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Brief Article

Bivalent Diketopiperazine-Based Tropomysin Receptor Kinase C (TrkC) Antagonists

Jing Liu,[†] Fouad Brahimi,[‡] H. Uri Saragovi,*[,‡] and Kevin Burgess*[,†]

[†]*Department of Chemistry, Texas A&M University, Box 30012, College Station, Texas 77842-3012, and* [‡]*Lady Davis Institute-Jewish General Hospital, Department of Pharmacology and Therapeutics, McGill University, Montréal, Quebec, Canada*

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Bivalent molecules containing two β-turn mimics with side chains that correspond to hot-spots on the neurotrophin NT-3 were prepared. Binding assays showed the mimetics to be selective TrkC ligands, and biological assays showed one mimetic to be an *antagonist* of the TrkC receptor.

Introduction

Neurotrophin growth factors have activities that might be useful in clinical settings, particularly with respect to maladies that affect the nervous system such as neurodegeneration or pain.[1,2] These growth factors are also implicated in cancer progression (e.g., TrkC[a] in breast cancer). However, even apart from the usual problems associated with protein-based pharmaceuticals (e.g., cost, proteolytic and metabolic stabilities, immune responses), there are side-effects and potential toxicity factors that could logically be attributed to the fact that the neurotrophins are not entirely selective for their corresponding Trk receptors, and they all bind the p75 receptor.[3] Binding to the latter is particularly undesirable because it tends to cause very different effects to activation of the Trk receptors.[4] For these reasons, there is a pressing need for the development of small molecules that *selectively* bind to and regulate the function of Trk receptors.

Our approach to the design of Trk ligands has been to mimic the β-turn regions of the parent neurotrophins.[5−7] Cyclic monovalent compounds (one turn mimic) have proven to be useful *Trk agonists* (or partial agonists)[8] or antagonists.[9] Bivalent compounds based on two macrocyclic turn mimics in one molecule[10] have been identified as *TrkA antagonists*,[11] or *TrkC agonists*.[12] Selectivities for the TrkA and C receptors were achieved by using amino acid side chains corresponding to β-turns in the parent neurotrophin ligands that constitute hot-spots for the interactions of these with their Trk receptors. However, the factors that determine if the ligand is an agonist or an antagonist are more subtle. Two key molecular parameters that influence this are likely to be the scaffold used to form the turn mimic, and the spacing between them in the bivalent constructs.

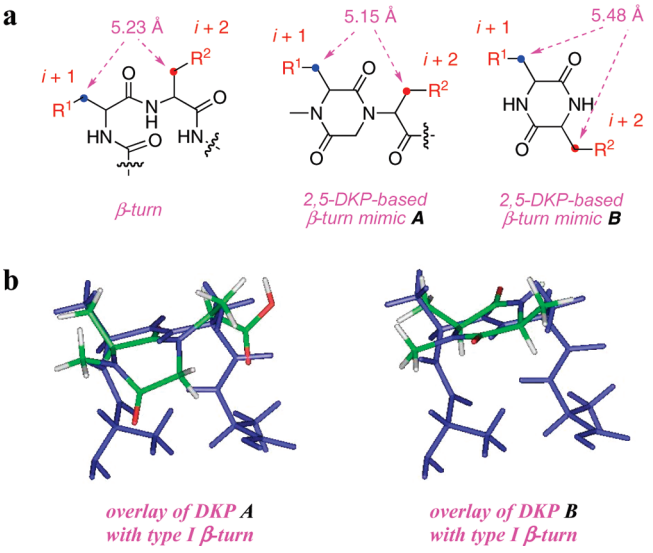

Figure 1. (a) Key distance of Cβ-separations of the $i + 1$ to $i + 2$ residues of a type I β-turn and of the monovalent turn mimics **A** and **B** featured here; (b) comparative overlay of the two types of 2,5-DKP mimics (colored) onto a type I β-turn (blue).

This communication introduces a new type of turn mimic **A** based on diketopiperazines (DKPs), a scaffold that is more commonly used for forming compounds of the type **B**. A strategy for making bivalent molecules containing two type-**A** units at variable spacings is also described. Cell-based binding and biological and biochemical signal transduction assays indicate that one of these bivalent molecules is one of the first small molecule TrkC *antagonists* to be reported to date.[9]

Results and Discussion

The guiding hypothesis behind our latest designs of β-turn mimics[12,13] is that the separation between the Cβ atoms is critical. Figure 1 shows this distance for an ideal type I turn is ca. 5.2 Å. Recently we reported β-turn mimics that could readily attain conformations with Cβ-separations corresponding to this distance, even though they were not the global minimum.[12,13] Modeling shows that DKPs **B** have Cβ-separations of almost 5.5 Å, i.e., a little too long. In any case, these molecules are well represented in many compound

*To whom correspondence should be addressed. For K.B.: phone, (979) 845-4345; fax, (979) 845-8839; E-mail, Burgess@tamu.edu. For H.U.S.: phone, (514) 340-8222 ext 5055; E-mail, horacio.saragovi@mcgill.ca.

