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Synthesis and PTP1B Inhibition of 1,2-Naphthoquinone Derivatives as Potent Anti-Diabetic Agents

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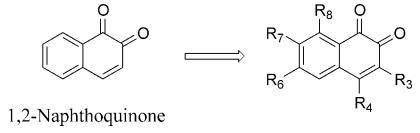
Abstract—A new series of 1,2-naphthoquinone derivatives was synthesized by various synthetic methods and evaluated for their ability to inhibit protein tyrosine phosphatase 1B (PTP1B). 1,2-Naphthoquinone derivatives with substituent at R_4 position showed submicromolar inhibitory activity, and compound **24** demonstrated 10- to 60-fold selectivity against the tested phosphatases. Also, several 4-aryl-1,2-naphthoquinone derivatives with substituents at R_3, R_6, R_7, or/and R_8 showed submicromolar inhibitory activity and good plasma stability.

Protein tyrosine phosphatase 1B (PTP1B) plays a role in the negative regulation of insulin signaling and is involved in the insulin resistance associated with Type 2 diabetes.[1] Kennedy et al. have demonstrated that mice lacking the PTP1B gene showed enhanced insulin sensitivity.[2] Treatment of these mice with insulin resulted in prolonged and increased protein phosphorylation of the insulin receptor in liver and muscle tissue, suggesting that PTP1B is critical in the dephosphorylation of the activated insulin receptor and that inhibition of this enzyme would be an excellent strategy for the treatment of Type 2 diabetes. Thus, PTP1B inhibitor could potentially ameliorate insulin resistance and normalize plasma glucose and insulin without inducing hypoglycemia, and could, therefore, be a major advance in the treatment of Type 2 diabetes.[3] Recently, small molecule inhibitors of PTP 1B as well as peptide mimetics were reported in papers and patents.[4,5]

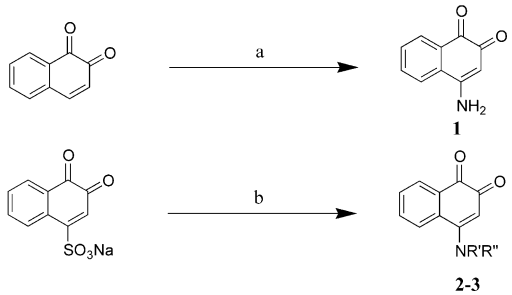
In the course of the search for protein tyrosine phosphatase inhibitor through HTS (high throughput screening) using chemical library of Korea Chemical Bank, 1,2-naphthoquinone skeleton was discovered as a hit toward PTP1B inhibitor.

We now report the synthesis of 1,2-naphthoquinone derivatives by various synthetic methods and their structure–activity relationship (SAR) study as a PTP1B inhibitor.



1,2-Naphthoquinone

A series of 1,2-naphthoquinone derivatives was synthesized according to the synthetic Schemes 1–12. First, the preparation of 1,2-naphthoquinone with substitutents at R_4 position was carried out as outlined in Schemes 1–6.



Scheme 1. (a) NaN_3, AcOH, 40 °C; (b) $HNR'R''$, K_2CO_3, H_2O, room temperature.

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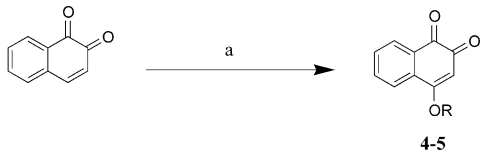
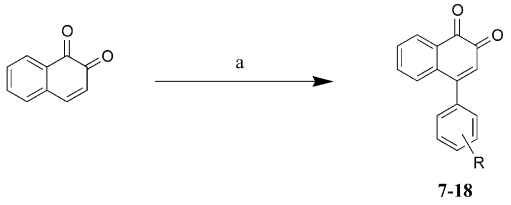
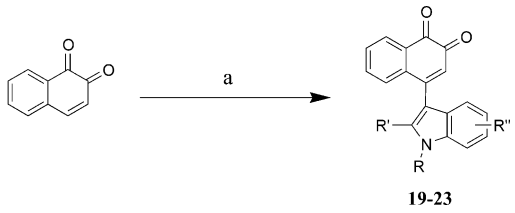


