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# Relationships between molecular descriptors, drug-likeness scores, ADMET parameters and biological activity of tyrosine kinase inhibitors in a series of quinoline, quinazoline, pyrido- and pyrimido-pyrimidine derivatives


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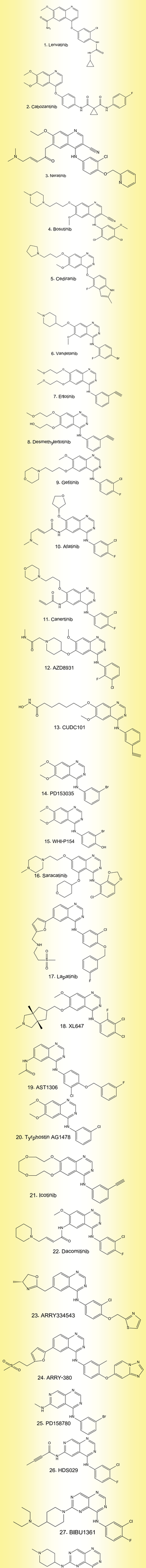
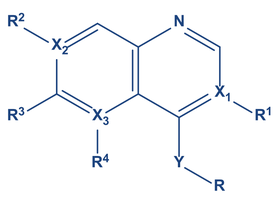



## BACKGROUND AND AIMS

The design of specific inhibitors of protein tyrosine kinases (PTKIs) is important both for fundamental research and for therapeutic strategies development in treatment of diseases such as cancer. The aim of this work was to explore the relationships between molecular descriptors (MDs), drug-likeness scores (DLs) and ADMET parameters of PTKIs, derivatives of quinoline, quinazoline, pyrido- and pyrimido-pyrimidine, in correlation studies with their experimentally obtained IC50 of target kinase activity.

## METHODS

MDs and DLs of investigated PTKIs were calculated using Molinspiration engines v2011.04 and v2011.06. TIs were calculated using *DRAGON* 6.0 *software* and ADMET properties by MedChem StudioTM and ADMET PredictorTM 6.5 (Simulations Plus, Inc., USA). All analyses were performed by OriginPro 8.0 (Origin Laboratories, USA).




Quinolines **1** - **4**: X1, X2, X3 = C
Quinazolines **5** - **24**: X1 -= N; X2, X3 = C
Pyrido-pyrimidines **25** - **26**: X1, X2 = N; X3 = C
Pyrimido-pyrimidines **27** - **28**: X1 - X3 = N

**Fig. 1.** General structure of investigated PTKIs

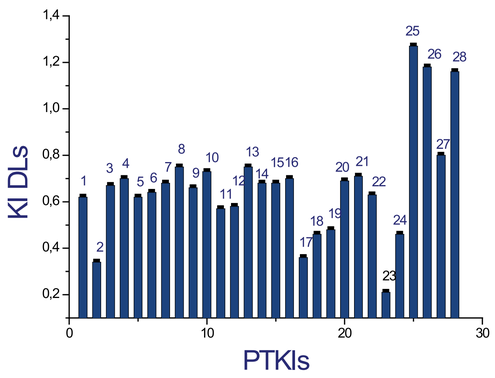



Fig. 2. Kinase drug-likeness scores (KI DLs) per each PTKI molecule

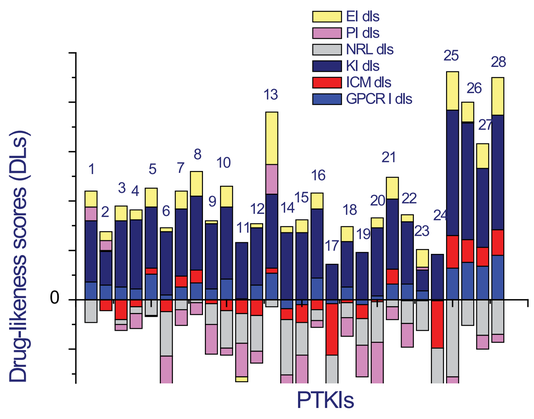



Fig. 3. Proportions od drug-likeness scores (DLs) per each PTKI

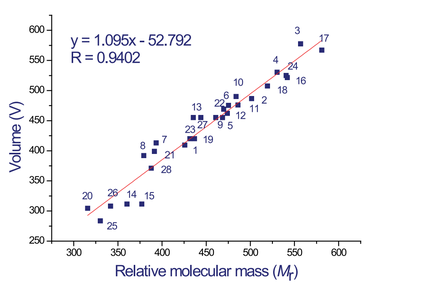



Fig.4 . The relationship between relative molecular mass and ($M_r$) and volume (V) of investigated PTKIs

