SciMedCentral

Journal of Pharmacology & Clinical Toxicology

Research Article

Identification of Novel Neurotensin Receptor 1 Inhibitors by Combinatorial Support Vector Machine

Panpan Wang[1a], Jie Hu[1a], Yinghong Li[1], Feng Xu[3#], Feng Zhu[1*] and Yuzong Chen[2]

[1]*Innovative Drug Research Centre, School of Public Affairs and College of Chemistry and Chemical Engineering, Chongqing University, China*

[2]*Bioinformatics and Drug Design Group, Department of Pharmacy, and Center for Computational Science and Engineering, National University of Singapore, Singapore*

[3]*College of Pharmacy and Tianjin Key Laboratory of Molecular Drug Research, Nankai University, China*

[#]*Author contributes equally as corresponding author*

[a]*Author contributes equally as first author*

***Corresponding author**

Feng Zhu, Innovative Drug Research Centre, School of Public Affairs and College of Chemistry and Chemical Engineering, Chongqing University, Chongqing, P. R. 401331, China, Tel: 86-023-6567-8468; E-mail: zhufeng@cqu.edu.cn

Submitted: 13 February 2014

Accepted: 26 February 2014

Published: 04 March 2014

ISSN: 2333-7079

Keywords

- Neurotensin
- Neurotensin receptor 1
- Virtual screening
- Support vector machines

Abstract

Neurotensin (NT) contributes to pathophysiology of neurodegenerative and psychiatric diseases, and the signal of NT and neurotensin receptor 1 (NTR1) is closely associated with cancer, inflammation and immunomodulatory disease. So far, drug targeting NTR1 has not reached any primary endpoint in clinical trial or approval, and the number of reported active compounds against NTR1 is too small to provide any novel scaffold in facilitating NTR1-based lead identification. Thus, the search for new inhibitors is of great interest to current drug discovery. This work explored the use of support vector machine (SVM) combined with putative non-inhibitor generation method as a virtual screening (VS) tool. SVM developed by NTR1 inhibitors published before 2011 was verified by cross validation and by 20 independent test inhibitors published after 2011. By scanning large chemical libraries, low false-hit rates of 0.026% (3,452 out of 13.56M PubChem chemicals) and 0.065% (109 out of 168K MDDR chemicals) were identified. A further investigation of 115 compounds identified by this work found 17 novel scaffolds against NTR1, 29% of which have been reported to show CNS and cancer-related therapeutic effects. Therefore, SVM is effective in identifying novel NTR1 inhibitors, which can be a good starting point to facilitate CNS and anticancer drug discovery in the near future.

INTRODUCTION

Neurotensin (NT) is an endogenous tridecapeptide found in the central nervous system (CNS), which acts in brain as a primary neurotransmitter or neuromodulator[1]. Physiological functions of NT are predominantly mediated through its cognate high-affinity receptor, neurotensin receptor 1 (NTR1) [2]. In spite of extensive exploration on its physiologic roles in both the central nervous system and periphery [3-6], NTR1 was reported to show significant stimulatory activity in human neoplastic tissues [7] and closely associated with proliferation, apoptosis, invasion, and metastasis of multiple malignancies including prostate cancer [8], head and neck squamous cell carcinoma [9] and breast cancer [10]. This provides a great potential to exploit novel targeted therapeutics based on NTR1, which may contribute to the discovery of new CNS and anticancer drugs.

However, no drug targeting NTR1 was approved by FDA due to poor pharmacokinetic properties and/or side effects induced in human subjects. Only a few candidates were in clinical trial, but none of them met their therapeutic expectations so far. For example, SR-48692 (a nonpeptide antagonist that binds preferentially to NTR1) and CGX-1160 (a potent NTR1 activator) have completed Phase III trial for lung cancer [11] and Phase I trial for acute pain [12] respectively, but none of them shows any positive clinical trial results [13]. Currently, reported bioactive molecules against NTR1 are in small amount and sparsely distributed in the chemical space [14,15]. In particular, only 300

bioactive compounds were so far reported as NTR1 antagonists [14], and just 14 are described in the Therapeutic Target Database (TTD) [16,17]. Therefore, there is a strong need for searching new NTR1 inhibitors to provide more candidates for developing CNS and anticancer drugs.

In order to find novel active compound, efforts have been directed at expanded search of larger chemical space [18,19]. As a rapid and effective strategy for lead identification, virtual screening (VS) has long been applied to predict lead from large chemical libraries [20]. As reported, the prediction performance of VS is often constrained by the small number of known active compounds sparsely distributed in the active regions of chemical space [21]. However, one of the tools, support vector machine (SVM), was reported to have substantial capability in identifying novel active compounds from sparse active data sets at low false-hit rates [21]. So far, SVM has already been used to discover inhibitors of ERK [22], RAF [23], HIV-1 protease [24], ABL [19], mGluR1 [25], dopamine receptor [26] for treating infectious disease, nervous disorder and many cancers.

In this work, we used the most comprehensive set of NTR1 inhibitors to develop a SVM model for discovering new lead scaffolds. First of all, inhibitors were divided into two groups by their publication date. Data published before 2011 were used to construct SVM model via 5-fold cross validation, while post-2011 data were used as independent testing. The discovery performance of the constructed model was evaluated by independent test and a screening of large chemical libraries. Finally, scaffolds of new leads identified were further analyzed based on their reported therapeutic effects.