[a] Abbreviations: TrkC, Tropomysin receptor kinase C; DKP, diketopiperazine; EDCI, 1-ethyl-(3-dimethylaminopropyl) carbodiimide hydrochloride; HOBt, 1-hydroxybenzotriazole; NMM, *N*-methylmorpholine; TFA, trifluoroacetic acid; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; FACS, fluorescence activated cell sorting; IGF-1R, insulin-like growth factor 1 receptor; SFM, serum-free media; NT-3, neurotrophin-3; pTyr, phosphotyrosine; Erk, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; mAb, monoclonal antibody; NGF, nerve growth factor.

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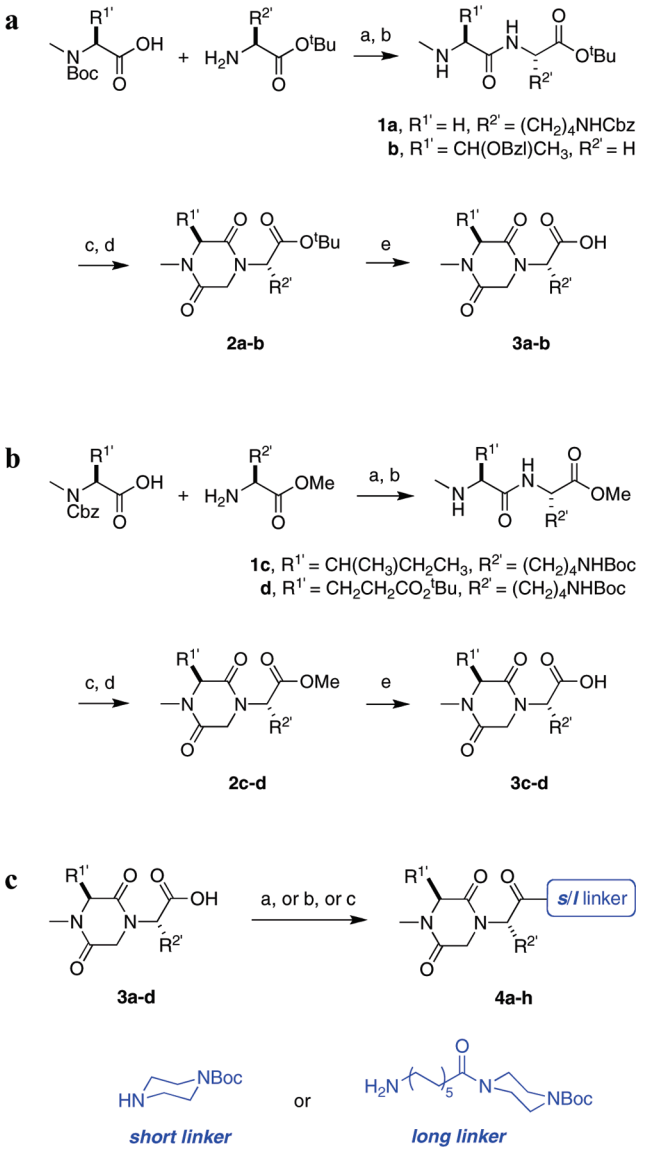
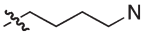
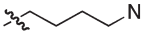
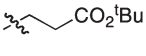
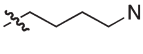
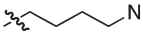
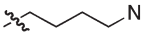
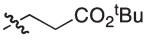
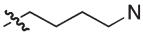
Scheme 1. Solution Phase Synthesis of Monomeric DKP-Based Peptidomimetics: (a,b) Refer to Syntheses of the Monovalent Scaffolds, (c) Deals with Functionalization of These with Linker Fragments[a]



