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PERIODINATES: A NEW CLASS OF PROTEIN TYROSINE PHOSPHATASE INHIBITORS

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Abstract: A series of periodinates has been synthesized and tested as protein tyrosine phosphatase substrates. Their potency is comparable to or higher than that of vanadates but much lower than that of peroxovanadates.

Protein tyrosine phosphatases (PTP) play important roles in glucose metabolism.[1] By the dephosphorylation of the tyrosine residues of the insulin receptor, the PTP deactivates the receptor. Thus inhibition of PTP preserves the active insulin receptor and mimics the insulin activity. Peroxovanadium compounds have been shown to be very active in the inhibition of the PTP.[2] The activity is believed to be due to the oxidation of active cysteine residue by the metal complex. While many peroxovanadium compounds have been synthesized and studied for their insulin-mimetic effects,[2,3] their application to clinical use is limited by their toxicity, poor absorption, and lack of specificity.[4] Our research interest is to design some organic compounds as PTP inhibitors. We thought that an organic oxidizing agent, preferably an analog of phosphotyrosine, might also inhibit the action of PTP.

Hypervalent iodine compounds such as Dess - Martin reagent are well known oxidizing agents in organic synthesis.[5,6] Some of them, like the trivalent iodine reagent phenyliodine(III) bis(trifluoroacetate), can oxidize phenyl or benzyl thiol in methanol or ethanol to form sulfinic esters.[7] Periodinates should also be able to modify the cysteine residue of the PTP because like those peroxovanadium compounds, they too are oxidizing agents. We therefore have synthesized a number of tri- and pentavalent periodinates to test their PTP inhibitory activity.

Preparation of periodinate compounds

Most periodinates were prepared (Table 1) by oxidation of iodides either with potassium perbromate or with peracetic acid. The *tert*-butylperoxy group of **4** was introduced on 2-iodosobenzenoic acid by addition of *t*-butylhydroperoxide-boron trifluoride.[8]

Characterization

All compounds have been characterized by infra-red, ^{1}H and ^{13}C NMR.[15] The iodoxy compounds show the two characteristic -IO_2 absorption peaks at 715 - 750 and 765 - 800 cm^{-1}. These two peaks were assigned as I-O stretching.[9]

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Result of biological test

All compounds have been tested by the 3,6-fluorescein diphosphate (FDP) assay[10] in which fluorescein is liberated by the action of protein tyrosine phosphatase 1B (PTP1B). The PTP inhibition activity is then measured by UV fluorescence. In addition, the PTP inhibition in rat liver endosomes was studied in another in vitro assay, namely the insulin receptor (IR) dephosphorylation assay[11] in which the insulin receptor is phosphorylated with ATP-P^{32}. The radioactive P^{32}-phosphate is eliminated from the receptor by the action of PTP enzyme that is obtained from rat liver extract. The PTP inhibition activity is then evaluated by radioactivity.