In the cross validation, inhibitors and non-inhibitors were randomly divided into 5 groups of approximately equal size with 4 groups as training data and the remaining as testing. This process was conducted for all five possible training-testing compositions, and their average accuracy was calculated to determine the best parameters for constructing SVM model. By screening large chemical libraries (PubChem and MDDR), yield and false hit rate of the constructed model are further evaluated [27]. PubChem and MDDR contain high percentages of inactive compounds significantly different from the reported NTR1 inhibitors, which may artificially enhance the prediction enrichments. Therefore, a more strict test of the SVM model is applied by using a subset of true NTR1 non-inhibitors structurally similar to the known inhibitors, so that enrichment is not simply a separation of easily distinguishable features [28].

METHODS

Compound collection and construction of training and testing data sets

A total of 382 NTR1 inhibitors with structure information were collected from ChEMBL [14] and TTD [16]. In this work, 119 inhibitors with IC50/Ki ≤ 10μM were considered as active, which includes 99 and 20 inhibitors published before and after 2011. These known inhibitors cover a diverse set of compound scaffolds, which is very feasible for constructing SVM model. As illustrated in Figure 1, 12 scaffolds representing all 119 structures are ranked in descending order according to the number of known active inhibitors within each scaffold. In Figure 2, 12 examples out of 84 inhibitors within scaffold 1 together with their inhibitory activities (IC50 or Ki) against NTR1 are shown.

Sufficient negative data (non-inhibitors) are vital for reducing false-hits in constructing SVM model(*29*), but so far only a small amount of them were reported. Thus, putative non-inhibitors were generated by applying the same method as suggested by Liu et al [19] to represent the whole non-inhibitor chemical space. In this work, 67,054 putative non-inhibitors were generated by choosing representatives from families without active compounds, and virtual hit and false-hit rate in searching large chemical libraries were evaluated by using 13.56M PubChem and 168K MDDR compounds together with 322 MDDR compounds structurally similar to the known NTR1 inhibitors. Molecular similarity matching together with visual inspection were used to distinguish whether compounds are similar or not [21].

Molecular descriptor

Molecular descriptors are quantitative representations of structural and physicochemical features of molecules, which have been extensively used in deriving quantitative structure activity relationships (QSAR) and VS tools [19,24-26,30,31]. A total of 98 molecular descriptors listed in Supplementary Table 1 were used in this work, which include 18 descriptors in the class of simple molecular properties, 3 descriptors in the class of chemical properties, 35 descriptors in the class of molecular connectivity and shape, 42 descriptors in the class of electro-topological state.

SVM modeling and molecular similarity matching

SVM is a supervised learning and classification method used for distinguishing NTR1 inhibitors from non-inhibitors. Given a set of training data, SVM training algorithm constructs a model assigning new compound into the class of either inhibitors or non-inhibitors, which makes SVM a binary classifier [19].

Molecular similarity matching method used in this work is the Tanimoto similarity searching. Compounds similar to at least one known NTR1 inhibitor in the training set can be identified by calculating the Tanimoto similarity coefficient as list blow [32].

$$sim(i,j)=\frac{\sum_{d=1}^{l}x_{di}x_{dj}}{\sum_{d=1}^{l}(x_{di})^2+\sum_{d=1}^{l}(x_{dj})^2-\sum_{d=1}^{l}x_{di}x_{dj}}$$

Two compounds can be defined as similar to each other, when the similarity coefficient is larger than 0.9. More detail descriptions of the SVM modeling and similarity matching methods used in this work can be found in Supplementary Methods 1.

Measurement of VS performance in screening large libraries

VS performance in screening large chemical libraries is measured by several indicators [33], including yield (percentage of known positives predicted as virtual hits), hit-rate (percentage of virtual hits that are known positives), false-hit rate (percentage of virtual hits that are known negatives) and enrichment factor (magnitude of hit-rate improvement over random selection from chemical libraries).

RESULTS AND DISCUSSION

SVM model construction via 5-fold cross validation

5-fold cross validation was conducted to test SVM model in indentifying NTR1 inhibitors. The accuracies for predicting