[a] Reagents and conditions for part (a): (a) 1-ethyl-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI), 1-hydroxybenzotriazole (HOBt), *N*-methylmorpholine (NMM), CH_2Cl_2, 25 °C, 12 h; (b) trifluoroacetic acid (TFA)/CH_2Cl_2, 0−25 °C, 2 h; (c) bromoacetyl bromide, 0.5 M K_2CO_3 (aq), CH_2Cl_2, 0 °C, 2 h; (d) 50% NaOH(aq), CH_2Cl_2, 25 °C, 12 h; (e) TFA, $^iPr_3SiH$, CH_2Cl_2, 25 °C, 10 h. Reagents and conditions for part (b): (a) EDCI, HOBt, NMM, CH_2Cl_2, 25 °C, 12 h; (b) H_2, Pd/C, MeOH, 25 °C, 12 h; (c) bromoacetyl bromide, 0.5 M K_2CO_3 (aq), CH_2Cl_2, 0 °C, 2 h; (d) 50% NaOH (aq), CH_2Cl_2, 25 °C, 12 h; (e) Me_3SnOH, 1,2-dichloroethane, 80 °C, 6 h. Reagents and conditions for part (c): for **4a** and **4e**: **3a**, (a) (i) short or long linker, EDCI, HOBt, NMM, CH_2Cl_2, 25 °C, 12 h, (ii) H_2, Pd/C, MeOH, 25 °C, 16 h, (iii) Boc anhydride, Et_3N, CH_2Cl_2, 25 °C, 12 h; for **4b** and **4f**: **3b**, (b) (i) short or long linker, EDCI, HOBt, NMM, CH_2Cl_2, 25 °C, 12 h, (ii) H_2, Pd/C, MeOH, 25 °C, 16 h; for **4c**,**d** and **4g**,**h**: **3c** or **3d**, (c) short or long linker, EDCI, HOBt, NMM, CH_2Cl_2, 25 °C, 12 h.

collections.[14] Consequently, the less common substitution pattern in **A** was considered.[11,15,16] Here the Cβ-spacing, 5.1−5.2 Å, matches type I turns closely, and the structures explore a different region of diversity space.

Table 1. Monovalent Peptidomimetics **4a**−**h**

compound	$R^{1'}$	$R^{2'}$	linker
4a	H		short
4b		H	short
4c			short
4d			short
4e	H		long
4f		H	long
4g			long
4h			long

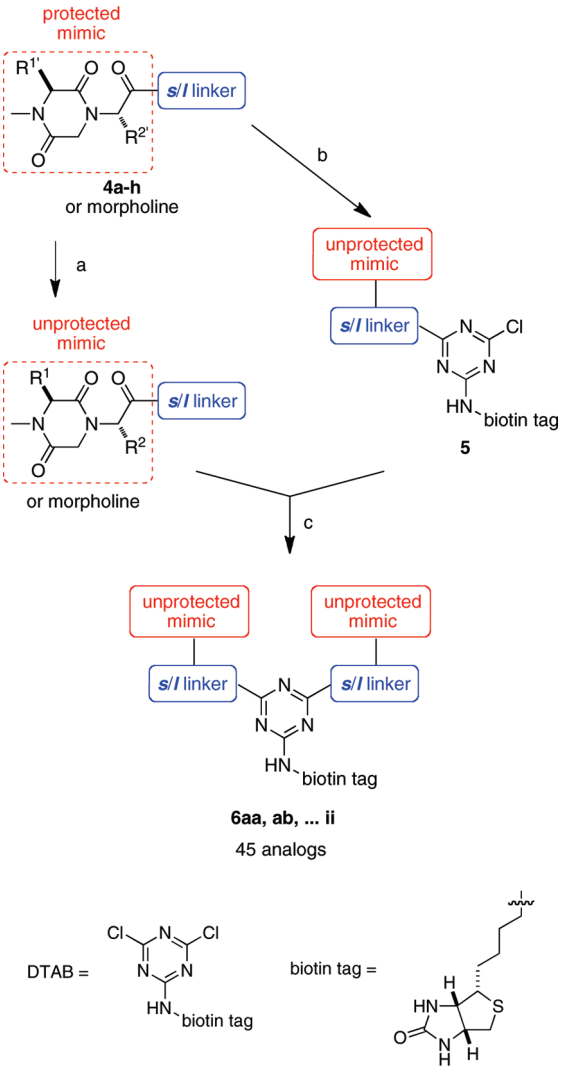
Parts a and b of Scheme 1 illustrate two approaches used to make the target type **A** DKPs (full details are given in the Supporting Information). Two approaches were necessary to make it possible to use the most readily available protected amino acids and the appropriate side-chain masking groups. The key difference between the two routes is that in the first, acid-based deprotection of Boc groups (without removing the *tert*-butyl ester)[17] is involved early in the synthesis, whereas this is replaced by hydrogenolysis of Cbz protection in the second.

