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Antitumor Activities and QSAR Analysis of Piperazinediones

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Introduction

Twenty four piperazinediones, screened on MDA-MB-231 breast cancer cell line, exhibited profound anticancer activities with IC_{50} ranged between 10^{-6} to 10^{-8} M (Teng and Wang etal, US patent no. US Patent no. 6,635,649 B2, Fig. 1). The lead TW01 demonstrated (1) inhibition on 18 cancer-related serine/threonine kinases (IC_{50} 1.73 μM/PKBa/Akt1, 2.32 μM/Fyn, 1.4 μM/Erk & 11.1 μM/MEK), PI 3 kinases, abl tyrosine kinase and tyrosine phosphatase (IC_{50} 1 ~ 0.1 μM) with activity comparable to that of Gleevec (Table 1). A receptor-independent 4D-QSAR paradigm was adopted for constructing the structure-based quantitative inhibition models as a function of conformation, alignment, and putative enzyme-binding, as well as for searching the pharmacophore of this series of inhibitors.

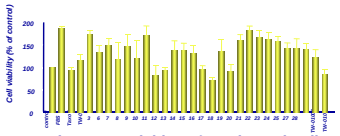

Fig. 1. Anticancer activities of 24 piperazinediones against MDA-MB-231 human breast CA.

Table 1. Comparison of TW01 with Gleevec.

	TW01	Gleevec
Tyrosine Kinase Abl	0.78 uM	0.25 uM*
K562 CML	0.03 uM	0.47uM**

.*Buchdunger E, Biochim Biophys Acta, 2001.
** Gottschalk S, Clin Can Res, 2004.

Method

Receptor-independent 4D-QSAR Formalism

QSAR models are constructed based on IC_{50} values (Fig. 2). The inhibitory measures are skewed toward potent inhibition. The range of –log IC_{50} values of the training set are small and spans 2 orders of magnitude (7.54 to 5.3).

GCOD (grid cell occupation descriptors) for building quantitative models as a function of conformation, alignment, and putative binding pharmacophore (IPE, Fig. 3). GCOD IPE types are represented as any ((all atoms in the molecule); np (nonpolar atoms); p+ (polar + atoms); p- (polar - atoms); hba (hydrogen bond acceptor atoms); hbd (hydrogen bond donor atoms); ar(aromatic atoms). Sets of 13 trial alignments were used in constructing the 4D-QSAR models. The selection criteria was with correlation coefficients R^2>0.8 and the cross-validation correlation coefficient Q^2 > 0.7. Significant models should reflect subtle differences in training set compounds leading to differentiation in high activity.

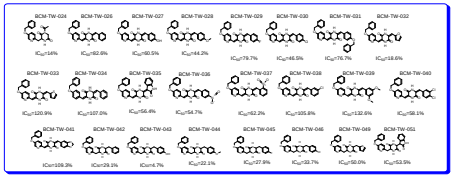

Fig. 2. IC_{50} against MDA-MB-231 breast cancer cell line

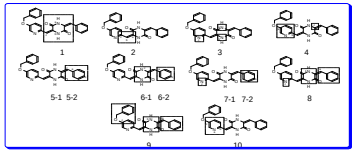

Fig. 3. Set of 13 trial alignments used in constructing 4D-QSAR models with position on BCM-TW-026.

Results and discussion

A four term model (Eq 1) and a five term model (Eq 2) were obtained. Reliability of the models are depicted as the residual plot between predicted and observed response, with the largest difference (–logIC_{50}) < 0.23 in the case of BCM-TW-032 (Fig. 4). The 3D pharmacophores suggested that non-polar type atom is significant on the right arm of the analogues.

Eq 1: -log IC_{50} = 5.88 + 3.76*GCOD(3,-4,-1,np) + -1.66*GCOD (2,-3,0,np)+1.40* GCOD(1,6,2,any) + -1.19*GCOD(2,2,2,any)
N=24 R^2 = 0.897 Q^2 = 0.825 LOF = 0.024

Eq 2: -log IC_{50} = 5.89 + 3.74*GCOD(3,-4,-1,np) + -1.79*GCOD (2,-3,0,np) +1.30*GCOD(1,6,2,np) + -1.18*GCOD(2,2,2,any) +0.29*GCOD(2,-4,-1,np)
N=24 R^2 = 0.906 Q^2 = 0.818 LOF = 0.028

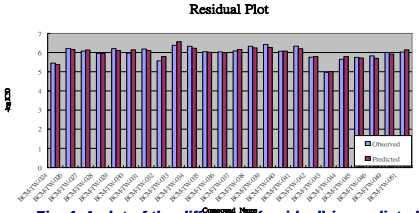

Fig. 4. A plot of the difference (residual) in predicted activity (Eq 1) and the observed activity of TW01 analogues analyzed.

Possible pharmacophore binding models were postulated (Fig. 5). Aromatic and hydrophobic pharmacohpores spreads over the binding site, similar to the ATP binding proposed by McGregor on pharmacophore mapping of 220 inhibitors on protein kinases. The piperazinediones might bind to the ATP binding site of tyrosine kinases corresponding to the "non-type" GCODs discovered by Eq 1 and Eq 2. Direction of structural modifications for activity are proposed. The active conformation are much contributed by GCOD (-2,1,10,np), implying that the non-polar property for analogues is important especially on the right arm. The model is used to predict the structures for Optimization of the activity (Fig. 6).

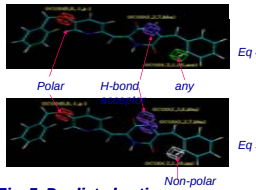

Fig. 5. Predicted active conformation using (a) Eq 1 and (b) Eq 2 with alignment 3. Green grid cells are IPE type "any" and white grid cells are IPE type "non-polar".

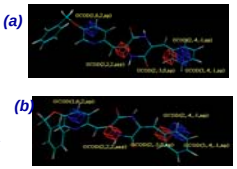

Fig. 6. (a) Predicted active (–log IC_{50} 7.19) and (b) predicted inactive (–log IC_{50} 4.10) using Eq 2. Blue grid cells are those contribute positively to inhibition potency, while the red grid cells reduce potency.

Conclusion

The piperazinediones are assumed to bind to protein kinases based on the inhibition profile of the lead TW01. Our receptor-independent 4D-QSAR analysis indicated that the non-polar property of piperazinediones has important contribution for binding to the ATP site of protein kinases according to McGregor's pharmacophore mapping of 220 protein kinase inhibitors,.

References

1. Correspondence: Hui-po Wang (hpw@tmu.edu.tw)
2. Hopfinger A. J.; Tseng, Y.; etal, Evaluation of Alignment Dependence in 3D-QSAR Model Construction Using 4D-QSAR Analysis", Internet J Chem, 2000, 3, 10.;
3. McGregor, M. J., A Pharmacophore Map of Small Molecule Protein Kinase Inhibitors, J. Chem. Inf. Model, 2007, 47(6), 2374-2382.