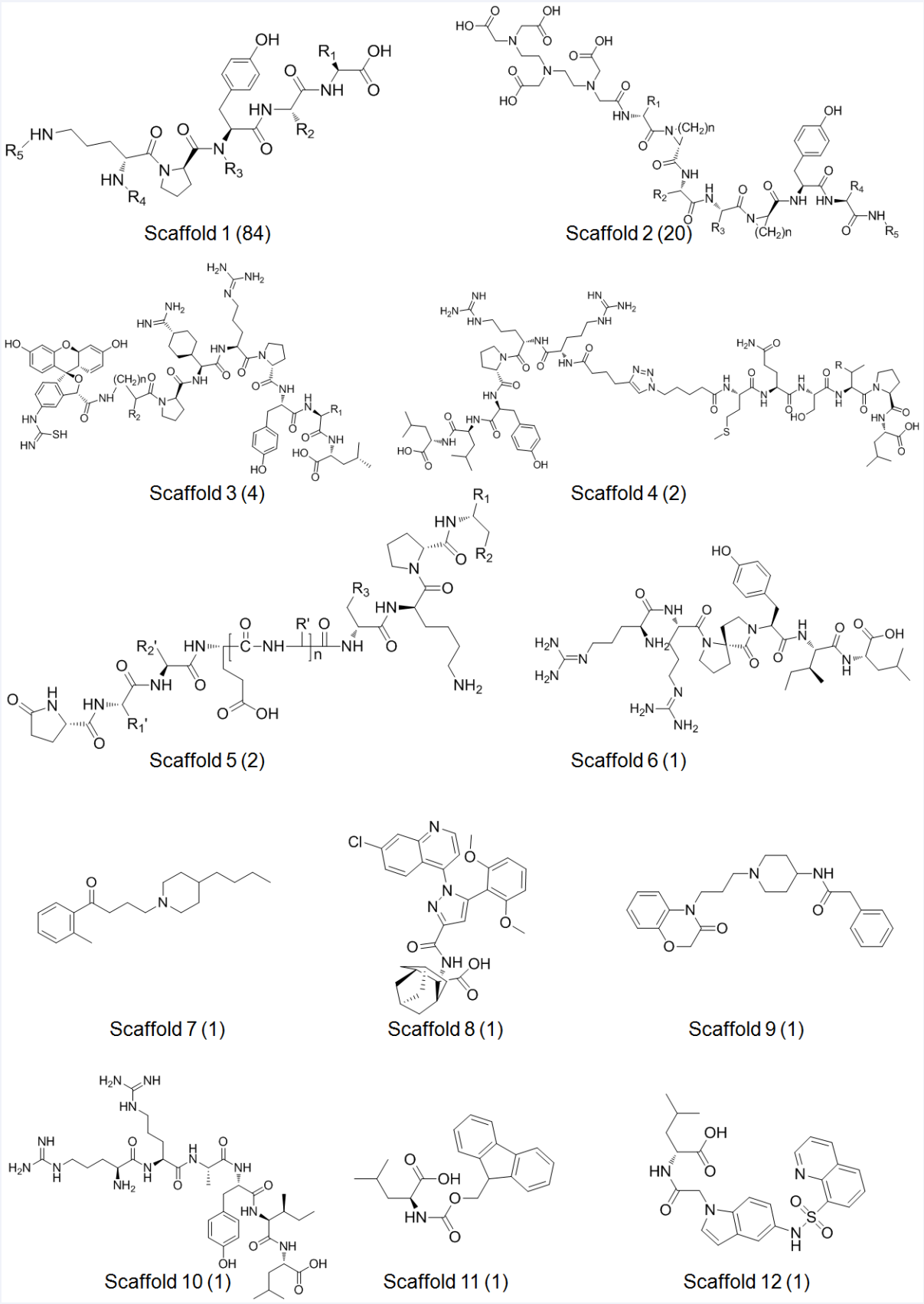


Figure 1 12 molecular scaffolds representing 119 known NTR1 inhibitors and the corresponding number of inhibitors within each scaffold (in bracket).