Scheme 1c illustrates how "short" ***s*** and "long" ***l*** piperazine-based linkers were coupled to the different peptidomimetics. At the conclusion of the synthesis, four different monovalent peptidomimetics were generated, each of these was functionalized with the short ***s*** and long ***l*** linker systems to give a total of eight monovalent starting materials (Table 1). The short linker was chosen because it is a compact structure formed from a heterocycle that is common in drug design. Simple modeling experiments showed that when two long linkers of the type shown were combined then this would give a spacing of the turn mimics that is appropriate for the largest separations of the turns in the neurotrophins. Combinations of the long and short linkers would span appropriate intermediate distances.

The next step in syntheses was to form a library of bivalent molecules **6** from the eight key monovalent systems **4**. Solution phase methodology for doing this type of combination has been published by us.[13] Briefly, this relies on suppression of the rate of S_NAr reactions in apolar solvents to stop the initial reaction after one displacement, then completion of the reaction in a more polar solvent. Scheme 2 shows how this method was used to form compounds **4**.

Methods used in Scheme 2 mean that a triazine forms the core of every bivalent molecule **6**. However, this heterocycle can be used; it has a substitution site for a "third group" to facilitate in vitro assays (or for other purposes, not relevant here). In this study, biotin derivatives were chosen to occupy this position ("biotin tag") because they facilitate direct

Scheme 2. Solution Phase Synthesis of Biotin-Labeled Bivalent Peptidomimetic Library[a]



[a] Reagents and conditions: (a) 1:1 TFA/CH_2Cl_2, 25 °C, 10 h; (b) (i) 1:1 TFA/CH_2Cl_2, 25 °C, 10 h, (ii) DTAB, K_2CO_3, DMSO, 25 °C, 2 h; (c) K_2CO_3, DMSO, 25 °C, 5−7 d.

binding assays via fluorescence activated cell sorting (FACS), tend to increase the water solubilities of the molecules but do not impact the measured outputs from other assays (e.g., 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide {MTT} in cell survival assays).

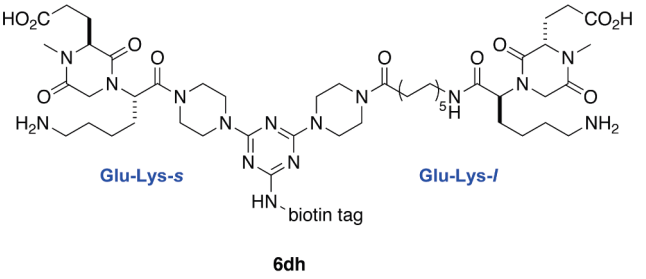
Table 2 shows the purities obtained for the library of crude samples from Scheme 2. All the compounds were then purified via preparative reverse phase HPLC (RP-HPLC) to give samples that were more than 95% pure in all cases.

The compounds in the DKP library described above were assayed in binding assays, biological assays, and biochemical signal transduction assays as described previously.[18] In the binding studies, the biotinylated compounds were assayed by flow cytometry FACS, using avidin conjugated with fluorescein isothiocyanate for detection. FACS assays measuring the direct binding to NIH-3T3 cells stably transfected to express TrkC. As controls, NIH-3T3 cells were stably transfected to express neurotrophin receptors TrkA, or p75, or a different receptor tyrosine kinase, insulin-like growth factor 1 receptor (IGF-1R). Of the 45 compounds scanned by FACS, one compound, the one made from combination of deprotected forms of **4d** and **4h**, hereafter called **6dh**, showed selective TrkC binding (Figure 2). This compound binds selectively to TrkC-expressing cells, but it does not bind to

Table 2. HPLC Purities of the Bivalent Turn Mimics **6** Prepared from Monovalent Mimics **4a**−**h** as Assessed by UV Detection[a]

i[a]	6ii						purities(%)		
4a	6ai	6aa					below 70		
4b	6bi	6ab	6bb				70 - 85		
4c	6ci	6ac	6bc	6cc			85 and up		
4d	6di	6ad	6bd	6cd	6dd				
4e	6ei	6ae	6be	6ce	6de	6ee			
4f	6fi	6af	6bf	6cf	6df	6ef	6ff		
4g	6gi	6ag	6bg	6cg	6dg	6eg	6fg	6gg	
4h	6hi	6ah	6bh	6ch	6dh	6eh	6fh	6gh	6hh
	i	4a	4b	4c	4d	4e	4f	4g	4h

[a] "i" stands for morpholine, which was used as "cap" in place of the monovalent peptidomimetics to give control compounds that have none or one peptidomimetic and biotin.