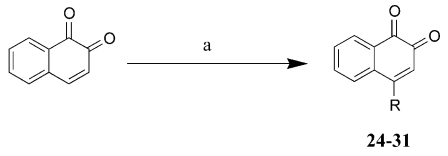
Scheme 2. (a) ROH, $CeCl_3 \cdot 7H_2O$, $NaIO_3$.



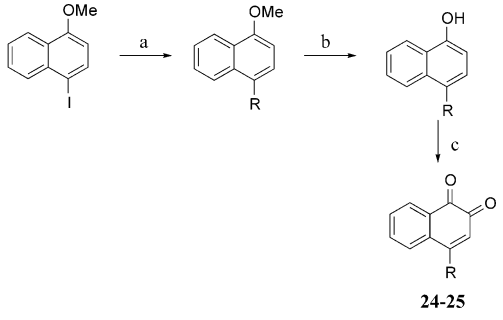
Scheme 3. (a) $Pd(OAc)_2$, acetic acid, arene, reflux.



Scheme 4. (a) Indole derivatives, $CeCl_3 \cdot 7H_2O$, $NaIO_3$, *t*-BuOH, 40 °C.

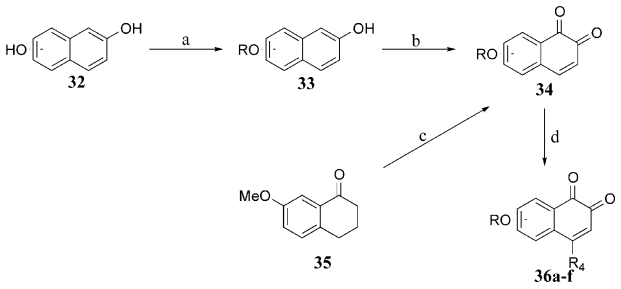


Scheme 5. (a) Copper(I) cyanide, alkyl or aryl Grignard reagents, −78 → −20 °C, THF.

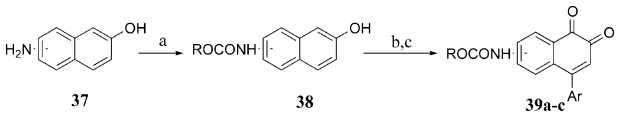


Scheme 6. (a) Benzyl or cyclohexylmagnesium halide, $Ni(dppp)Cl_2$, ether, reflux; (b) BBr_3, CH_2Cl_2, −78 °C; (c) benzene seleninic anhydride, THF, 50 °C.

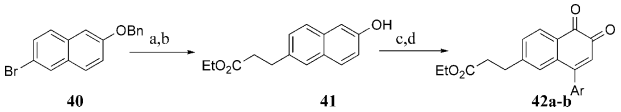
Commercially available 1,2-naphthoquinone was treated with sodium azide in glacial acetic acid to afford 4-amino-1,2-naphthoquinone (**1**).[6] 1,2-Naphthoquinone-4-sulfonic acid sodium salt (from Aldrich, **6**) reacted with alkyl or aryl amines in the presence of K_2CO_3 to produce the corresponding 4-alkyl or arylamino substituted-1,2-naphthoquinones (**2** and **3**). Introduction of alkoxy group at R_4 position was achieved by Takuwa procedure using cerium chloride and sodium iodate in alcohol to give the corresponding compounds (**4**–**5**) (Scheme 2).[7]