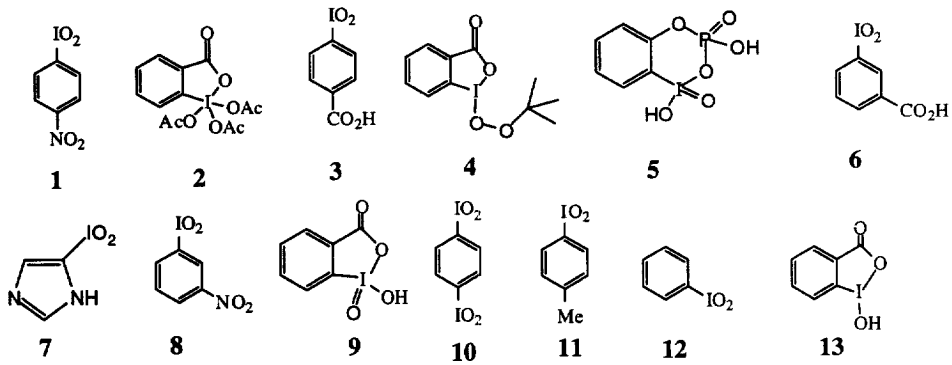

Figure 1. Structures of periodinate compounds

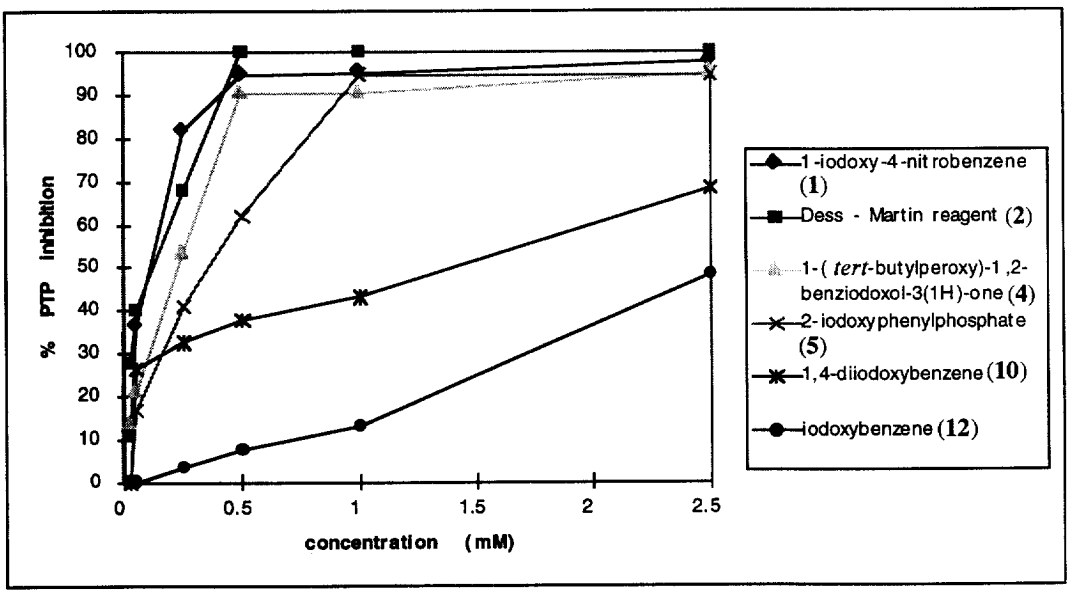

Figure 2. PTP inhibition activities of periodinates in FDP assay

Compd	Name	IC_{50}(mM) from FDP assay	% PTP inhibition from IR assay 1 mM (0.1 mM)	Yield	Preparation
1	1-iodoxy-4-nitrobenzene	0.13	90 % (30 %)	84 %	12*
2	Dess - Martin reagent	0.13	69 % (50 %)	90 %	13
3	4-iodoxybenzoic acid	0.20	69 % (36 %)	68 %	9
4	1-(*tert*-butylperoxy)-1,2-benziodoxol-3(1H)-one	0.23	78 % (48 %)	11 %	8
5	2-iodoxyphenylphosphate	0.35	----- (17 %)	70 %	14
6	3-iodoxybenzoic acid	0.89	67 % (32 %)	91 %	9
7	4-iodoxyimidazole	1.05	43 % (22 %)	85 %	12*
8	1-iodoxy-3-nitrobenzene	1.14	86 % (27 %)	85 %	12*
9	2-iodoxybenzoic acid	1.16	98 % (36 %)	82 %	6
10	1,4-diiodoxybenzene	1.41	30 %	66 %	12*
11	4-iodoxytoluene	1.51	47 % (6 %)	90 %	12*
12	iodoxybenzene	2.65	88 % (0 %)	99 %	12
13	2-iodosobenzoic acid	No inhibition	10 %	93 %	9
14	sodium vanadate	—	25 % (0 %)		
15	hydrogen peroxide	—	65 % (0 %)		

*: prepared in analogy to literature method

Table 1. IC_{50} values of periodinates and IR assay result

Discussion

In our studies, two in vitro assays were used. The relative PTP inhibition activities observed for the periodinates in FDP assay were different from that in IR assay. This discrepancy may be due to the fact that the PTP enzymes used in both assays were different.

There are many studies that focus on the use of vanadium compounds as antidiabetic agents due to their PTP inhibition ability.[2] Here we compare the activities of periodinates with that of sodium vanadate and hydrogen peroxide. All periodinate compounds except for **13** were more effective than vanadate in PTP inhibition.[11] Periodinates **1 - 6** were also significantly more effective than hydrogen peroxide in PTP inhibition.[11] This result is interesting because it indicates that periodinates might be good candidates for the design of antidiabetic drugs. Vanadium compounds are toxic and their toxicity is cumulative. On the other hand, periodinate compounds contain no metal atom and may not have this toxicity problem.

Compounds **9** and **13** are different in the valency of iodine. In **9** the iodine atom is pentavalent whereas in **13** it is trivalent. Compound **9** has an IC_{50} value of 1.16 mM whereas compound **13** does not show any inhibition even at 2.5 mM. On the other hand, a trivalent iodine compound with peroxy ligand (**3**), is significantly more potent than **9**. This shows that the PTP inhibition ability is correlated with the oxidizing power of the periodinate compounds. The table also shows the substituent effect. Among the compounds studied, the iodoxy compounds with para substituted electron withdrawing group are the most potent against PTP1B.

Conclusion

Many periodinates have been found to have PTP inhibition activity better than vanadate. The treatment of the thyroid gland involved organic iodides. However, the use of hypervalent iodine compound in medicine is

unprecedented. Since both the synthesis of aromatic iodides and their transformation to their oxidation products is relatively simple, we plan to explore more complex periodinates which may bind more specifically to the appropriate PTP enzymes.

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14. Preparation of 2-iodoxyphenylphosphate (**5**): To a solution of 100 mg of 2-iodophenylphosphate in 1 mL acetic acid at 0 °C was added 0.5 mL of 37% peracetic acid dropwise. The solution was warmed to room temperature and stirred for 30 min. The product 2-iodoxyphenylphosphate was precipitated by the addition of 3 mL dichloromethane in 70% yield. IR (Nujol): 746 cm^{-1}, 779 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 7.89 (d, 1 H, J = 8.0 Hz), 7.38 (m, 2 H), 7.11 (d, 1 H, J = 6.0 Hz); ^{13}C NMR (50 MHz, DMSO-d_6): δ 154.3, 142.1, 132.4, 128.6, 123.0, 115.0; ^{31}P NMR (121 MHz, DMSO-d_6): δ 0.39. MS (EI): m/z 345 (M^+ - 1), 235 (M^+ - HPO_4), 219 (235 - OH).
15. Characterization of selected compounds: (**1**): IR (Nujol): 725 cm^{-1}, 774 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 8.09 (d, 2 H, J = 8.2 Hz), 7.95 (d, 2 H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 146.0, 137.5, 123.9, 103.6. (**7**): IR (Nujol): 742 cm^{-1}, 767 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 7.95 (s, 1 H), 7.58 (s, 1 H), 7.56 (s, 1H), ^{13}C NMR (50 MHz, DMSO-d_6): δ 142.4, 130.2, 112.4. (**10**): IR (Nujol): 725 cm^{-1}, 760 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ 7.52 (s, 4 H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 139.2, 94.7.