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Cyclic 1H-phospolane Oxides as a Potential Candidate Forcancer Therapy [†]

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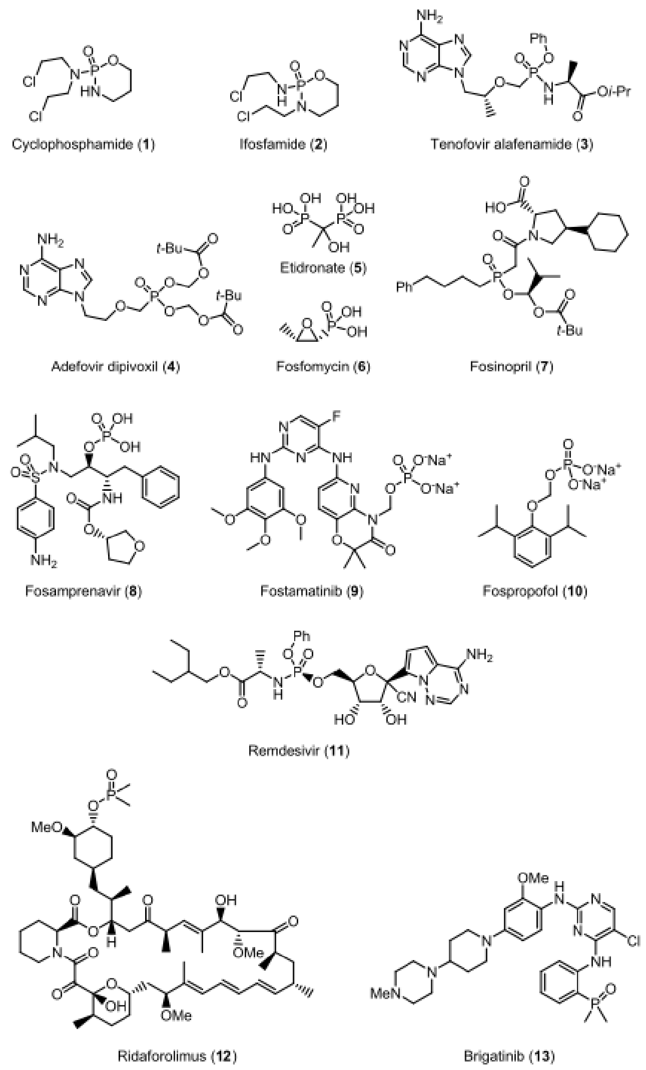
Abstract: Organophosphorus compounds have been investigated for applications in agricultural and medicinal applications for decades, and a considerable number of phosphorus-containing drugs have achieved commercial success. Recently by P. Finkbeiner atc in review have shown, that phosphine oxides and related phosphorus-containing functional groups are valuable polar structural elements and that they deserve to be considered as a routine part of every medicinal chemist's toolbox. A new approach to the synthesis of previously hard-to-obtained 3-alkyl-1H-phospholanes oxides was developed by us. In order to assess the potential of five-membered cyclic organophosphorus compounds in cancer therapy, we carried out docking 3-buthyl-1H-phospholanes oxide and 2,3-dihydrophosphole in the binding site of 24 human proteins involved in oncogenesis processes. Proteins were selected using the PharmMapper in-house pharmacophore model database. The results are presented in the article.

Keywords: 1H-phospolane oxides; docking; cancer therapy

1. Introduction

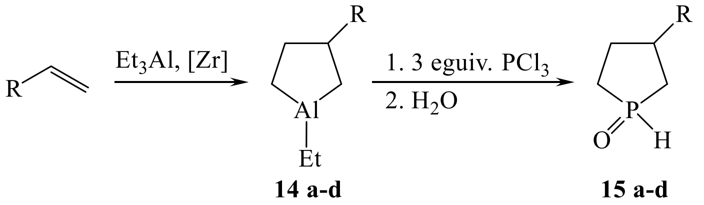
It is well known that organophosphorus compounds are used in medicine, moreover, a significant number of phosphorus-containing drugs have achieved commercial success. [1]. Recently by P. Finkbeiner atc in review have shown [2], that most of the approved phosphoruscontaining pharmaceuticals, for example drugs 1-6, contain a phosphate, a phosphoramide, or a phosphonate group, while phosphines, phosphinates, and phosphine oxides are rare (Scheme 1). For example, the phosphinate-based drug used to treat hypertension is fosinopril. (7). Recently that ridaforolimus (12), a dimethylphosphinic ester containing inhibitor of mammalian target of rapamycin (mTOR), progressed into phase III clinical studies for the treatment of sarcoma and that the anaplastic lymphoma kinase (ALK) inhibitor brigatinib (13) became the very first drug containing a phosphine oxide motif that was approved for the treatment of patients with metastatic non-small-cell lung cancer (NSCLC) [3,4].