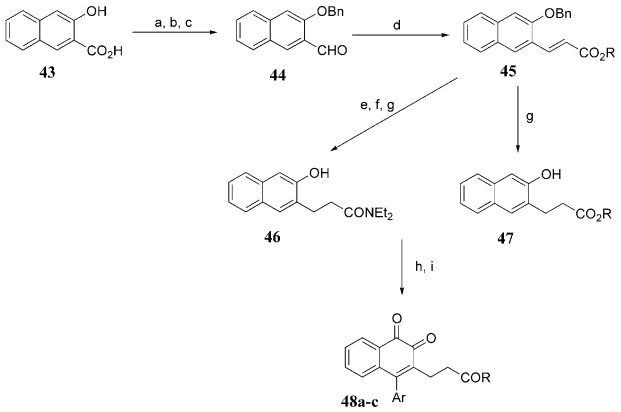
Scheme 7. (a) Bromopentane, K_2CO_3, acetone, reflux or methyl 2-hydroxy-3-phenylpropionate, DEAD, PPh_3, benzene, room temperature; (b) $(PhSeO)_2O$, THF, 50 °C; (c) SeO_2, AcOH, 60 °C; (d) $Pd(OAc)_2$, benzene, AcOH, reflux or indole, $CeCl_3$ $7H_2O$, $NaIO_3$, *t*-BuOH, 40 °C.



Scheme 8. (a) Benzyl chloroformate or ethyl chloroformate, Na_2CO_3, THF/H_2O, 0 °C → room temperature; (b) $(PhSeO)_2O$, THF, 50 °C; (c) $Pd(OAc)_2$, benzene, AcOH, reflux or indole, $CeCl_3$ $7H_2O$, $NaIO_3$, *t*-BuOH, 40 °C.



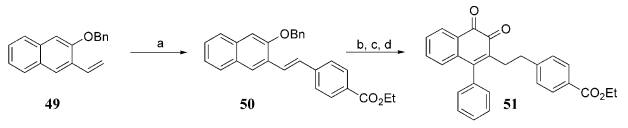
Scheme 9. (a) Methyl acrylate, $Pd(OAc)_2$, *n*-Bu_4NCl, KOAc, DMF, 150 °C; (b) 10% Pd/C, H_2, methanol, room temperature; (c) $(PhSeO)_2O$, THF, 50 °C; (d) $Pd(OAc)_2$, benzene, AcOH, reflux or indole, $CeCl_3$ $7H_2O$, $NaIO_3$, *t*-BuOH, 40 °C.



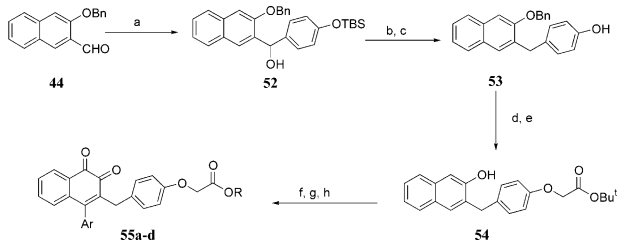
Scheme 10. (a) BnBr, K_2CO_3, acetone, reflux; (b) $LiAlH_4$, THF, 0 °C, (c) MnO_2, dioxane, room temperature; (d) $PPh_3{=}CHCO_2R$, THF; (e) NaOH, THF/H_2O; (f) Et_2NH, HOBt, EDCI; (g) 10% Pd/C, H_2, methanol, room temperature; (h) $(PhSeO)_2O$, THF, 50 °C; (i) $Pd(OAc)_2$, benzene, AcOH, reflux or indole, $CeCl_3$ $7H_2O$, $NaIO_3$, *t*-BuOH, 40 °C.