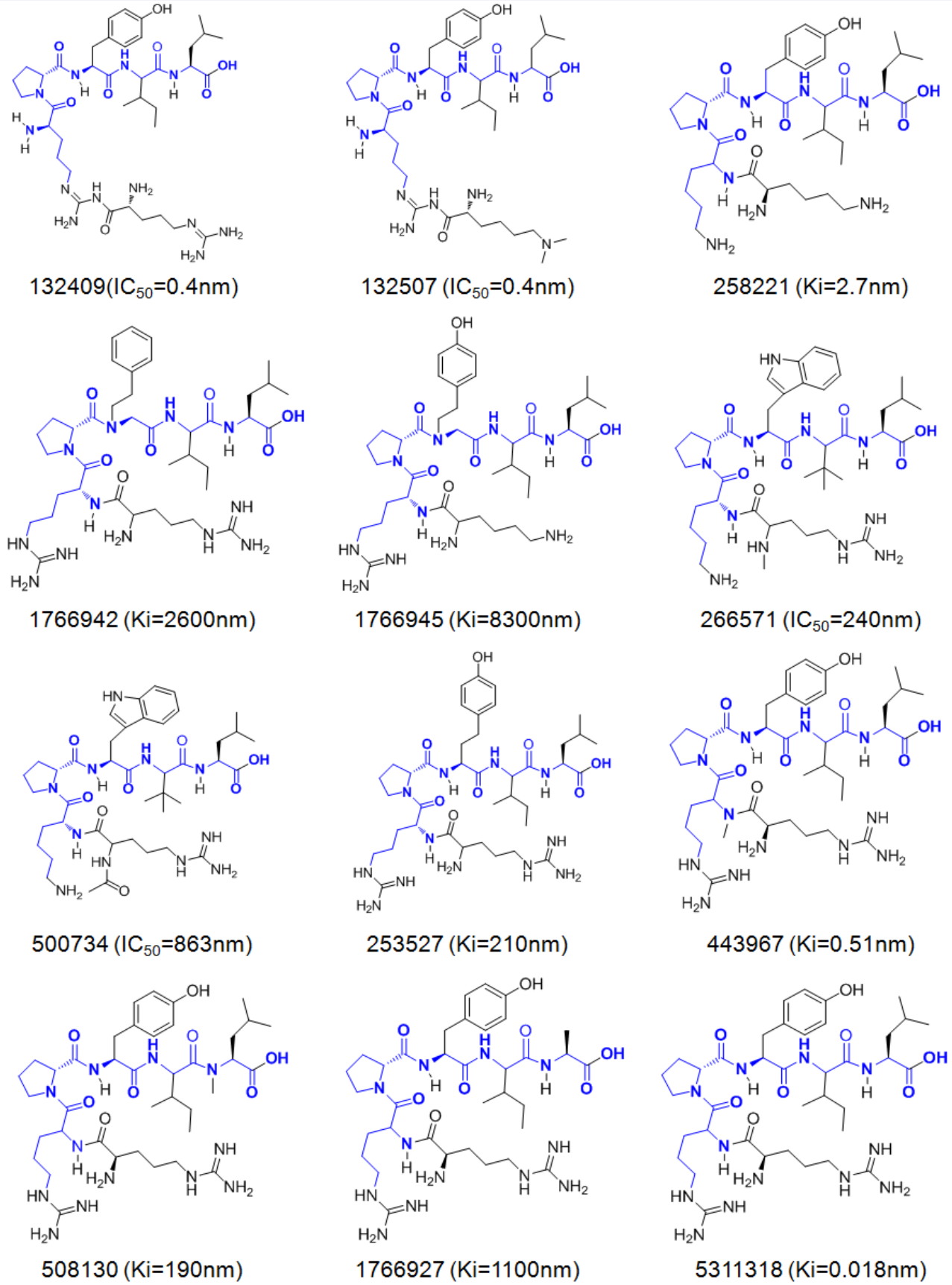


Figure 2 12 representative structures in scaffold 1 of known NTR1 inhibitors (blue color indicate the common structure shared by all inhibitors).

inhibitors and non-inhibitors in each fold are 75~95% and 99.9776~100% respectively, and the average accuracies are 84.8% and 99.9911% for inhibitor and non-inhibitors. According to a comprehensive literature review, no VS study was conducted to identify NTR1 inhibitors so far, therefore it is difficult to evaluate the prediction performance of SVM model by comparing to that of existing study. However, the prediction accuracy of NTR1 inhibitor is comparable to or better than that of studies of other targets [19,29, 32,34,35]. Moreover, prediction accuracy of non-inhibitor (99.9911%) statistically indicates a very low false-hit rate, which is key to guarantee the success rate of *in vitro* and *in vivo* inhibitor identification. Thus, SVM constructed in this work shows good prediction capability for indentifying known NTR1 inhibitor.

Independent test and virtual screening of large compound libraries

The SVM developed by pre-2011 NTR1 inhibitors were used to independently test 20 post-2011 inhibitors. The yield of independent testing data is 90% (18 out of 20), which is comparable to the reported 50~94% yields of various VS tools [36]. It may be inappropriate to directly compare the testing percentage of this work with that of the reported literatures, because the differences in molecular types, descriptors and parameters can lead to fluctuated results. However, among those 20 independent testing inhibitors, all 16 structurally similar to known NTR1 inhibitors and 2 out of 4 novel inhibitors are correctly predicted, which shows certain level of capacity in indentifying novel NTR1 inhibitors.

In addition to good hit identification performance reflected by 5-fold cross validation and independent test, the constructed SVM model demonstrates a substantially low false-hit rate. 3,452 compounds are identified as active in screening 13.56M PubChem compounds that exclude the known NTR1 inhibitors, representing only 0.0255% of all compounds in PubChem. In screening 168K MDDR compounds of protein families other than NTR1 related one (G-protein coupled receptor family), the estimated false-hit rate is 0.0684%. According to the substantially low false-hit rate in screening large chemical libraries, the constructed SVM model is like to show good capacity in reducing false-positive inhibitors.

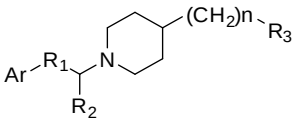
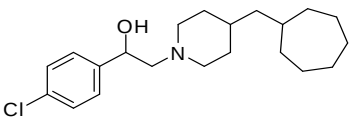
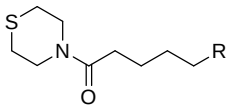
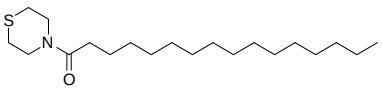
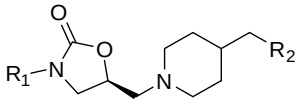
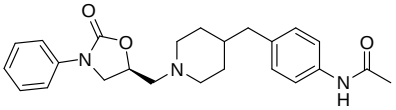
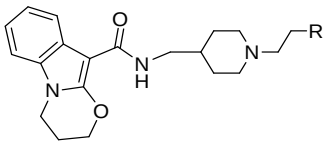
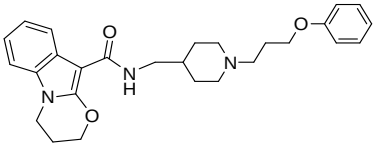
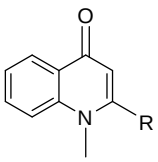
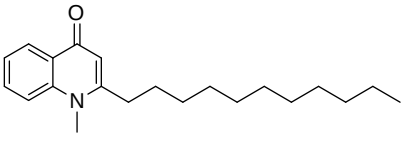
Moreover, false-hit rate of the constructed model was further evaluated by using 62 true NTR1 non-inhibitors indicated in ChEMBL, 6 of which are structurally similar to known inhibitor. All non-inhibitors, especially those 6, are correctly predicted as inactive, which suggests that SVM is capable of distinguishing NTR1 inhibitors from non-inhibitors that are structurally similar to know inhibitors.