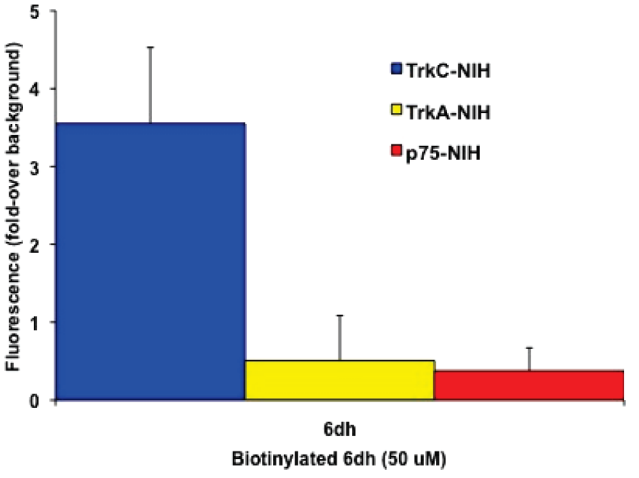


Figure 2. Direct binding of biotin-peptidomimetic **6dh** to TrkC-expressing cells. Cells expressing the indicated receptor were first bound at 4 °C with test ligand (50 μM), followed by fluorescein-avidin. After washing, cells were analyzed by FACScan/CellQuest. The background mean channel fluorescence (MCF) of NIH-IGF-1R were subtracted to analyze the specific MCF binding to test cells. Results shown are fluorescence ± standard error of mean (SEM), $n = 3$ independent experiments.

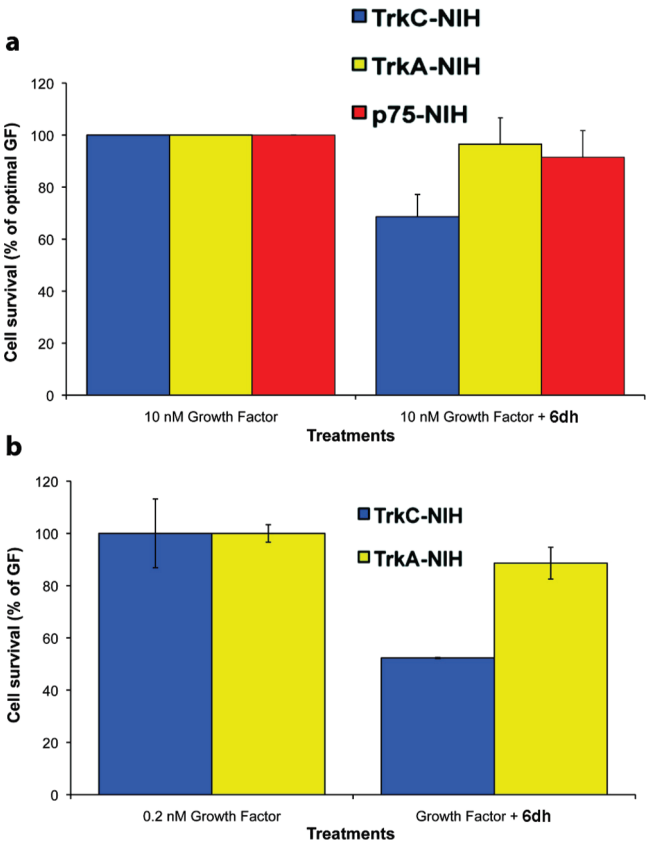


Figure 3. Mimetic **6dh** antagonizes NT-3 action in cell survival assays. NIH-3T3 cells expressing either TrkA or TrkC or IGF-1R were cultured in SFM supplemented with optimal ((a) 10 nM) or suboptimal ((b) 0.2 nM) concentrations of the appropriate growth factor (GF) ± peptidomimetic (20 μM). Survival was measured in MTT assays and was calculated relative to optimal growth factor-mediated survival (100%). Results shown are average ± SD.

