Supplementary Information

Targefrin: a potent agent targeting the ligand binding domain of EphA2

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Table of Contents.

- Supplementary Table S1 reports mass spectroscopy data of investigated compounds. Page S3
- Supplementary Table S2 reports tested agents with 4-phenyl-L-phenylalanine fixed in position 4 and relative $K_d$ values (nM) from ITC. Page S5
- Supplementary Table S3 reports tested agents with 4-(2-Methylphenyl)-L-phenylalanine fixed in position 4 and relative $K_d$ values (nM) from ITC. Page S6
- Supplementary Figure S1 reports the synthetic scheme used to prepare monomeric peptides. Page S7
- Supplementary Figure S2 reports the synthetic scheme used to prepare dimeric peptides. Page S8
- Supplementary Figure S3 reports the synthetic scheme used to prepare targefrin-motif. Page S9
- Supplementary Figure S4 reports the synthetic scheme used to prepare targefrin-dimer-motif. Page S10
- Supplementary Figure S5 reports the synthetic scheme used to prepare targefrin-PTX. Page S11
- Supplementary Figure S6 reports the synthetic scheme used to prepare targefrin-dimer-PTX. Page S12
- Supplementary Figure S7 reports the synthetic scheme used to prepare targefrin-dimer-TAMRA. Page S13
- Supplementary Figure S8 reports HPLC traces of keys compounds. Page S14
- Supplementary Figure S9 reports pharmacokinetics studies. Page S16
- Supplementary Figure S10 reports uncropped western blots that generated the data in Figures 4, 5 and 8. Page S17
- Supplementary Figure S11 reports cell migration assay of BxPC3 at 12 h (relative to Figure 9). Page S20
• Supplementary Figure S12 reports cell viability assay of MIA PaCa-2 treated with targefrin or ephrinA1-Fc. Page S21
• Supplementary Figure S13 reports chemistry analysis for mice treated with targefrin-dimer. Page S22
• Supplementary Figure S14 reports repeated doses toxicity studies with targefrin-dimer-PTX versus PTX alone. Page S23
Table S1. Mass-spectrometry data of investigated compounds. All the compounds were analyzed using an Agilent 6545 QTOF LC/MS instrument.