Novel NTR1 inhibitors identified by SVM model

Studies suggested that SVM shows the capability of indentifying novel lead candidates rather than membership of compound families covered by the known active compounds [19,30]. In this work, the constructed SVM model identified 115 compounds from MDDR as active inhibitor, 96 of which are structurally similar to know NTR1 inhibitors. These 96 inhibitors can be grouped to scaffold 1, 2, 7, 10 and 11 in Figure 1 with 30, 1, 2, 62 and 1 compounds respectively.

17 novel scaffolds were identified in this study. Although no direct inhibitory activity against NTR1 has been reported, 5 of these scaffolds have already shown therapeutic effects on CNS disease or cancer. As shown in Table 1, Scaffold N1 (4-(cycloalkylalkyl) piperidine derivatives) was found to demonstrate neurotrophic and neuroprotective properties *in vivo* by regenerating

Table 1: 5 novel scaffolds with reported therapeutic effects on CNS disease or cancer together with a representative compound of the scaffold.

Index	Novel scaffold identified	Representative compound of the scaffold	Reported therapeutic effects of the scaffold
N1			Possess anti-allergic activity by facilitating the passage of active substances through physiological barriers (CNS related)
N2			Show *in vivo* neurotrophic and neuroprotective properties by the regeneration of animal sciatic nerve (CNS related)
N3			Affect the central nervous system and have sedative, tranquillizing, neuroleptic and/or antidepressant actions (CNS related)
N4			Treat CNS and gastrointestinal disorders which is primarily modulated by neurotensin and it corresponding receptor (CNS related)
N5			Demonstrate μM cytotoxic activities against several cancer cell lines, including HL60, N87, H460 and Hep G_2 (cancer related)

animal sciatic nerve [37]. Scaffold N2 (N-substituted aliphatic heterocyclic compounds) was reported to possess anti-allergic activity by facilitating the passage of active substances through physiological barriers, which is similar to the mechanism of NTR1 agonist NT8-13 in increasing CNS penetration and metabolic stability [38]. Scaffold N3 (piperidinylmethyloxazolidin-2-one derivatives) was proposed to affect central nervous system and have sedative, tranquillizing, neuroleptic and/or antidepressant actions without a noticeable cataleptic action [39]. Scaffold N4 (N-((1-substituentpiperidin-4-yl)methyl)-3,4-dihydro-2H-[1,3] oxazino[3,2-a]indole-10-carboxamide derivatives) was used as pharmaceuticals in the treatment of CNS and gastrointestinal disorders which is primarily modulated by neurotensin[40]. Scaffold N5 (quinolone alkaloids) provided a serial of compounds with μM cytotoxic activities against several cancer cell lines, including HL60, N87, H460 and Hep G_2 [41].

Besides their therapeutic effect on CNS disease and cancer, the identified novel inhibitors demonstrate certain level of correlation to other NT-related indications like inflammation and immunomodulatory disease [42-53], as shown in Figure 3. Involvement in multiple indications reflects the sophisticated nature of biological signaling networks affected by NTR1 [54-57]. In sum, some identified novel NTR1 inhibitors have already shown affects on NT-related diseases, but more predicted candidates are waiting for further evaluation. Large chemical libraries like PubChem provides a comprehensive pool of candidates in identifying more novel lead scaffolds, which asks for more effective VS tool with robustness and low false-hit rate to facilitate novel drug discovery.

CONCLUSION

Combinatorial SVM was used as a VS tool to identify NTR1 inhibitors and showed good prediction performance. SVM model developed by NTR1 inhibitors found before 2011 successfully

