 (m, 3H), 3.0- 3.4 (m, 2H), 3.7 (m, 1H), 4.2 (m, 1H), 4.4 (m, 1H), 4.7- 5.1 (m, 3H), 5.7 (m, 1H), 7.1- 7.4 (m, 19 H). MS (ESI): $m/z = 982$ (M$^{+}$Na$^+$).

**Diphenyl 1- [((benzenesulfonylamino-O-tert-butyl-D-seryl)-L-alanyl]amino-2-[4-(N,N'-bis(tert-butyloxy carbonyl)guanidino)phenyl]ethane phosphonate. (9b)**

Yield: 32 %. $^1$H NMR (CDCl$_3$) $\delta$ 1.1 (d, 9H), 1.2 (m, 3H), 1.5 (d, 18H), 3.2 (m, 2H), 4.1 (m, 0.5H$^a$), 4.2 (m, 0.5H$^b$), 5.0 (m, 1H), 5.5 (s, 1H), 7.0- 7.4 (m, 19H), 10.1 (s, 1H), 11.5 (s, 1H). MS (ESI): $m/z = 982$ (M$^{+}$Na$^+$).

**Diphenyl 1- [((N-benzoyle amino-O-tert-butyl-D-seryl)-L-alanyl]amino-2-[4-(N,N'-bis(tert-butyloxy carbonyl)guanidino)phenyl]ethane phosphonate. (9c)**

Yield: 20 %. $^1$H NMR (CDCl$_3$) $\delta$ 1.1 (d, 9H), 1.2 (m, 3H), 1.5 (d, 18H), 3.0 (m, 1H), 3.3 (m, 2H), 3.4 (m, 1H), 4.1 (d, 2H), 4.2 (m, 1H), 5.0 (m, 1H), 5.5 (d, 1H), 7.0- 7.5 (m, 21H), 10.1 (d, 1H), 10.5 (d, 1H). MS (ESI): $m/z = 979$ (M$^{+}$Na$^+$).

**Diphenyl 1- [((N-benzylamino-O-tert-butyl-D-seryl)-L-alanyl]amino-2-[4-(N,N'-bis(tert-butyloxy carbonyl)guanidino)phenyl]ethane phosphonate (9d)**

Yield: 26%. $^1$H NMR (CDCl$_3$) $\delta$ 1.1- 1.2 (m, 9H), 1.3 (d, 3H), 1.5 (d, 18H), 3.0 (m, 1H), 3.4 (m, 2H), 3.7 (d, 2H), 3.9- 4.0 (dm, 1H), 4.4- 4.6 (m, 2H), 5.1 (m, 1H), 7.0- 7.5 (m, 21 H), 10.3 (d, 1H), 10.6 (s, 1H). MS (ESI): $m/z = 951$ (M$^{+}$Na$^+$).

**Diphenyl 1- [(N-naftalenesulfonylamino-O-tert-butyl-D-seryl)-L-alanyl]amino-2-[4-(N,N'-bis(tert-butyloxy carbonyl)guanidino)phenyl]ethane phosphonate (9e)**

Yield: 45%. $^1$H NMR (CDCl$_3$) $\delta$ 0.7- 0.9 (m, 9H), 1.0 (m, 3H), 1.5 (d, 18H), 3.0- 3.5 (m, 3H), 3.5 (m, 2H), 4.1 (m, 1H), 5.0 (m, 1H), 6.8- 8.2 (m, 21H), 10.2 (d, 1H), 11.5 (s, 1H). MS (ESI): $m/z = 1036$ (M$^{+}$Na$^+$).

**Diphenyl 1- [(N-2-thiophenesulfonyl-O-tert-butyl-D-seryl)-L-alanyl]amino-2-[4-(N,N'-bis(tert-butyloxy carbonyl)guanidino)phenyl]ethane phosphonate. (9f)**

Yield: 16%. $^1$H NMR (CDCl$_3$) $\delta$ 1.1 (2s, 9H), 1.3 (m, 3H), 1.5 (m, 18H), 3.4 (m, 2H), 3.7 (m, 2H), 4.2 - 4.4 (m, 2H), 5.1 (m, 1H), 5.8 (m, 1H), 7.0- 7.6 (m, 17 H), 10.3 (s, 1H), 11.6 (s, 1H). MS (ESI): $m/z = 993$ (M$^{+}$Na$^+$).