| ID   | Sequence                                                                 | Calcd [M]  | Obs. [M+H]^+ (m/z) |
|------|--------------------------------------------------------------------------|------------|---------------------|
| 147B4 2 | H$_2$N-YSA-Bip-PDSVPFRP-COH$_2$                                          | 1456.7080  | 1457.7160           |
| 152B6 3 | H$_2$N-YSA-(Thyronine)-PDSVPFRP-COH$_2$                                   | 1488.7038  | 1489.7111           |
| 152A5 4 | H$_2$N-YSA-(2-MeO-Bip)-PDSVPFRP-COH$_2$                                   | 1486.7245  | 1487.7335           |
| 152A11 5 | H$_2$N-YSA-(4-Cl-Bip)-PDSVPFRP-COH$_2$                                    | 1490.6750  | 1491.6783           |
| 152A12 6 | H$_2$N-YSA-(2,6DiMeO-Bip)-PDSVPFRP-COH$_2$                               | 1516.7351  | 1517.7389           |
| 152B1 7 | H$_2$N-YSA-(4-Me-Bip)-PDSVPFRP-COH$_2$                                   | 1470.7296  | 1471.7347           |
| 152B2 8 | H$_2$N-YSA-(2-Me-Bip)-PDSVPFRP-COH$_2$                                   | 1470.7296  | 1471.7366           |
| 152C11 9 | H$_2$N-YSA-(2-CF$_3$-Bip)-PDSVPFRP-COH$_2$                               | 1524.7013  | 1525.7113           |
| 152D1 10 | H$_2$N-YSA-(2Me-4MeO-Bip)-PDSVPFRP-COH$_2$                               | 1500.7402  | 1501.7491           |
| 152A1 11 | MorphAcAcid-YSA-Bip-PDSVPFRP-COH$_2$                                     | 1583.7773  | 1584.7852           |
| 152A9 12 | PiperazineAcAcid-YSA-Bip-PDSVPFRP-COH$_2$                                | 1582.7932  | 1583.7960           |
| 152A7 13 | H$_2$N-WSA-Bip-PDSVPFRP-COH$_2$                                          | 1479.7299  | 1480.7402           |
| 152A4 14 | H$_2$N-(5-OH-Trp)SA-Bip-PDSVPFRP-COH$_2$                                 | 1495.7248  | 1496.7326           |
| 152C7 15 | H$_2$N1Nal-SA-Bip-PDSVPFRP-COH$_2$                                       | 1490.7347  | 1491.7431           |
| 152C8 16 | H$_2$N-2Nal-SA-Bip-PDSVPFRP-COH$_2$                                      | 1490.7347  | 1491.7432           |
| 152C9 17 | H$_2$N-(Me-Tyr)-SA-Bip-PDSVPFRP-COH$_2$                                  | 1470.7296  | 1471.7389           |
| 152C10 18 | H$_2$N-(2-NO$_2$-Phe)SA-Bip-PDSVPFRP-COH$_2$                             | 1485.7041  | 1486.7136           |
| 152D5 19 | H$_2$N-(2-NH$_2$-Phe)-SA-Bip-PDSVPFRP-COH$_2$                            | 1455.7299  | 1456.7380           |
| 152D12 20 | H$_2$N-(pyridyl-Ala)-SA-Bip-PDSVPFRP-COH$_2$                             | 1441.7143  | 1442.7207           |
| 152C5 21 | H$_2$N-Y-L-A-Bip-PDSVPFRP-COH$_2$                                        | 1482.7660  | 1483.7757           |
| 152D8 22 | H$_2$N-Y-T-A-Bip-PDSVPFRP-COH$_2$                                        | 1470.7296  | 1471.7438           |
| 152A8 23 | H$_2$N-YSA-Bip-PDS-Chg-PFRP-COH$_2$                                      | 1496.7452  | 1497.7493           |
| 152D6 24 | PiperazAcAcid-(2Nal)-L-A-(2-CF$_3$-Bip)-PDS-Chg-P-(4Cl-Phe)-RP-COH$_2$  | 1784.8457  | 1785.8530           |
| 152D11 25 | PiperazAcAcid-(2NH$_3$-Phe)-SA-(2-CF$_3$-Bip)-PDS-Chg-PFRP-COH$_2$       | 1689.8279  | 1690.8374           |
| 152E1 26 | PiperazAcAcid-(2NH$_2$-Phe)-L-A-(2-CF$_3$-Bip)-PDS-Chg-PFRP-COH$_2$      | 1715.8800  | (z = 3) 573.3014    |
|         |                                                                         |            | (z = 2) 858.9478    |
| Targefrin (152E2) 27 | PiperazAcAcid-(2NH$_2$-Phe)-L-A-(2-CF$_3$-Bip)-PD-A-Chg-PFRP-COH$_2$ | 1699.8850  | (z = 3) 567.9696    |
|         |                                                                         |            | (z = 2) 851.4519    |