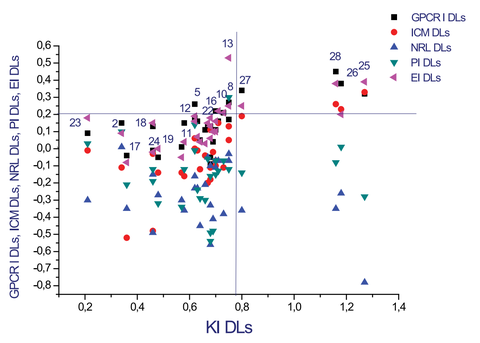



Fig. 5. Relationships kinase-likeness scores (KI DLs) with other DLs

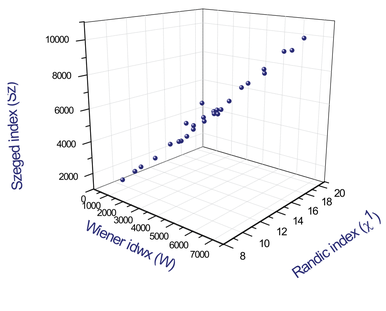



Fig. 6. Relationships betwen computed topological indices (TIs), Wiener index, Randic index connectivity and Szeged index

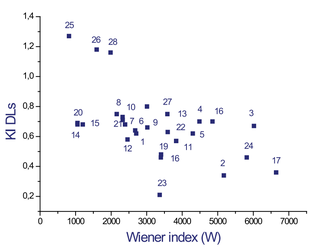



Fig. 7. The relationship between topological Wiener index and kinase-likeness score (KI DLs)

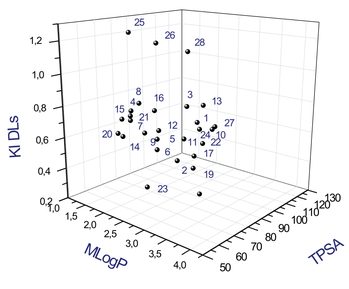



Fig. 8. Relationships between MLogP, TPSA and KI DLs of investigated PTKIs

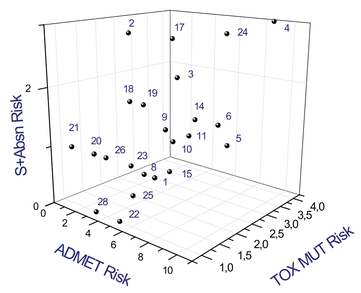



Fig. 9. Relationships between ADMET Risk, TOX MUT Risk and S+Absn Risk of investigated PTKIs

## RESULTS AND CONCLUSIONS

Protein tyrosine kinase inhibitors (PTKIs) (n = 28) with general structure displayed in Fig. 1 were explored in correlation studies between computed molecular descriptors (MDs), topological indices (TIs), drug-likeness scores (DLs) and predicted ADMET parameters (Table 1). The highest scores for kinase inhibitor likeness (KI DLs 0.90 - 1.27) were computed for pyrimido[5.4-d]pyrimidin-4-amine and pyrido[3.4-d]pyrimidin-4,6-diamines (**25** - **28**, Fig. 2). For these compounds DLs with GPCR ligand (0.21 - 0.45), ion channel modulator, ICM, (0.22 - 0.33) and enzyme inhibitor, EI, (0.21 - 0.36) were also computed (Fig. 5). Lower KI DLs (0.36 - 0.74) were computed for quinazoline derivatives (Fig. 2, Fig. 3). Significant correlations (R = 0.8869 – 0.9873) were obtained between MDs ($M_r$, *V*, TPSA) and TIs, *i.e.* Wiener number (W), Randić connectivity index ($X^1$) and Szeged index (Sz). (Fig. 4, Fig. 6) ADMET Predictor analyses of PTKIs with multiple DLs revealed that they are CYP 2D6 and CYP 3A4 substrates, with CYP Risk 1, CYP Code D6, and TOX Risk 3 or 4.
No significant correlations were found between MDs, TIs or ADMET parameters and IC50 of investigated compounds in series of anilinoquinazolines **5** - **24**.