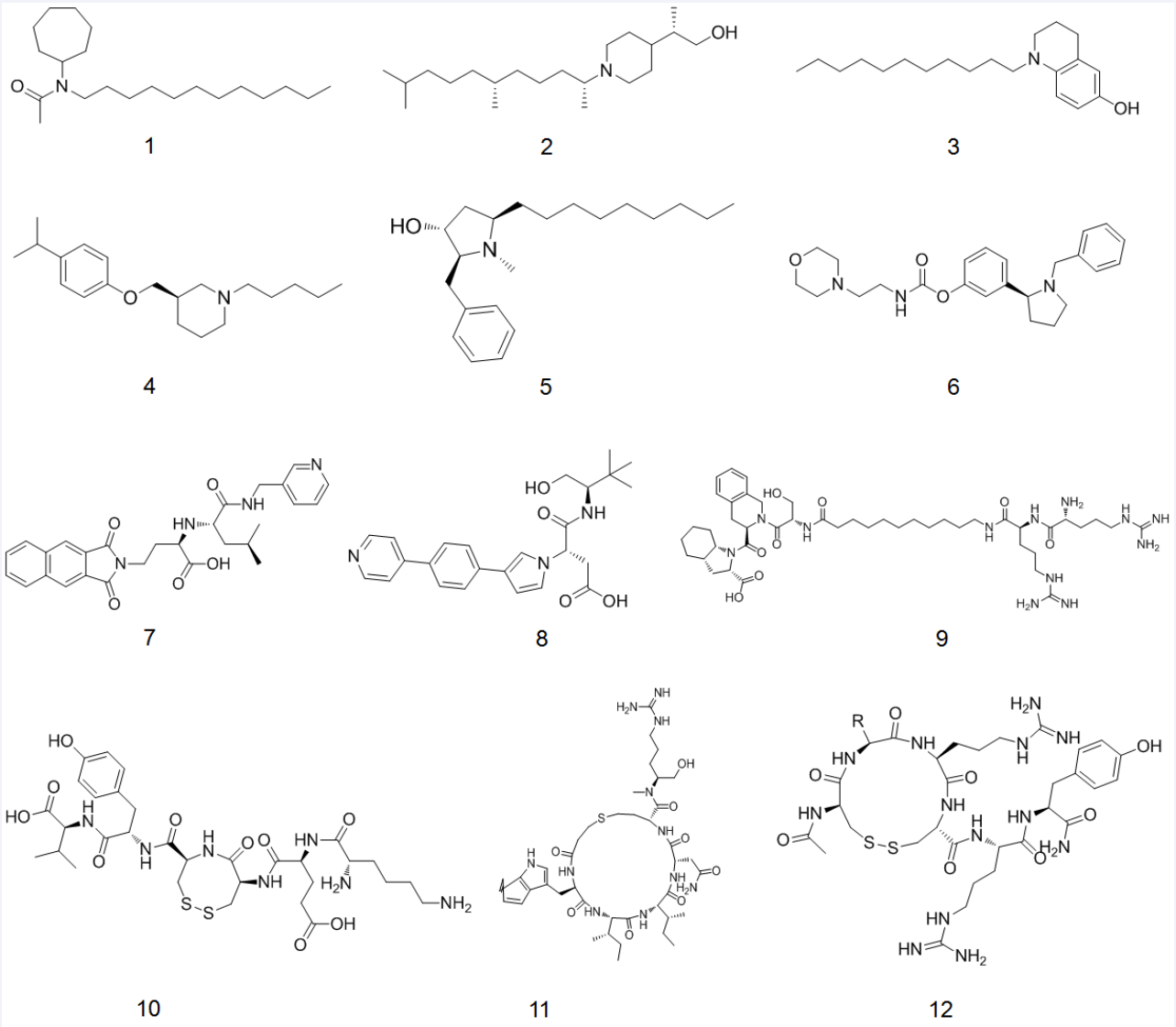


Figure 3 12 molecular examples identified as novel NTR1 inhibitor in this work with no effects on CNS disease and cancer reported so far, but with effects on other NT-related indications like inflammation and immunomodulatory disease.

identified 90% of post-2011 inhibitors, which demonstrates its capacity in indentifying novel NTR1 inhibitors. Virtual screening of large chemical libraries shows substantially low false-hit rates of 0.0255% and 0.0684% of 13.56M PubChem and 168K MDDR compounds. 62 experimentally verified NTR1 non-inhibitors were all correctly predicted as inactive, which suggests the capacity of SVM model in distinguishing NTR1 inhibitors from non-inhibitors. Some novel inhibitors proposed in this work have already shown clear therapeutic effect on both CNS disease and cancer, which raises urgent needs on conducting more comprehensive screening of a even larger chemical space to identify more inhibitors targeting NTR1.