| Targefrin-dimer 152E3 28 | [PiperazAcAcid-(2-NH$_2$-Phe)-L-A-(2-CF$_3$-Bip)-PD-A-Chg-PFRP]$_2$-K-COH$_2$ | 3625.8848  | (z = 5) 726.3855    |
|         |                                                                         |            | (z = 4) 907.7288    |
|         |                                                                         |            | (z = 3) 1209.9690   |
| 152E5 29 | [PiperazAcAcid-(2-NH$_2$-Phe)-L-A-(2-CF$_3$-Bip)-PD-A-Chg-PFRP-(β-Ala)]$_2$-K-COH$_2$ | 3653.9161  | (z = 5) 731.9890    |
|         |                                                                         |            | (z = 4) 914.7353    |
|         |                                                                         |            | (z = 3)             |
| 152E6 30                  | [PiperazAcAcid-(2-NH₂-Phe)-L-A-(2-CF₃-Bip)-PD-A-Chg-PFRP-(GABA)]₂-K-CONH₂ | 3681.9474  |
|---------------------------|------------------------------------------------------------------------------|------------|
|                           | (z = 5) 737.5954 (z = 4) 921.7432 (z = 3) 1228.6543                         |            |
| Targetfrin- PTX 152F1     | [PiperazAcAcid-(2-NH₂-Phe)-L-A-(2-CF₃-Bip)-PD-A-Chg-PFRP-G- (Linker)-PTX | 2972.4522  |
|                           | (z = 4) 744.1197 (z = 3) 991.8244 (z = 2) 1487.2337                      |            |
| Targetfrin- dimer- PTX 152E4 | [PiperazAcAcid-(2-NH₂-Phe)-L-A-(2-CF₃-Bip)-PD-A-Chg-PFRP]₂-KGK-(Linker)-PTX | 4898.4519  |
|                           | (z = 6) 817.5799 (z = 5) 980.8969 (z = 4) 1225.6179 (z = 3) 1633.8200 |            |
| Targetfrin- dimer- TAMRA 152E7 | [PiperazAcAcid-(2-NH₂-Phe)-L-A-(2-CF₃-Bip)-PD-A-Chg-PFRP]₂-KGK-(Linker)-TAMRA | 4461.3179  |
|                           | (z = 7) 638.3418 (z = 6) 744.3911 (z = 5) 893.0693 (z = 4) 1116.0822 |            |
| 152B8 31                  | PiperazineAcAcid-YSA-Bip-PDS-Chg-PFRP-CONH₂                                 | 1622.8245  |
|                           | 1623.8279                                                                 |            |
| 152D7 32                  | PiperazAcAcid-YSA-(Bip)-PDS-Chg-P-(4Cl-Phe)-RP-CONH₂                      | 1656.7856  |
|                           | 1657.7900                                                                 |            |
| 152D9 33                  | PiperazAcAcid-Y-L-A-(Bip)-PDS-Chg-PFRP-CONH₂                              | 1648.8766  |
|                           | 1649.8886                                                                 |            |
| 152D10 34                 | PiperazAcAcid-(2Nal)-SA-(Bip)-PDS-Chg-PFRP-CONH₂                         | 1656.8453  |
|                           | 1657.8520                                                                 |            |
| 152B12 35                 | PiperazineAcAcid-YSA-(2Me-Bip)-PDS-Chg-PFRP-CONH₂                        | 1636.8402  |
|                           | 1637.8480                                                                 |            |
| 152C12 36                 | PiperazAcAcid-(2Nal)-L-A-(2Me-Bip)-PDS-Chg-P-(4Cl-Phe)-RP-CONH₂        | 1730.8740  |
|                           | (z = 2) 866.9478                                                           |            |
| 152D2 37                  | PiperazAcAcid-Y-L-A-(2Me-Bip)-PDS-Chg-P-(4Cl-Phe)-RP-CONH₂               | 1696.8533  |
|                           | 1697.8605                                                                 |            |
Table S2. Tested agents with 4-phenyl-L-phenylalanine fixed in position 4 and relative K\textsubscript{d} values (nM) from ITC.