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Table 1. Computed molecular descriptors (MDs), Drug-likeness scores (DLs) and ADMET parameters of investigated protein kinase inhibitors (PTKIs).

| No. | 'nib' molecule | MLogP | S+LogP | Mr | V | TPSA | Rule of 5 | ADMET Risk | S+Absn Risk | CYP Risk | TOX MUT Risk | TOX Risk | TOX FHM | TOX ATTP | TOX DM | TOX BCF | TOX hERG | TOX RAT | TOX BRM Rat | TOX BRM Mouse | GPCR l-dls | ICM-dls | KI-dls | NRL-dls | PI-dls | EI-dls | Platt index | Randić index | Balaban index | Harary index | Hyper Wiener index | Szeged index | Wiener index | Wiener polariity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Lenvatinib (E7080) | 2.35 | 2.938 | 425.874 | 409.5 | 103.54 | 0 | 2 | 0 | 1 | 3 | 1 | 0.386 | 4.307 | 4.307 | 4.307 | 5.476 | 1466.135 | 25.192 | 605.108 | 0.18 | 0.00 | 0.62 | -0.23 | 0.14 | 0.16 | 94 | 14.44 | 1.17 | 117.09 | 12818 | 4295 | 2706 | 48 |
| 2 | Cabozatinib | 1.998 | 4.469 | 501.518 | 486.5 | 98.78 | 1 | 6 | 3 | 1 | 1 | 2 | 0.004 | 2.303 | 2.303 | 2.303 | 5.521 | 702.524 | 2.672 | 179.946 | 0.15 | -0.11 | 0.34 | 0.01 | 0.10 | 0.09 | 118 | 17.91 | 0.93 | 155.25 | 30584 | 7823 | 5173 | 62 |
| 3 | Neratinib | 1.775 | 4.354 | 557.056 | 577.5 | 112.4 | 1 | 4 | 2 | 0 | 3 | 2 | 0.001 | 1.635 | 1.635 | 1.635 | 5.926 | 840.818 | 6.956 | 39.605 | 0.13 | -0.20 | 0.67 | -0.05 | -0.06 | 0.15 | 116 | 19.37 | 1.24 | 173.46 | 34336 | 9180 | 6020 | 62 |
| 4 | Bosutinib | 1.375 | 4.962 | 530.46 | 530.46 | 82.88 | 1 | 9 | 3 | 1 | 4 | 4 | 0.004 | 4.676 | 4.676 | 4.676 | 6.729 | 644.724 | 10.925 | 20.562 | 0.11 | -0.07 | 0.70 | -0.07 | -0.15 | 0.10 | 108 | 17.43 | 1.18 | 151.3 | 24042 | 7142 | 4488 | 60 |
| 5 | Cediranib | 2.462 | 5.101 | 468.507 | 455 | 72.5 | 0 | 8 | 1 | 2 | 3 | 4 | 0.01 | 3.532 | 3.532 | 3.532 | 6.192 | 217.82 | 21.998 | 50.335 | 0.26 | 0.06 | 0.62 | -0.16 | -0.01 | 0.19 | 110 | 17.01 | 1.02 | 145.13 | 23681 | 6907 | 4301 | 57 |
| 6 | Vandetanib | 2.959 | 5.342 | 475.37 | 475.37 | 59.51 | 0 | 5 | 1 | 1 | 4 | 2 | 0.028 | 4.511 | 4.511 | 4.511 | 6.348 | 346.438 | 8.294 | 36.165 | 0.05 | -0.12 | 0.64 | -0.45 | -0.29 | 0.04 | 92 | 14.53 | 1.19 | 117.55 | 12499 | 4515 | 2677 | 48 |
| 7 | Erlotinib | 1.698 | 3.136 | 393.445 | 413 | 74.73 | 0 | 2 | 0 | 1 | 3 | 1 | 0.488 | 11.51 | 11.51 | 11.51 | 5.502 | 1068.392 | 6.867 | 41.358 | 0.13 | 0.11 | 0.68 | -0.10 | -0.16 | 0.18 | 80 | 14.25 | 1.44 | 110.02 | 10435 | 3792 | 2396 | 43 |
| 8 | Desmethyl-erlotinib | 1.479 | 2.53 | 379.418 | 392 | 85.73 | 0 | 1 | 0 | 0 | 3 | 1 | 1.639 | 6.731 | 6.731 | 6.731 | 5.376 | 1188.766 | 6.422 | 45.236 | 0.17 | 0.13 | 0.75 | -0.03 | -0.12 | 0.25 | 78 | 13.75 | 1.49 | 105.19 | 9180 | 3477 | 2161 | 42 |