REFERENCES

1. White JF, Noinaj N, Shibata Y, Love J, Kloss B, Xu F, et al. Structure of the agonist-bound neurotensin receptor. Nature. 2012; 490: 508-513.
2. Valerie NC, Casarez EV, Dasilva JO, Dunlap-Brown ME, Parsons SJ, Amorino GP, et al. Inhibition of neurotensin receptor 1 selectively sensitizes prostate cancer to ionizing radiation. Cancer Res. 2011; 71: 6817-6826.
3. Hui Ma, Yinglin Huang, Bo Zhang, Jingying Li, Yuan Wang, Xiaofeng Zhao, et al. Association between neurotensin receptor 1 (NTR1) gene polymorphisms and schizophrenia in a Han Chinese population. Journal of molecular neuroscience. 2013.
4. Hernandez ME, Rembao JD, Hernandez-Baltazar D, Castillo-Rodriguez RA, Tellez-Lopez VM, Flores-Martinez YM, et al. Safety of the intravenous administration of neurotensin-polyplex nanoparticles in BALB/c mice. Nanomedicine. 2013 .
5. Smith KE, Boules M, Williams K, Richelson E. NTS1 and NTS2 mediate analgesia following neurotensin analog treatment in a mouse model for visceral pain. Behav Brain Res. 2012; 232: 93-97.
6. Choi KE, Hall CL, Sun JM, Wei L, Mohamad O, Dix TA, et al. A novel stroke therapy of pharmacologically induced hypothermia after focal cerebral ischemia in mice. FASEB J. 2012; 26: 2799-2810.
7. Amorino GP, Deeble PD, Parsons SJ. Neurotensin stimulates mitogenesis of prostate cancer cells through a novel c-Src/Stat5b pathway. Oncogene. 2007; 26: 745-756.
8. Swift SL, Burns JE, Maitland NJ. Altered expression of neurotensin receptors is associated with the differentiation state of prostate cancer. Cancer Res. 2010; 70: 347-356.
9. Shimizu S, Tsukada J, Sugimoto T, Kikkawa N, Sasaki K, Chazono H, et al. Identification of a novel therapeutic target for head and neck squamous cell carcinomas: a role for the neurotensin-neurotensin receptor 1 oncogenic signaling pathway. Int J Cancer. 2008; 123: 1816-1823.
10. Souazé F, Dupouy S, Viardot-Foucault V, Bruyneel E, Attoub S, Gespach C, et al. Expression of neurotensin and NT1 receptor in human breast cancer: a potential role in tumor progression. Cancer Res. 2006; 66: 6243-6249.
11. Moody TW, Chan DC2, Mantey SA3, Moreno P3, Jensen RT3. SR48692 inhibits non-small cell lung cancer proliferation in an EGF receptor-dependent manner. Life Sci. 2014; .
12. Kern SE, Allen J, Wagstaff J, Shafer SL, Yaksh T. The pharmacokinetics of the conopeptide contulakin-G (CGX-1160) after intrathecal administration: an analysis of data from studies in beagles. Anesth Analg. 2007; 104: 1514-1520, table of contents.
13. Olszewski-Hamilton U, Hamilton G. Dependence of Relative Expression of NTR1 and EGFR on Cell Density and Extracellular pH in Human Pancreatic Cancer Cell Lines. Cancers (Basel). 2011; 3: 182-197.
14. Bento AP, Gaulton A, Hersey A, Bellis LJ, Chambers J, Davies M, et al. The ChEMBL bioactivity database: an update. Nucleic Acids Res. 2014; 42: D1083-1090.
15. Zhu F, Shi Z, Qin C, Tao L, Liu X, Xu F, et al. Therapeutic target database update 2012: a resource for facilitating target-oriented drug discovery. Nucleic Acids Res. 2012; 40: D1128-1136.
16. Qin C, Zhang C, Zhu F, Xu F, Chen SY, Zhang P, et al. Therapeutic target database update 2014: a resource for targeted therapeutics. Nucleic Acids Res. 2014; 42: D1118-1123.
17. Zhu F, Han B, Kumar P, Liu X, Ma X, Wei X, et al. Update of TTD: Therapeutic Target Database. Nucleic Acids Res. 2010; 38: D787-791.
18. Bolden JE, Peart MJ, Johnstone RW. Anticancer activities of histone deacetylase inhibitors. Nat Rev Drug Discov. 2006; 5: 769-784.
19. Liu XH, Ma XH, Tan CY, Jiang YY, Go ML, Low BC, et al. Virtual screening of Abl inhibitors from large compound libraries by support vector machines. J Chem Inf Model. 2009; 49: 2101-2110.
20. Shoichet BK. Virtual screening of chemical libraries. Nature. 2004; 432: 862-865.
21. Ma XH, Wang R, Yang SY, Li ZR, Xue Y, Wei YC, et al. Evaluation of virtual screening performance of support vector machines trained by sparsely distributed active compounds. J Chem Inf Model. 2008; 48: 1227-1237.
22. Jin F, Gao D, Wu Q, Liu F, Chen Y, Tan C, et al. Exploration of N-(2-aminoethyl)piperidine-4-carboxamide as a potential scaffold for development of VEGFR-2, ERK-2 and Abl-1 multikinase inhibitor. Bioorg Med Chem. 2013; 21: 5694-5706.
23. Jin F, Gao D, Zhang C, Liu F, Chu B, Chen Y, et al. Exploration of 1-(3-chloro-4-(4-oxo-4H-chromen-2-yl)phenyl)-3-phenylurea derivatives as selective dual inhibitors of Raf1 and JNK1 kinases for anti-tumor treatment. Bioorg Med Chem. 2013; 21: 824-831.
24. Spaltenstein A, Kazmierski WM, Miller JF, Samano V. Discovery of next generation inhibitors of HIV protease. Curr Top Med Chem. 2005; 5: 1589-1607.
25. Li GB, Yang LL, Feng S, Zhou JP, Huang Q, Xie HZ, et al. Discovery of novel mGluR1 antagonists: a multistep virtual screening approach based on an SVM model and a pharmacophore hypothesis significantly increases the hit rate and enrichment factor. Bioorg Med Chem Lett. 2011; 21: 1736-1740.
26. Zhang J, Han B, Wei X, Tan C, Chen Y, Jiang Y. A two-step target binding and selectivity support vector machines approach for virtual screening of dopamine receptor subtype-selective ligands. PLoS One. 2012; 7: e39076.
27. Wang Y, Suzek T, Zhang J, Wang J, He S, Cheng T, et al. PubChem BioAssay: 2014 update. Nucleic Acids Res. 2014; 42: D1075-1082.
28. Huang N, Shoichet BK, Irwin JJ. Benchmarking sets for molecular docking. J Med Chem. 2006; 49: 6789-6801.
29. Chen B, Harrison RF, Papadatos G, Willett P, Wood DJ, Lewell XQ, et al. Evaluation of machine-learning methods for ligand-based virtual screening. J Comput Aided Mol Des. 2007; 21: 53-62.
30. Han LY, Ma XH, Lin HH, Jia J, Zhu F, Xue Y, et al. A support vector machines approach for virtual screening of active compounds of single and multiple mechanisms from large libraries at an improved hit-rate and enrichment factor. J Mol Graph Model. 2008; 26: 1276-1286.
31. Xue Y, Yap CW, Sun LZ, Cao ZW, Wang JF, Chen YZ. Prediction of P-glycoprotein substrates by a support vector machine approach. J Chem Inf Comput Sci. 2004; 44: 1497-1505.

32. Ma XH, Wang R, Tan CY, Jiang YY, Lu T, Rao HB, et al. Virtual screening of selective multitarget kinase inhibitors by combinatorial support vector machines. Mol Pharm. 2010; 7: 1545-1560.