The 1,2-naphthoquinones with aryl substituent at R_4 position (**7**–**18**) were prepared by literature modification (Scheme 3) using $Pd(OAc)_2$ in arene and acetic acid under the reflux condition.[8]

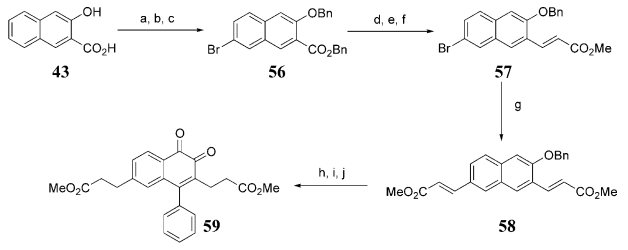
Another aryl substitution at R_4-position with indole was presented according to Scheme 4. 1,2-Naphthoquinone



Scheme 11. (a) Ethyl *p*-bromobenzoate, $Pd(OAc)_2$, *n*-Bu_4NCl, KOAc, DMF, 150 °C; (b) 10% Pd/C, H_2, methanol, room temperature; (c) $(PhSeO)_2O$, THF, 50 °C; (d) $Pd(OAc)_2$, benzene, AcOH, reflux.



Scheme 12. (a) (4-Bromophenoxy)-tert-butyldimethylsilane, *n*-BuLi, THF, 0 °C then THF, −20 → 0 °C, THF; (b) Et_3SiH/TFA, CH_2Cl_2, 0 °C; (c) TBAF, THF, 0 °C; (d) $BrCH_2CO_2Bu^t$, K_2CO_3, KI, acetone, reflux; (e) 10%-Pd/C, H_2, EtOH, room temperature; (f) $(PhSeO)_2O$, THF, 50 °C; (g) $Pd(OAc)_2$, benzene, AcOH, reflux or indole, $CeCl_3$ $7H_2O$, $NaIO_3$, *t*-BuOH, 40 °C; (h) TFA, CH_2Cl_2, 0 °C.



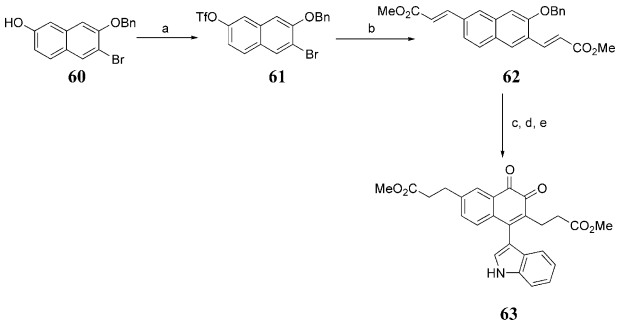
Scheme 13. (a) Br_2, AcOH, 0 °C → reflux; (b) Sn, 12 N HCl, AcOH, reflux; (c) BnBr, K_2CO_3, acetone reflux; (d) $LiAlH_4$, THF, 0 °C, (e) MnO_2, dioxane, room temperature; (f) $PPh_3{=}CHCO_2R$, THF; (g) methyl acrylate, $Pd(OAc)_2$, *n*-Bu_4NCl, KOAc, DMF, 150 °C; (h) 10%-Pd/C, H_2, EtOH, room temperature; (i) $(PhSeO)_2O$, THF, 50 °C; (j) $Pd(OAc)_2$, benzene, AcOH, reflux.

reacted with indole or indole derivatives in the presence of $CeCl_3{\cdot}7H_2O$ and $NaIO_3$ to afford 4-(indol-3-yl)-1,2-naphthoquinones (entries 19–23).[9]

A methodology to introduce alkyl or aryl group at R_4 position from 1,2-naphthoquinone using Grignard reagent with copper cyanide was attempted as shown in Scheme 5.[10]

Cyclohexyl or benzyl group at R_4 could be obtained by three-step synthesis from 1-iodo-4-methoxynaphthalene (Scheme 6). 1-Iodo-4-methoxynaphthalene was coupled with benzyl or cyclohexyl Grignard reagents in the presence of $Ni(dppp)Cl_2$ in ether under the reflux condition to produce the coupling product, followed by demethylation using BBr_3, and oxidation with benzene seleninic anhydride to afford the desired compounds (**24** and **25**).

4-Aryl-1,2-naphthoquinone derivatives with substituents at R_3, R_6, R_7, or/and R_8 were prepared according to the synthetic Schemes 7–14. First, alkoxy-linked 4-aryl-1,2-naphthoquinones were prepared by Scheme 7.