| 9 | Gefitinib | 2.304 | 4.826 | 460.94 | 455 | 68.74 | 0 | 3 | 1 | 0 | 3 | 2 | 0.057 | 19.758 | 19.758 | 19.758 | 6.398 | 700.22 | 9.748 | 45.247 | 0.11 | -0.04 | 0.66 | -0.21 | -0.30 | 0.03 | 92 | 15.14 | 1.12 | 120.93 | 14698 | 4768 | 3020 | 48 |
| 10 | Afatinib | 3.48 | 5.218 | 483.98 | 490 | 79.38 | 0 | 5 | 1 | 0 | 2.5 | 4 | 0.019 | 5.069 | 5.069 | 5.069 | 6.135 | 745.817 | 21.708 | 132.533 | 0.21 | -0.11 | 0.73 | -0.38 | -0.07 | 0.21 | 84 | 13.74 | 1.2 | 104.75 | 11010 | 3574 | 2325 | 42 |
| 11 | Canertinib | 2.529 | 4.296 | 485.95 | 476 | 88.61 | 0 | 5 | 1 | 0 | 3 | 4 | 0.007 | 5.092 | 5.092 | 5.092 | 5.722 | 956.461 | 3.501 | 104.206 | 0.01 | -0.14 | 0.57 | -0.30 | -0.34 | -0.05 | 100 | 16.53 | 1.24 | 137.97 | 19338 | 6023 | 3831 | 52 |
| 12 | AZD8931 | 1.886 | 3.985 | 473.94 | 462 | 88.61 | 0 | 2 | 0 | 0 | 3 | 2 | 0.279 | 6.465 | 6.465 | 6.465 | 5.746 | 824.303 | 4.62 | 70.334 | 0.15 | -0.16 | 0.58 | -0.36 | -0.12 | 0.04 | 100 | 15.98 | 1.29 | 134.52 | 17022 | 5660 | 2464 | 54 |
| 13 | CUDC101 | 2.52 | 3.416 | 435.483 | 455 | 102.8 | 0 | 3 | 1 | 1 | 3 | 1 | 0.008 | 3.991 | 3.991 | 3.991 | 5.74 | 746.442 | 6.034 | 89.725 | 0.27 | 0.05 | 0.75 | -0.07 | 0.30 | 0.53 | 88 | 15.64 | 1.32 | 121.93 | 19855 | 5291 | 3583 | 47 |
| 14 | PD153035 | 2.285 | 4.144 | 360.217 | 311.5 | 56.27 | 0 | 3 | 1 | 1 | 4 | 1 | 0.941 | 24.24 | 24.24 | 24.24 | 5.501 | 528.973 | 7.699 | 75.385 | -0.09 | -0.11 | 0.68 | -0.56 | -0.54 | 0.06 | 66 | 10.71 | 1.62 | 76.62 | 3649 | 1853 | 1054 | 35 |
| 15 | WHI-P154 | 1.513 | 3.685 | 377.201 | 311.5 | 73.7 | 0 | 2 | 0 | 0 | 3.5 | 2 | 0.376 | 12.864 | 12.864 | 12.864 | 5.242 | 462.183 | 217.518 | 467.437 | -0.05 | -0.18 | 0.68 | -0.33 | -0.49 | 0.13 | 70 | 11.12 | 1.55 | 81.69 | 4339 | 2098 | 1202 | 38 |
| 16 | Saracatinib | 1.71 | 4.107 | 542.04 | 521.5 | 90.44 | 1 | 5 | 1 | 1 | 4 | 2 | 0.029 | 2.247 | 2.247 | 2.247 | 6.468 | 666.879 | 22.67 | 144.818 | 0.22 | -0.10 | 0.70 | -0.11 | -0.07 | 0.16 | 120 | 18.64 | 1.08 | 168.00 | 24405 | 7925 | 4855 | 61 |
| 17 | Lapatinib | 2.179 | 4.968 | 581.069 | 567 | 106.35 | 1 | 9 | 3 | 1 | 1 | 4 | 0.012 | 14.961 | 14.961 | 14.961 | 6.206 | 1461.938 | 1.264 | 37.286 | -0.04 | -0.52 | 0.36 | -0.35 | -0.21 | -0.08 | 124 | 19.23 | 1 | 169.66 | 42954 | 10002 | 6645 | 59 |
| 18 | XL647 | 3.868 | 7.047 | 519.45 | 507.5 | 59.51 | 1 | 6 | 2 | 1 | 1 | 2 | 0.006 | 14.142 | 14.142 | 14.142 | 6.558 | 328.736 | 14.657 | 85.4 | 0.13 | -0.03 | 0.46 | -0.15 | -0.19 | 0.15 | 108 | 15.92 | 1.15 | 136.82 | 16336 | 5449 | 3401 | 55 |