| ID      | R\textsubscript{1} | R\textsubscript{2} | R\textsubscript{3} | R\textsubscript{4} | R\textsubscript{5} | Kd (nM) - ITC |
|---------|---------------------|---------------------|---------------------|---------------------|---------------------|----------------|
| 152B8 (31) | ![Structure](image) | ![Structure](image) | ![Structure](image) | ![Structure](image) | H               | 54             |
| 152D7 (32) | ![Structure](image) | ![Structure](image) | ![Structure](image) | ![Structure](image) | Cl              | 68             |
| 152D9 (33) | ![Structure](image) | ![Structure](image) | ![Structure](image) | ![Structure](image) | H               | 39             |
| 152D10 (34) | ![Structure](image) | ![Structure](image) | ![Structure](image) | ![Structure](image) | H               | 74             |
Table S3. Tested agents with 4-(2-Methylphenyl)-L-phenylalanine fixed in position 4 and relative $K_d$ values (nM) from ITC.

| ID     | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $K_d$ (nM) - ITC | IC50 (nM) |
|--------|-------|-------|-------|-------|-------|-----------------|-----------|
| 152B12 (35) | ![Structure](structure_152B12.png) | ![Structure](structure_152B12.png) | ![Structure](structure_152B12.png) | ![Structure](structure_152B12.png) | H | 8.6 | 22.7 |
| 152C12 (36) | ![Structure](structure_152C12.png) | ![Structure](structure_152C12.png) | ![Structure](structure_152C12.png) | ![Structure](structure_152C12.png) | Cl | --- | 30.8 |
| 152D2 (37) | ![Structure](structure_152D2.png) | ![Structure](structure_152D2.png) | ![Structure](structure_152D2.png) | ![Structure](structure_152D2.png) | Cl | 49 | 16.5 |
Figure S1. Synthetic scheme for the synthesis of Targefrin. Conditions: (a) Rink Amide resin + 3 equiv. of Fmoc-Pro-OH, 3 equiv. of DIC, 1 equiv. of OximaPure, in 4.5 mL of DMF. Reaction for 5 min at 90°C in the microwaved-assisted Liberty Blue peptide synthesizer. (b) Fmoc deprotection with 20% N-methylpiperidine in DMF twice for 3 min at 90°C in the microwaved-assisted Liberty Blue peptide synthesizer; (c) Peptides growth using previous conditions on Liberty Blue system; (d) TFA/TIS/water/phenol (94:2:2:2), 5 h, rt.
Figure S2. Synthetic scheme for the synthesis of Targefrin-dimer. Conditions: (a) Rink Amide resin + 3 equiv. of Fmoc-Lys(Fmoc)-OH, 3 equiv. of DIC, 1 equiv. of OximaPure, in 4.5 mL of DMF. Reaction for 5 min at 90°C in the microwaved-assisted Liberty Blue peptide synthesizer; (b) Fmoc deprotection with 20% N-methylpiperidine in DMF twice for 3 min at 90°C in the microwaved-assisted Liberty Blue peptide synthesizer; (c) Peptides growth using previous conditions but using double equivalents for dimer growth: 6 equiv. of Fmoc-Amino Acid, 6 equiv. of DIC, 2 equiv. of OximaPure, in 4.5 mL of DMF. Reaction for 5 min at 90°C in the microwaved-assisted Liberty Blue peptide synthesizer; (d) TFA/TIS/water/phenol (94:2:2:2), 5 h, rt.
Figure S3. Synthetic scheme for the synthesis of compound Targetrin-motif. Conditions: (a) Rink Amide resin + 3 equiv. of Fmoc-Lys(ivDde)-OH, 3 equiv. of HATU, 3 equiv. of OximaPure, and 5 equiv. of DIPEA in 1 mL of DMF, 1 h, rt; (b) Fmoc deprotection with 20% piperidine in DMF twice; (c) 3 equiv. of Fmoc-Gly-OH, 3 equiv. of HATU, 3 equiv. of OximaPure, and 5 equiv. of DIPEA in 1 mL of DMF, 1 h, rt; (d) Peptides growth using previous conditions or LibertyBlue; (e) ivDde deprotection using 4% N$_2$H$_2$ in DMF (3 × 5 mL), rt; (f) 3 equiv. of 5-Hexynoic acid, 3 equiv. of HATU, 3 equiv. of OximaPure, and 5 equiv of DIPEA in 1 mL of DMF, 1 h, at rt; (g) TFA/TIS/water/phenol (94:2:2:2), 5 h, rt.
Figure S4. Synthetic scheme for the synthesis of compound *Targefrin-dimer-motif*. Conditions: (a) Rink Amide resin + 3 equiv. of Fmoc-Lys(ivDde)-OH, 3 equiv. of HATU, 3 equiv. of OximaPure, and 5 equiv. of DIPEA in 1 mL of DMF, 1 h, rt. (b) Fmoc deprotection with 20% N-methylpiperidine in DMF twice. (c) 3 equiv. of Fmoc-Gly-OH, 3 equiv. of HATU, 3 equiv. of OximaPure, and 5 equiv. of DIPEA in 1 mL of DMF, 1 h, rt. (d) 3 equiv. of Fmoc-Lys(Fmoc)-OH, 3 equiv. of HATU, 3 equiv. of OximaPure, and 5 equiv. of DIPEA in 1 mL of DMF, 1 h, rt. (e) Peptides growth double equivalents for dimer growth: 6 equiv. of Fmoc-Amino Acid, 6 equiv. of DIC, 2 equiv. of OximaPure, in 4.5 mL of DMF. Reaction for 5 min at 90°C in the microwaved-assisted Liberty Blue peptide synthesizer. (f) ivDde deprotection using 4% N2H2 in DMF (3 x 5 mL), rt; (g) 3 equiv. of 5-Hexynoic acid, 3 equiv. of HATU, 3 equiv. of OximaPure, and 5 equiv of DIPEA in 1 mL of DMF, 1 h, at rt; (h) TFA/TIS/water/phenol (94:2:2:2), 5 h, rt.
Figure S5. Synthetic scheme for the synthesis of Targefrin-PTX. Conditions: (a) Targefrin-moif crude, 1 equiv. of PTX-Azide in 4 mL of 4:1 DMSO:water solution. Add 50 uL of CuSO4 1M and 50 uL of Sodium Ascorbate 1M. Mix at rt for 48 h.
Figure S6. Synthetic scheme for the synthesis of Targefrin-dimer-PTX. Conditions: (a) Targefrin-dimer-motif crude, 1 equiv. of PTX-Azide in 4 mL of 4:1 DMSO:water solution. Add 50 uL of CuSO$_4$ 1M and 50 uL of Sodium Ascorbate 1M. Mix at rt for 48 h.
Figure S7. Synthetic scheme for the synthesis of Targefrin-dimer-TAMRA. Conditions: (a) Targefrin-dimer-motif crude, 1 equiv. of 5-TAMRA-Azide in 4 mL of 4:1 DMSO:water solution. Add 50 uL of CuSO4 1M and 50 uL of Sodium Ascorbate 1M. Mix at rt for 48 h.
**Figure S8. HPLC traces for tested compounds.** Analytical run was accomplished using Atlantis T3 3µm 4.6x150 mm (H₂O/ACN gradient from 20% to 100% in 45 min). All compounds displayed purity > 95%.