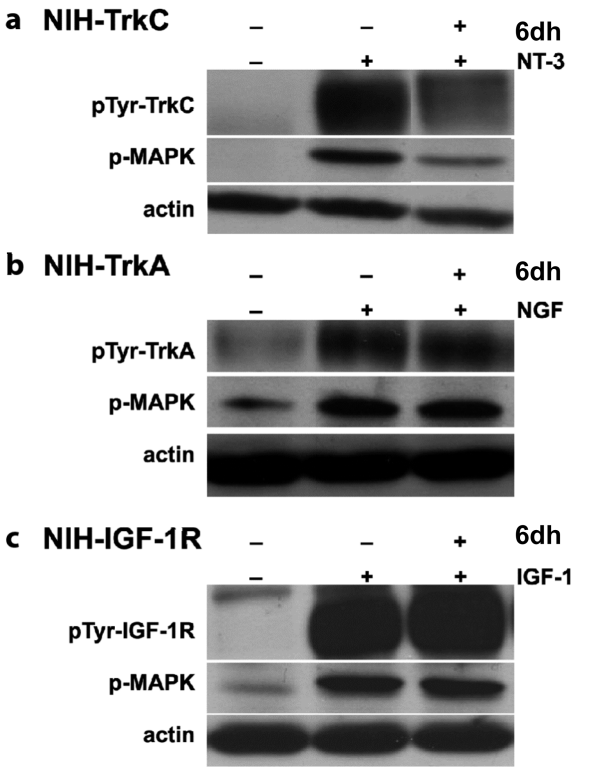


Figure 4. Effect of **6dh** on TrkC receptor phosphorylation and MAPK activation in NIH3T3 TrkC cells. Cells were exposed to the indicated peptidomimetic (20 μM) and growth factor (2 nM) for 20 min. Detergent lysates were analyzed by Western blotting with anti-pTyr monoclonal antibody (mAb) 4G10 or antiphospho-MAPK. Membranes were reblotted with anti-actin to verify protein loading. Blots were quantified by densitometry.

NIH-3T3 cells expressing TrkA or p75 (Figure 2), or IGF-1R (not shown).

The effects of the peptidomimetics on receptor-mediated cell survival of NIH-3T3 cells expressing TrkA, TrkC or IGF-1R were also tested. Biological assays tested cell survival in quantitative MTT assays. When cells were placed in serum-free media (SFM), they died by apoptosis. In these conditions, cell death can be prevented by their appropriate growth factors (NIH-TrkA is protected by NGF, NIH-TrkC is protected by neurotrophin-3 {NT-3}, NIH-IGF-1R is protected by IGF-1). Growth factor protection of cells from apoptosis in SFM is dose-dependent, and suboptimal doses of growth factor can be used that result quantitatively and consistently in reduced survival.

Compound **6dh** at 20 μM was significantly antagonistic to TrkC−NT-3 functional interactions. It reduced the trophic activity of optimal (10 nM) NT-3 to ~70% (Figure 3a). Antagonism was TrkC selective because this mimetic did not antagonize the protective function of NGF upon TrkA cells or the function of IGF-1 on IGF-1R (Figure 3a).

For comparison, suboptimal doses of NT-3 (0.2 nM) which affords ~40−50% of maximal cell survival were also tested. The data show the effects of NT-3 on TrkC cells is antagonized more easily by **6dh** under these conditions, but also in a selective manner (Figure 3b). In addition, control cell cytotoxicity assays demonstrated **6dh** were nontoxic at all doses tested (data not shown) indicating selective antagonism is due to antagonism of functional TrkC−NT-3 interactions, and not due to selective cytotoxicity.

Biochemical assays of signal transduction were also performed on the lead compound, **6dh**. The phosphotyrosine (pTyr) content of TrkC can be used as a measure of activation because this receptor is a receptor tyrosine kinase. Moreover, the phosphorylated state of the downstream signaling protein with extracellular signal-regulated kinase (Erk) 1,2 can also be measured; as it is known to be activated by TrkC-signals (Figure 4).[19] Cells were exposed to growth factor (2 nM) for 20 min ± **6dh** (20 μM), and detergent lysates were analyzed by Western blotting with antibodies directed to phospho-tyrosine or to phospho-Erk1,2. Antibodies directed to actin demonstrated equal protein loading and this signal is used to standardize the results.

In NIH3T3-TrkC cells, **6dh** significantly blocked (40%) the level of TrkC-pTyr that was stimulated by NT-3 (Figure 4a). No significant effect was observed in NIH3T3-TrkA cells stimulated with NGF (Figure 4b) or in NIH3T3-IGF-1R cells stimulated with IGF-1 (Figure 4c). Together, these data indicate **6dh** is a selective inhibitor of NT-3-mediated activation leading to TrkC phosphotyrosinylation.

Conclusions

The inhibition of TrkC-pTyr correlates with the inhibition of the phosphorylation of the mitogen-activated protein kinase (MAPK) Erk1,2 protein, which is a major signal transduction pathway activated by neurotrophin receptor. Mimic **6dh** blocks the activation of MAPK by

TrkC (70%) (Figure 4a) but not by TrkA or by IGF-1R (Figure 4b,c).