At the same time, new approaches to the synthesis of previously undescribed cyclic phospholane oxides are being developed.



Scheme 1. Selected examples of phosphorus-containing drugs.

We have accumulated significant experience in the development of effective one-pot methods for the synthesis of five-membered phosphacarbocycles via transmetalation of aluminacarbocycles, obtained by catalytic cycloalumination [5–7] of olefins with $AlEt_3$ in the presence of Cp_2ZrCl_2 as a catalyst by PCl_3.



[Zr] = Cp_2ZrCl_2;
R = Bu (**a**), Hex (**b**), Oct (**c**), Bn (**d**).

Scheme 2. Synthesis of the 3-alkyl(aryl)-1*H*-phospholane oxides via transmetalation of alumolanes with PCl_3.

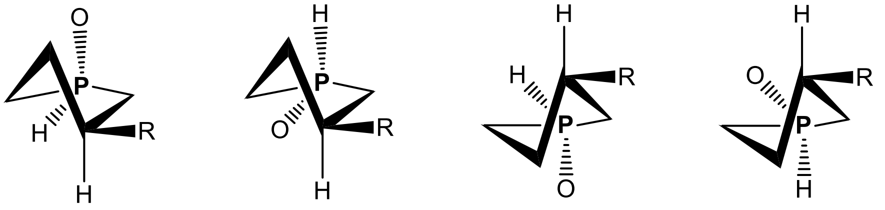
The synthesized compounds are chemically stable and may be promising in cancer therapy. In order to predict the biological properties for oncotherapy of a number of phospholane oxides, we screened using the PharmMapper. Then docking was employed using AutoDock to find out the mechanism of binding of the macromolecular targets to small active components under consideretion, which made it possible to determine the role of the P=O(H) group in the interaction with targets.

2. Methods

A search for potential protein targets for the studied ligands was carried out using the PharmMapper in-house pharmacophore model database. [8] For this, the optimized ligand structures were saved as SDF files, which were then uploaded to a web server available at http://www.lilab-ecust.cn/pharmmapper/. Pharmacophore mapping was carried out for the human protein targets set. From the resulting list of the potential human protein targets, only those involved in the processes of oncogenesis were selected for further study. AutoDock Tools (ADT) version 4.2.6 was used to carry out protein-ligand docking simulations [9]. Для визуализации результатов докинга использовалась the software Discovery Studio Visualizer version 21.1.0.20298 [10].

3. Results and Discussion

The potential human protein targets were identified for model compound 15a. Two diastereomers were taken into consideration with lowest twist conformation (Scheme 3). The screening results showed 17 ranked targets listed in Table 1, suggesting a correlation between the model compound and some indications. The highest fit scores for both isomers is androgen receptor, which is a member of the steroid/nuclear receptor superfamily and functions as a transcription factor. [11] This receptor is activated by binding to androgenic hormones that regulate male sex development. [12] Reactivation of the androgen receptor occurs in recurrent prostate cancer [13], making this protein a potential target for prostate cancer therapy.



R_PS; δ S_P,S; δ S_P,R; λ R_P,R; λ

Scheme 3. Diastereomers of phospholane.

The receptor was selected for the molecular docking simulation (Figure 1). Accordingly, the lowest energy docked conformation from the bioactive molecule forming intermolecular interactions P=O group with the residues which are somewhat different from the active sites of the co-crystallised binding region in the receptors taken for comparison.

Table 1. Potential targets and indications of compound 2a (RR configuration) by PharmMapper.