| 19 | AST1306 | 3.176 | 4.635 | 436.88 | 420 | 76.14 | 0 | 7 | 2 | 1 | 1 | 3 | 0.017 | 30.676 | 30.676 | 30.676 | 5.781 | 1124.598 | 3.684 | 100.206 | -0.05 | -0.14 | 0.48 | -0.27 | -0.32 | 0.00 | 96 | 15.51 | 1.23 | 125.72 | 17803 | 5433 | 3407 | 49 |
| 20 | Tyrphostin AG1478 | 2.166 | 4.042 | 315.761 | 304.5 | 56.27 | 0 | 3 | 1 | 0 | 1 | 2 | 4.092 | 79.669 | 79.669 | 79.669 | 5.632 | 963.807 | 9.08 | 79.481 | 0.04 | -0.02 | 0.69 | -0.41 | -0.48 | 0.10 | 66 | 10.71 | 1.62 | 76.624 | 3649 | 1853 | 1054 | 35 |
| 21 | Icotinib | 1.698 | 2.958 | 391.429 | 399 | 74.73 | 0 | 1 | 1 | 0 | 1 | 0 | 0.812 | 10.516 | 10.516 | 10.516 | 5.377 | 765.663 | 4.916 | 42.542 | 0.16 | 0.15 | 0.71 | -0.07 | -0.13 | 0.22 | 84 | 14.33 | 1.28 | 113.18 | 9980 | 4602 | 2326 | 46 |
| 22 | Dacomitinib | 3.277 | 4.937 | 469.95 | 469 | 79.38 | 0 | 5 | 0 | 2 | 1 | 3 | 0.031 | 4.496 | 4.496 | 4.496 | 6.098 | 726.835 | 19.651 | 144.921 | 0.16 | -0.01 | 0.63 | -0.23 | -0.24 | 0.07 | 98 | 16.03 | 1.24 | 132.03 | 18.293 | 5510 | 3594 | 51 |
| 23 | ARRY334543 (Varlitinib) | 1.833 | 3.816 | 431.52 | 420 | 81.52 | 0 | 6 | 1 | 1 | 1 | 3 | 0.047 | 7.375 | 7.375 | 7.375 | 5.695 | 1641.326 | 1.323 | 5.12 | 0.09 | -0.01 | 0.21 | -0.30 | 0.03 | 0.18 | 100 | 15.64 | 1.09 | 127.01 | 17383 | 5243 | 3368 | 46 |
| 24 | ARRY-380 | 1.718 | 4.157 | 540.604 | 525 | 124.5 | 1 | 10 | 3 | 1 | 2 | 5 | 0.03 | 0.582 | 0.582 | 0.582 | 5.66 | 3911.614 | 1.908 | 3.579 | -0.01 | -0.48 | 0.46 | -0.49 | -0.12 | -0.02 | 128 | 18.82 | 0.94 | 169.69 | 35501 | 9138 | 5818 | 61 |
| 25 | PD158780 | 2.205 | 3.678 | 330.19 | 283.5 | 62.73 | 0 | 3 | 0 | 0 | 2 | 3 | 6.568 | 17.203 | 17.203 | 17.203 | 5.555 | 765.642 | 3.632 | 37.808 | 0.32 | 0.33 | 1.27 | -0.78 | -0.28 | 0.39 | 60 | 9.76 | 1.44 | 66.45 | 2665 | 1444 | 815 | 30 |
| 26 | HDS029 | 2.176 | 2.817 | 341.734 | 308 | 79.8 | 0 | 4 | 1 | 0 | 1 | 3 | 3.661 | 15.336 | 15.336 | 15.336 | 4.922 | 1000.906 | 5.787 | 20.74 | 0.38 | 0.23 | 1.18 | -0.26 | 0.01 | 0.20 | 74 | 12.06 | 1.37 | 89.89 | 6426 | 2590 | 1596 | 38 |
| 27 | BIBU1361 | 3.824 | 5.052 | 443.96 | 455 | 70.07 | 0 | 3 | 1 | 0 | 1 | 1 | 0.053 | 4.998 | 4.998 | 4.998 | 6.769 | 697.746 | 10.422 | 54.901 | 0.34 | 0.19 | 0.80 | -0.36 | -0.14 | 0.25 | 94 | 15.07 | 1.13 | 122.04 | 14805 | 5024 | 3010 | 50 |
| 28 | BIBX1382 | 2.948 | 3.912 | 387.85 | 371 | 78.86 | 0 | 3 | 0 | 0 | 1 | 3 | 0.73 | 6.458 | 6.458 | 6.458 | 6.129 | 814.289 | 7.673 | 31.32 | 0.45 | 0.26 | 1.16 | -0.35 | -0.08 | 0.38 | 84 | 13.08 | 1.31 | 101.35 | 8512 | 3398 | 1986 | 42 |