There are relatively few small molecule ligands for the neurotrophin receptors.[8,20−26] One of the earliest, a compound we call **D3** was designed to mimic putative β-turn hot-spots in the nerve growth factor (NGF).[6,7,27] In vitro and in vivo tests on **D3** indicate this is a partial TrkA agonist, that has no significant binding to the other Trk receptors. This compound shows promise for the treatment of stroke and glaucoma. Whereas similar compounds from our laboratories have been shown to be agonists or partial agonists for the TrkC receptor (the one that has greatest affinity for NT-3),[18,28] this paper demonstrates a molecule that contains not one but two β-turn mimics at an optimized separation can serve as a TrkC *antagonist*. The most active of the molecules **6** (*ie* **6dh**, the one from **4d** and **4h**) contains two DKPs with side chains from Glu and Lys (EK); this mimics the sequence D**EK**Q corresponding to murine NGF *and not NT-3*, but the molecule was active on TrkC and not on TrkA. The 92−95 turn region of NT-3 (human or mouse) contains the **ENN**K motif. Consequently, it is possible that this compound mimics the *i* and $i+3$ residues of this turn rather than the $i+1$ and $i+2$ regions.

In summary, peptidomimetic **6dh** is a ligand of TrkC, and an antagonist of TrkC−NT-3 activity. Our findings further demonstrate that peptidomimetic molecules can be made to act specifically on certain Trk receptors. Finding a small, stable molecule with selective agonist/antagonistic activity may be useful as a therapeutic agent.