**Diphenyl 1- [(N-thienyl-O-tert-butyl-D-seryl)-L-alanyl]amino-2-[4-(N,N'-bis(tert-butyloxy carbonyl)guanidino)phenyl]ethane phosphonate. (9g)**

Yield: 65%. $^1$H NMR (CDCl$_3$) $\delta$ 1.1 (2s, 9H), 1.3 (m, 3H), 1.5 (m, 18H), 3.0 (m, 1H), 3.3 (m, 1H), 3.4 (m, 1H), 3.8 (m, 1H), 4.3-4.5 (m, 2H), 5.1 (m, 1H), 7.0- 7.6 (m, 17 H). MS (ESI): $m/z = 957$ (M$^{+}$Na$^+$).

**Diphenyl 1- [(N-1-adamantanyl-O-tert-butyl-D-seryl)-L-alanyl]amino-2-[4-(N,N'-bis(tert-butyloxy carbonyl)guanidino)phenyl]ethane phosphonate. (9h)**

Yield: 57%. $^1$H NMR (CDCl$_3$) $\delta$ 1.1 (2s, 9H), 1.3 (m, 3H), 1.5 (m, 18H), 1.7 (m, 6H), 1.8 (s, 6H), 2.0 (m, 3H), 3.1 (m, 1H); 3.3 (m, 2H), 3.7 (m, 1H), 4.3 (m, 1H), 4.4 (m, 1H), 5.1 (m, 1H), 7.0- 7.6 (m, 14H). MS (ESI): $m/z = 988$ (M$^{+}$).
Diphenyl 1-[(N-p-methoxybenzenesulfonylamino-O-tert-butyl-D-seryl)-L-alanyl]amino-2-[4-(N,N′-bis(tert-butylloxycarbonyl)guanidino)phenyl]ethanephosphonate. (9i)
Yield: 52%. $^1$H NMR (CDCl$_3$) $\delta$ 1.0 (m, 9H), 1.2 (d, 3H), 1.5 (d, 18H), 3.1 (m, 1H), 1.5 (m, 2H), 3.6-3.7 (dm, 2H), 3.8 (m, 3H), 4.3-4.5 (m, 2H), 5.0 (m, 1H), 5.7 (d, 1H), 6.9-8.0 (m, 18H) MS (ESI): $m/z$ = 1017.60 (M$^+$Na$^+$).

Diphenyl 1-[(N-p-bromobenzenesulfonylamino-O-tert-butyl-D-seryl)-L-alanyl]amino-2-[4-(N,N′-bis(tert-butylloxycarbonyl)guanidino)phenyl]ethanephosphonate (9j)
Yield: 42%. $^1$H NMR (CDCl$_3$) $\delta$ 1.0 (m, 9H), 1.3 (d, 3H), 1.5 (d, 18H), 3.1 (m, 1H), 3.3 (m, 2H), 3.8-4.0 (dm, 2H), 4.3 (m, 2H), 5.0 (m, 1H), 5.8-6.0 (m, 1H), 7.1-7.8 (m, 18H) MS (ESI): $m/z$ = 1067 (M$^+$Na$^+$).

Diphenyl 1-[(N-p-cyanobenzenesulfonylamino-O-tert-butyl-D-seryl)-L-alanyl]amino-2-[4-(N,N′-bis(tert-butylloxycarbonyl)guanidino)phenyl]ethanephosphonate (9k)
Yield: 50 %.$^1$H NMR (CDCl$_3$) $\delta$ 1.0-1.2 (d, 9H), 1.3 (m, 3H), 1.5 (m, 18H), 3.0 (m, 1H), 3.4 (m, 1H), 3.6-3.8 (dm, 2H), 4.0-4.3 (m, 2H), 5.0 (m, 1H), 7.0-7.6 (m, 18H), 10.3 (s, 1H), 11.5 (s, 1H). MS (ESI) $m/z$ = 1012.7 (M$^+$Na$^+$).

Diphenyl 1-[(N-p-methylbenzoyl-O-tert-butyl-D-seryl)-L-alanyl]amino-2-[4-(N,N′-bis(tert-butylloxycarbonyl)guanidino)phenyl]ethanephosphonate (9l)
Yield: 56%. $^1$H NMR (CDCl$_3$): $\delta$ 1.1 (s, 9H), 1.3 (m, 3H), 1.5 (m, 18H), 2.3 (2s, 3H), 3.0 (m, 1H), 3.3 (m, 1H), 3.5 (m, 1H), 3.8 (m, 1H), 4.5 (m, 2H), 5.1 (m, 1H), 7.0-7.6 (m, 18H). MS (ESI): $m/z$ = 943 (M$^+$H$^+$).