33. Li H, Yap CW, Ung CY, Xue Y, Li ZR, Han LY, et al. Machine learning approaches for predicting compounds that interact with therapeutic and ADMET related proteins. J Pharm Sci. 2007; 96: 2838-2860.

34. Liew CY, Ma XH, Liu X, Yap CW. SVM model for virtual screening of Lck inhibitors. J Chem Inf Model. 2009; 49: 877-885.

35. Briem H, Günther J. Classifying "kinase inhibitor-likeness" by using machine-learning methods. Chembiochem. 2005; 6: 558-566.

36. Ma XH, Jia J, Zhu F, Xue Y, Li ZR, Chen YZ. Comparative analysis of machine learning methods in ligand-based virtual screening of large compound libraries. Comb Chem High Throughput Screen. 2009; 12: 344-357.

37. Lardenois P, Frost J, Pasau P. 4-(cycloalkyl) piperidine and 4-(cycloalkylalkyl) PIPERIDINE piperidine derivatives, preparation thereof and therapeutical applications. State Intellectual Property Office of the P.R. China, WIPO Patent 1997009309. 1997.

38. Meroni C, Maiorana S, Rugarli PL, Pagella PG. N-substituted aliphatic heterocyclic compounds able to facilitate the passage of active substances through physiological barriers. European Patent Office, EP 0314008 A2. 1989.

39. Prucher H, Bartoszyk G. Piperidinylmethyloxazolidinones. United States Patent. US5, 714,502. Feb 1998.

40. Gaster LM, Wyman PA. Condensed indole derivatives as 5HT. sub 4-receptor antagonists. United States Patent, US5,852,014. 1998.

41. Huang X, Li W, Yang XW. New cytotoxic quinolone alkaloids from fruits of Evodia rutaecarpa. Fitoterapia. 2012; 83: 709-714.

42. Peck JV, Maiorana G. Acetamide derivatives as penetration enhancers for transdermal delivery of systemic agents. European Patent Office. EP 268220 A2. 1988.

43. Brown FK, Brown PJ, Bickett DM, Chambers CL, Davies HG, Deaton DN, et al. Matrix metalloproteinase inhibitors containing a (carboxyalkyl) amino zinc ligand: modification of the P1 and P2' residues. J Med Chem. 1994; 37: 674-688.

44. Bender SL, et al., Heteroaryl succinamides and their use as metalloproteinase inhibitors. World Intellectual Property Organization. WIPO1998017643. 1989.

45. Dupouy S, Viardot-Foucault V, Alifano M, Souazé F, Plu-Bureau G, Chaouat M, et al. The neurotensin receptor-1 pathway contributes to human ductal breast cancer progression. PLoS One. 2009; 4: e4223.

46. Schwartz RE, Liesch J, Hensens O, Zitano L, Honeycutt S, Garrity G, et al. L-657,398, a novel antifungal agent: fermentation, isolation, structural elucidation and biological properties. J Antibiot (Tokyo). 1988; 41: 1774-1779.

47. Wannamaker MW, et al. Inhibition of 2, 3-oxidosqualene cyclase by N-alkylpiperidines. Bioorganic & Medicinal Chemistry Letters. 1993; 3: 1175.

48. Brown T, Cooper D. 3- substituted piperidine derivatives. World Intellectual Property Organization. WIPO1992002501. 1992.

49. Lasslo A, Quintana R, Dugdale M, Johnson R, Naylor J. Development of novel surface-active compounds for prophylaxis against and treatment of thromboembolic complications. ASAIO journal. 1983; 6: 47.

50. Wang XX, Zan K, Shi SP, Zeng KW, Jiang Y, Guan Y, et al. Quinolone alkaloids with antibacterial and cytotoxic activities from the fruits of Evodia rutaecarpa. Fitoterapia. 2013; 89: 1-7.

51. Eriksson T, Karabelas K, Lindvall M. Peptides with immunomodulatory effects. United States Patent. US006103697A. 2000.

52. Galoppini C, Meini S, Tancredi M, Di Fenza A, Triolo A, Quartara L, et al. A new class of pseudopeptide antagonists of the kinin B1 receptor containing alkyl spacers. J Med Chem. 1999; 42: 409-414.

53. Wettlaufer DG, Nemoto PA. (Pyrrolidinyl) phenyl carbamates, compositions and use. United States Patent. USO05338739A. 1994.

54. Brun P, Mastrotto C, Beggiao E, Stefani A, Barzon L, Sturniolo GC, et al. Neuropeptide neurotensin stimulates intestinal wound healing following chronic intestinal inflammation. Am J Physiol Gastrointest Liver Physiol. 2005; 288: G621-629.

55. Roussy G, Beaudry H, Lafrance M, Belleville K, Beaudet N, Wada K, et al. Altered morphine-induced analgesia in neurotensin type 1 receptor null mice. Neuroscience. 2010; 170: 1286-1294.

56. Theoharides TC, Asadi S, Patel AB. Focal brain inflammation and autism. J Neuroinflammation. 2013; 10: 46.

57. Kruger WA, Monteith GR, Poronnik P. NHERF-1 regulation of EGF and neurotensin signalling in HT-29 epithelial cells. Biochem Biophys Res Commun. 2013; 432: 568-573.

Cite this article

Wang P, Hu J, Li Y, Xu F, Zhu F, et al. (2014) Identification of Novel Neurotensin Receptor 1 Inhibitors by Combinatorial Support Vector Machine. J Pharmacol Clin Toxicol 2(2):1024.