**Targefrin**

![Chromatogram](image1)

**Targefrin-dimer**

![Chromatogram](image2)
Targefrin-PTX

Targefrin-dimer-PTX
Figure S9. Pharmacokinetics studies. Preliminary pharmacokinetic (PK) studies with Targetrin-dimer. The agent has been injected IV via the tail vein at a concentration of 50 mg/Kg in a formulation of 80% PBS, 10% Tween 80, and 10% Ethanol. Note that this formulation resulted in a clear solution containing 20mg/ml of Targetrin-dimer. $C_{\text{max}} \sim 650 \text{ ng/mL}$ after 2 hours from the injection. Estimated $t_{1/2} \sim 15 \text{ hr}$. 

![Graph showing concentration vs time](image-url)
Figure S10. Duplicate experiments reporting uncropped western blots that generated the data in Figures 4, 5 and 8.

**Figure 4. Expt 1**

**Figure 4. Expt 2**

**Figure 5. BxPC3 Expt 1**

**Figure 5. BxPC3 Expt 2**

**Figure 5. PANC-1 Expt 1**

**Figure 5. PANC-1 Expt 2**
Figure S11. Cell migration assay of BxPC3 from Figure 9 at 12 h. A) Cell migration assay of BxPC3 treated with 2 μg/mL ephrinA1-Fc and 10 μM targefrin or the indicated doses of targefrin-dimer. The yellow lines displayed initial scratches made at 0 h while the black lines displayed the location that the cells had migrated to after 12 h. B) Targefrin-dimer significantly inhibited cell migration at 12 h in a dose-dependent manner as shown by decreases in relative wound density. ***p < 0.01, ****p < 0.0001, as determined by a one-way analysis of variance using Dunnett’s post-test analysis.
Figure S12. Cell viability assay of MIA PaCa-2 at 72 h. A) MIA PaCa-2 cells were treated with 1 µg/mL ephrinA1-Fc, different doses of Targefrin or Targefrin-dimer for 72 h. Percent confluence was monitored with the IncuCyte S3 live-cell analysis system and percent cell viability was calculated by normalizing the confluency of the treatments to that of the DMSO control. Percent cell viability was not significantly affected across all the treatments, as determined by a two-way analysis of variance using Bonferroni post-test analysis. B) Time-response curves for the percent confluence of MIA PaCa-2 cells after the indicated treatments.
**Figure S13. Blood chemistry analysis for mice treated with Targefrin-dimer.** 5 Balb/c mice were treated with Targefrin-dimer 20 mg/mL (80% PBS, 10% Tween 80, 10% Ethanol) to obtain 50 mg/kg doses. After 24 hr mice were sacrificed and full chemistry panel analysis was conducted as listed below.