Diphenyl 1-[(N-o-methylbenzoyl-O-tert-butyl-D-seryl)-L-alanyl]amino-2-[4-(N,N′-bis(tert-butylloxycarbonyl)guanidino)phenyl]ethanephosphonate (9m)
Yield: 52%. $^1$H NMR (CDCl$_3$): $\delta$ 1.1 (s, 9H), 1.3 (m, 3H), 1.5 (m, 18H), 2.3 (2s, 3H), 3.1 (m, 1H), 3.3 (m, 1H), 3.5 (m, 1H), 3.7 (m, 1H), 4.4 (m, 2H), 5.1 (m, 1H), 7.0-7.6 (m, 18H). MS (ESI): $m/z$ = 943 (M$^+$H$^+$).

Diphenyl 1-[(N-o,o-dimethylbenzoyl-O-tert-butyl-D-seryl)-L-alanyl]amino-2-[4-(N,N′-bis(tert-butylloxycarbonyl)guanidino)phenyl]ethanephosphonate (9n)
Yield: 34%. $^1$H NMR (CDCl$_3$) $\delta$ 1.1 (s, 9H), 1.3 (m, 3H), 1.5 (m, 18H), 2.3 (2s, 3H), 3.0 (m, 1H), 3.3 (m, 1H), 3.5 (m, 1H), 3.8 (m, 1H), 4.6 (m, 2H), 5.1 (m, 1H), 7.0-7.6 (m, 18H). MS (ESI): $m/z$ = 957 (M$^+$H$^+$).

Di-(4-acetamidophenyl) 1-[(N-benzyloxycarbonyl-O-tert-butyl-D-seryl)-L-alanyl]amino-2-[4-(N,N′-bis(tert-butylloxycarbonyl)guanidino)phenyl]ethanephosphonate (paracetamol analogue of 9a)
Yield: 40%. $^1$H NMR (CDCl$_3$) $\delta$ 1.1 (d, 9H), 1.3 (m, 3H), 1.5 (d, 18H), 2.0 (s, 6H), 2.7 (m, 1H), 3.2 (m, 1H), 3.4 (m, 1H), 3.6 (m, 1H), 4.2 (m, 1H), 4.4 (m, 1H), 4.9 (m, 1H), 7.0-7.6 (m, 18H). MS (ESI): $m/z$ = 957 (M$^+$H$^+$).
5.1 (m, 2H), 7.1-7.6 (m, 17H), 8.7 (m, 2H), 10.2 (d, 1H), 11.5 (s, 1H). MS (ESI): m/z = 1095 (M+Na).
Data used to demonstrate irreversible properties of compound 4

I

II

III
IV

This figure shows that compound 4 is an irreversible inhibitor for uPA (I), and tPA (IV) and a reversible one for thrombin (III) and perhaps plasmin (II). Curve A is the control reaction in absence of inhibitor and curve B is the absorbance (405 nm) after dilution of the enzyme-inhibitor mixture with substrate. (The exact procedure is described in the experimental part as “determination of the inhibition type”).
Figures of compound 3a in the active pockets of uPA, plasmin, FXa, thrombin, trypsin and tPA.

uPA:

Plasmin:
FXa:

Thrombin:
Trypsin

These models were obtained by minimizing 3a as a flexible ligand in a rigid enzyme pocket (see experimental section). The following pdb files were used: uPA (1EJN), plasmin (1BUI), FXa (1FAX), thrombin (1GJ5), trypsin (1MAX) and tPA (1RTF).
Purity data for target compounds

Purity was verified using two diverse HPLC systems using respectively a mass and UV-detector. Water (A) and ACN (B), were used as eluents. LC-MS spectra were recorded on an Agilent 1100 Series HPLC system using a Alltech Prevail C18 column (2.1 X 50 mm, 3 μm) coupled with an Esquire 3000plus as MS detector and a 5-100% B, 20 min-gradient was used with a flow rate from 0.2 ml/min. 0.1% formic acid was added to solvent A and B. Reversed phase HPLC was run on a Gilson instrument equipped with an Ultrasphere ODS column (4.6 X 250 mm, 5 μm). A 10-100% B, 35 min gradient was used with a flow rate from 1ml/min. 0.1% TFA was added to solvent A and B. 214 nm was used as wavelength.

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<tr>
<th>Compound</th>
<th>HPLC (214 nm) t_r (% integration)</th>
<th>HPLC (254 nm) t_r (% integration)</th>
<th>LC-MS t_r (% integration)</th>
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<td>3a</td>
<td>19.98 (100)</td>
<td></td>
<td>14.4 (100)</td>
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<td>3b</td>
<td>19.24 (97)</td>
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