Target	PDBID	Normalised Fit Score
Androgen receptor	2ao6	0.7474
Progesterone receptor	1sqn	0.7377
Placenta growth factor-1	1fzv	0.5995
α-Catenin	1h6g	0.5987
α-Tocopherol transfer protein	1oiz	0.5734
Proto-oncogene tyrosine-protein kinase Src	1o4j	0.5167
Glyoxalase I	1qin	0.492
Prostatic acid phosphatase	1nd5	0.4819

Glycogen synthase kinase-3 β	1q4l	0.4192
Retinoic acid receptor beta	1xap	0.3296
Glucocorticoid receptor	1p93	0.3283
Growth factor receptor	1x0n	0.3272
Leukotriene A(4) hydrolase	1hs6	0.2997
Vitamin D nuclear receptor	1s0z	0.2799
Growth factor receptor-bound protein	2auh	0.256
Cysteine aspartyl protease-3	1nms	0.2223

An estimated free binding energy, final intermolecular energy as well as inhibition constant for each of the docked bioactive molecules were estimated (Table 2). In terms of inhibitory activity, phospholane is clearly lower to the co-crystalized ligand (FBE = -10.04 kcal/mol, Ki = 43.69 nM).

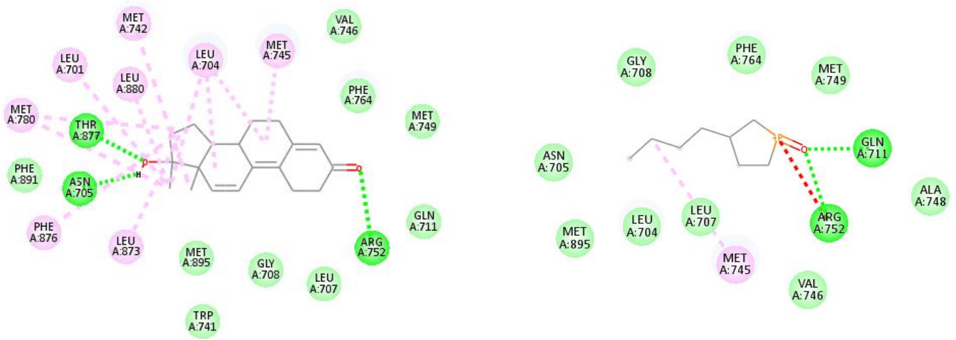


Figure 1. 2-D Diagram Showing the interactions of intermolecular interactions of co-crystalised ligand (left) and RR phospholane (right) with the active site residues of the androgen receptor. Hydrophobic interactions is colored in light pink, unfavorable positive-positive interaction is colored in red, van der Waals interactions is colored in mint green, conventional hydrogen bonding is colored in green.

Table 2. The lowest energy docked conformation для ряда изученных фосфороциклопентанов.

Ligand	FBE, kcal/mol	FIE, kcal/mol	Ki
15a RR_S	-5.13	-6.02	174.02 μM
15a SS_N	-5.19	-6.09	155.83 μM
15b RR_S	-5.47	-6.96	97.98 μM
15b SS_N	-5.69	-7.18	67.23 μM
15c RR_S	-6.00	-8.09	39.75 μM
15c SS_N	-6.07	-8.16	35.53 μM
15d RS_S	-6.18	-6.77	29.71 μM
15d SR_N	-6.30	-6.89	24.19 μM
15a' RR_S	-5.05	-6.24	199.21 μM
15a' SS_N	-5.80	-6.99	55.93 mM

In the case of RR phospholane interaction with the active site of the androgen receptor, the hydrogen interactions were formed between the P=O functional group Out of the total interactions there is a lack the hydrophobic contacts, obviously, therefore, with an increase of chain length of the alkyl substituent, an increase in the binding energy is observed. It should be noted that the effect of stereochemistry on the energy parameters is also manifested. Moreover, we have docked the tautomeric phosphine form P-OH [14], which can exist at the equilibrium concentration (denoted as 15') known for phosphine oxides (Table 2).

3. Conclusions

In summary, it was identified the potential anticancer activity for new 1H-phospolane oxides. The androgen receptor was selected for the molecular docking simulation which showed an active binding site between the P=O and protein. It was found that the design of the substituent in position 3 helps to model the binding activity.

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Conflicts of Interest: The authors declare no conflict of interest.

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