| Analyte Name       | Units  | Reference Ranges | 153E3/ IV #24 | 153E3/ IV #25 | 153E3/ IV #26 | 153E3/ IV #27 | 153E3/ IV #28 |
|--------------------|--------|------------------|---------------|---------------|---------------|---------------|---------------|
| Albumin            | ALB    | g/dL             | 2.5 - 4.8     | 3.1           | 3.6           | 3.7           | 4.1           | 3.0           |
| Alkaline Phosphatase| ALP    | U/L              | 62 - 209      | 95            | 107           | 102           | 105           | 76            |
| Alanine Transaminase| ALT    | U/L              | 28 - 132      | 182           | 88            | 64            | 50            | 244           |
| Amylase            | AMY    | U/L              | 1691 - 3615   | 927           | 979           | 938           | 828           | 830           |
| Bilirubin, total   | TBIL   | mg/dL            | 0.1 - 0.9     | 0.3           | 0.3           | 0.3           | 0.3           | 0.3           |
| Blood Urea Nitrogen| BUN    | mg/dL            | 18 - 29       | 15            | 14            | 15            | 14            | 21            |
| Calcium            | CA     | mg/dL            | 5.9 - 9.4     | 9.4           | 9.6           | 9.9           | 10.2          | 9.4           |
| Phosphorus         | PHOS   | mg/dL            | 6.1 - 10.1    | 7.0           | 7.0           | 6.3           | 5.5           | 9.2           |
| Creatinine         | CRE    | mg/dL            | 0.2 - 0.8     | 0.3           | 0.2           | 0.2           | 0.5           | 0.3           |
| Glucose            | GLU    | mg/dL            | 90 - 192      | 143           | 156           | 168           | 182           | 155           |
| Sodium             | NA+    | mmol/L           | 126 - 182     | 158           | 156           | 155           | 159           | 156           |
| Potassium          | K+     | mmol/L           | 4.7 - 6.4     | 6.5           | 6.8           | 7.0           | 7.1           | 7.2           |
| Total Protein      | TP     | g/dL             | 3.6 - 6.6     | 5.0           | 5.2           | 5.2           | 5.7           | 4.9           |
| Globulin, calculated| GLOB  | g/dL             | N/A           | 1.8           | 1.6           | 1.6           | 1.7           | 1.8           |
Figure S14: Repeated doses toxicity studies with Targefrin-dimer-PTX versus PTX alone. Balc/c mice received equimolar doses of PTX or targefrin-dimer-PTX daily (IV), and body weight were measured daily. FD = found dead. By day 5 all 3 mice in the PTX treated group were found dead. Mice treated with targefrin-dimer-PTX were lethargic after the first doses but recovered. No signs of toxicity were noted in the mice treated with targefrin-dimer.

| Mouse ID | Treatment          | Body weight (g) |   |   |   |   |
|---------|--------------------|----------------|---|---|---|---|
|         |                    | Monday         | Tuesday | Wednesday | Thursday | Friday |
| 6       | Targefrin-Dimer-PTX| 26.17          | 25.33   | 25.71     | 25.82     | 26.28   |
| 7       | Targefrin-Dimer-PTX| 25.63          | 24.98   | 25.14     | 24.21     | 24.71   |
| 8       | Targefrin-Dimer-PTX| 26.17          | 25.33   | 26.08     | 25.71     | 25.1    |
| 9       | PTX                | 23.77          | 23.22 (FD) | ----- | ----- | ----- |
| 10      | PTX                | 23.92          | 23.63 (FD) | ----- | ----- | ----- |
| 11      | PTX                | 23.61          | 21.82   | 21.85     | 21.95     | 22.11 (FD) |
| 12      | Targefrin-dimer    | 24.48          | 24.14   | 23.83     | 23.21     | 22.94   |
| 13      | Targefrin-dimer    | 22.63          | 22.25   | 22.71     | 22.58     | 22.11   |
| 14      | Targefrin-dimer    | 24.07          | 23.34   | 23.55     | 23.61     | 23.98   |