MLogP - lipophiliciy, TPSA - topological polar surface area, *Mr* - relative molecular mass, V – volume, Rule of 5 - absorption filter designed by Chris Lipinski et. al. , ADMET Risk - a global risk score, S+Absn Risk - low absorption risk, CYP Risk - MET Risk with inclusion of the CYP substrate rules, TOX Risk - risk of overall toxicity, including mutagenicity, TOX MUT Risk - risk of mutagenicity in *S. typhimurium*, TOX hERG - inhibition of the hERG potassium channel in human expressed as pIC50 in mol/L), TOX RAT - acute lethal toxicity in rat, TOX BRM Rat, - TD50 value of a particular compound in units of mg/kg/day, TD 50 - dose of a substance administered orally to rats over the course of their lifetimes that results in the appearance of tumors in 50 percent of their population) , TOX BRM Mouse - TD50 value in mice mg/kg/day, dls – drug-likeness score, GPCR l = G protein-coupled receptor ligand; ICM = ion channel modulator; KI = kinase inhibitor; NRL = nuclear receptor ligand; PI = protease inhibitor; EI = enzyme inhibitor.

5FIP 5-P-C

Drug Design and Discovery

Milena Jadrijevic-Mladar Takac

Poster presented at: MELBOURNE PSWC 2014 13-16 April

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