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Supporting Information Available: Details of the compound purities, procedure for syntheses of compounds **1**−**6**, and characterization of representative dimers. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Skaper, S. D. The biology of neurotrophins, signalling pathways, and functional peptide mimetics of neurotrophins and their receptors. *CNS Neurol. Disord.: Drug Targets* **2008**, *7*, 46–62.
(2) Ivanisevic, L.; Saragovi, H. U. The Neurotrophins. In *Handbook of Biologically Active Peptides*; Kastin, A. J., Ed. Elsevier: New York, 2006; pp 1407−1413.
(3) Pollack, S. J.; Harper, S. J. Small molecule Trk receptor agonists and other neurotrophic factor mimetics. *Curr. Drug Targets: CNS Neurol. Disord.* **2002**, *1*, 59–80.
(4) Friedman, W. J.; Greene, L. A. Neurotrophin signaling via Trks and p75. *Exp. Cell Res.* **1999**, *253*, 131–142.
(5) Feng, Y.; Pattarawarapan, M.; Wang, Z.; Burgess, K. Solid-phase S_N2 macrocyclization reactions to form β-turn mimics. *Org. Lett.* **1999**, *1*, 121–124.
(6) Feng, Y.; Burgess, K. Solid phase S_NAr macrocyclizations to give turn-extended-turn peptidomimetics. *Chem.—Eur. J.* **1999**, *5*, 3261–3272.
(7) Feng, Y.; Wang, Z.; Jin, S.; Burgess, K. S_NAr cyclizations to form cyclic peptidomimetics of β-turns. *J. Am. Chem. Soc.* **1998**, *120*, 10768–10769.
(8) Maliartchouk, S.; Feng, Y.; Ivanisevic, L.; Debeir, T.; Cuello, A. C.; Burgess, K.; Saragovi, H. U. A designed peptidomimetic agonistic ligand of TrkA nerve growth factor receptors. *Mol. Pharmacol.* **2000**, *57*, 385–391.
(9) Brahimi, F.; Malakhov, A.; Lee, H. B.; Pattarawarapan, M.; Ivanisevic, L.; Burgess, K.; Saragovi, H. U. A peptidomimetic of NT-3 acts as a TrkC antagonist. *Peptides* **2009**, *30*, 1833–1839.
(10) Pattarawarapan, M.; Reyes, S.; Xia, Z.; Zaccaro, M. C.; Saragovi, H. U.; Burgess, K. Selective formation of homo- and heterobivalent peptidomimetics. *J. Med. Chem.* **2003**, *46*, 3565–3567.
(11) Brahimi, F.; Liu, J.; Malakhov, A.; Chowdhury, S.; Purisima, E.; Ivanisevic, L.; Caron, A.; Burgess, K.; Saragovi, H. Dimerization of a monovalent small molecule ligand changes a TrkA receptor agonist into an antagonist: implications for conformational changes. **2010**, submitted for publication.
(12) Chen, D.; Brahimi, F.; Angell, Y.; Li, Y.-C.; Moscowicz, J.; Saragovi, H. U.; Burgess, K. Bivalent peptidomimetic ligands of TrkC are biased agonists, selectively induce neuritogenesis, or potentiate neurotrophin-3 trophic signals. *ACS Chem. Biol.* **2009**, *4*, 769–781.
(13) Angell, Y.; Chen, D.; Brahimi, F.; Saragovi, H. U.; Burgess, K. A combinatorial method for solution-phase synthesis of labeled bivalent β-turn mimics. *J. Am. Chem. Soc.* **2008**, *130*, 556–565.
(14) Martins, M. B.; Carvalho, I. Diketopiperazines: Biological activity and synthesis. *Tetrahedron* **2007**, *63*, 9923–9932.
(15) Gerona-Navarro, G.; Bonache, M. A.; Herranz, R.; Garcia-Lopez, M. T.; Gonzalez-Muniz, R. Entry to new conformationally constrained amino acids. First synthesis of 3-unsubstituted 4-alkyl-4-carboxy-2-azetidinone derivatives via an intramolecular N^{α}-C^{α}-cyclization strategy. *J. Org. Chem.* **2001**, *66*, 3538–3547.
(16) Bohn Rhoden, C. R.; Westermann, B.; Wessjohann, L. A. One-pot multicomponent synthesis of *n*-substituted tryptophan-derived diketopiperazines. *Synthesis* **2008**, 2077–2082.
(17) Mehta, A.; Jaouhari, R.; Benson, T. J.; Douglas, K. T. Improved efficiency and selectivity in peptide synthesis: use of triethylsilane as a carbocation scavenger in deprotection of *tert*-butyl esters and *tert*-butoxycarbonyl-protected sites. *Tetrahedron Lett.* **1992**, *33*, 5441–5444.
(18) Zaccaro, M. C.; Lee, B. H.; Pattarawarapan, M.; Xia, Z.; Caron, A.; L'Heureux, P.-J.; Bengio, Y.; Burgess, K.; Saragovi, H. U. Selective small molecule peptidomimetic ligands of TrkC and of TrkA receptors afford discrete or complete neurotrophic activities. *Chem. Biol.* **2005**, *12*, 1015–1028.
(19) Kaplan, D. R.; Miller, F. D. Neurotrophin signal transduction in the nervous system. *Curr. Opin. Neurobiol.* **2000**, *10*, 381–391.
(20) LeSauteur, L.; Wei, L.; Gibbs, B.; Saragovi, H. U. Small peptide mimics of nerve growth factor bind TrkA receptors and affect biological responses. *J. Biol. Chem.* **1995**, *270*, 6564–6569.
(21) LeSauteur, L.; Cheung, N. K. V.; Lisbona, R.; Saragovi, H. U. Small molecule nerve growth factor analogs image receptors in vivo. *Nature Biotechnol.* **1996**, *14*, 1120–1122.
(22) Maliartchouk, S.; Debeir, T.; Beglova, N.; Cuello, A.; Gehring, K.; Saragovi, H. Genuine monovalent ligands of TrkA nerve growth factor receptors reveal a novel pharmacological mechanism of action. *J. Biol. Chem.* **2000**, *275*, 9946–9956.
(23) Longo, F. M.; Manthorpe, M.; Xie, Y. M.; Varon, S. Synthetic NGF peptide derivatives prevent neuronal death via a p75 receptor-dependent mechanism. *J. Neurosci. Res.* **1997**, *48*, 1–17.
(24) Xie, Y.; Tisi, M. A.; Yeo, T. T.; Longo, F. M. Nerve growth factors(NGF) loop 4 dimeric mimetics activate ERK and AKT and promote NGF-like neurotropic effects. *J. Biol. Chem.* **2000**, *275*, 29868–29874.
(25) Xie, Y.; Longo, F. M. Neurotrophin small-molecule mimetics. *Prog. Brain Res.* **2000**, *128*, 333–347.
(26) O'Leary, P. D.; Hughes, R. A. Design of potent peptide mimetics of brain-derived neurotrophic factor. *J. Biol. Chem.* **2003**, *278*, 25738–25744.
(27) Feng, Y.; Wang, Z.; Jin, S.; Burgess, K. Conformations of peptidomimetics formed by S_NAr macrocyclizations: 13- to 16-membered ring systems. *Chem.—Eur. J.* **1999**, *5*, 3273–3278.
(28) Pattarawarapan, M.; Zaccaro, M. C.; Saragovi, U.; Burgess, K. New templates for synthesis of ring-fused C^{10} β-turn peptidomimetics leading to the first reported small-molecule mimic of neurotrophin-3. *J. Med. Chem.* **2002**, *45*, 4387–4390.