Scheme 14. (a) Trifluoromethanesulfonic anhydride, pyridine, CH_2Cl_2, 0 °C → room temperature; (b) methyl acrylate, $Pd(OAc)_2$, *n*-Bu_4NCl, $NaHCO_3$, DMF, 120 °C; (c) 10%-Pd/C, H_2, EtOH, room temperature; (d) $(PhSeO)_2O$, THF, 50 °C; (e) indole, $CeCl_3$ $7H_2O$, $NaIO_3$, *t*-BuOH, 40 °C.

Alkylation of naphthalenediol (**32**) produced the mono substituted compound (**33**), which upon treatment with benzene seleninic anhydride[11] afforded 1,2-naphthoquinone (**34**). Substitution of 1,2-naphthoquinone at R_4 position with benzene[8] or indole[9] produced 4-aryl-1,2-naphthoquinone with alkoxy group (**36**). Also methoxy substituted 1,2-naphthoquinone could be prepared from the corresponding tetralone (**35**) by SeO_2 oxidation.[12] The alkoxycarbonylamino-linked 1,2-naphthoquinones were prepared by Scheme 8. Amino-2-naphthol (**37**) reacted with benzyl or ethyl chlorofomate to give the corresponding carbamates (**38**), followed by oxidation and substitution (**39**) in a similar manner to Scheme 7.

The carbon-linked 1,2-naphthoquinones were achieved by various synthetic routes. Bromonaphthylbenzyl ether (**40**) was treated with ethyl acrylate and $Pd(OAc)_2$ in DMF to give α,β-unsaturated ester. Hydrogenation using Pd/C under H_2 atmosphere furnished **41**, and which was converted to **42** according to same oxidation and R_4 substitution procedure to Scheme 7.

Commercially available 3-hydroxy-2-naphthoic acid (**43**) was benzylated, and reduced by lithium aluminum hydride to produce alcohol, followed by oxidation (MnO_2) to afford benzyloxynaphtylaldehyde (**44**). Introduction of α,β-unsaturated ester using $PPh_3{=}CHCO_2R$ gave **45**.

Compound **45** was hydrogenated by Pd/C under H_2 gas to produce **47**, followed by oxidation and aryl substitution to afford the corresponding 1,2-naphthoquinones (**48**). In Scheme 11, vinyl naphthylether (**49**) was coupled with ethyl 4-bromobenzoate in the presence of $Pd(OAc)_2$ to give **50**, which was converted to **51** according to Scheme 7.

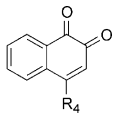
Treatment of *t*-butyldimethylsilyl protected 4-bromophenol with *n*-butyllithium followed by the addition of aldehyde (**44**) furnished the corresponding alcohol (**52**). Reduction of **52** with triethylsilane/trifluroacetic acid and desilylation with tetrabutylammonium fluoride afforded **53**, followed by alkylation using *t*-butyl bromoacetate, deprotection of benzyl group, and then converted to the final product **55**.

Tri-substituted 1,2-naphthoquinones were prepared according to Schemes 13 and 14.

3-Hydroxy-2-naphthoic acid (**43**) was brominated by bromine and benzylated to produce **56**. Compound **56** was reduced by lithium aluminum hydride to produce alcohol, followed by oxidation (MnO_2) afforded benzyloxynaphtylaldehyde. Introduction of α,β-unsaturated ester with $PPh_3{=}CHCO_2R$ gave **57**. Introduction of another α,β-unsaturated ester with methyl acrylate and $Pd(OAc)_2$ gave **58**. Compound **58** was hydrogenated by Pd/C under H_2 gas, followed by oxidation and aryl substitution produced **59**. Compound **60**[13] reacted with TfO_2 to give **61**. Coupling of **61** with methyl acrylate in the presence of $Pd(OAc)_2$ furnished di-unstaturated ester (**62**), which was further converted to final compound **63** according to Scheme 13.

The test compounds were evaluated for their in vitro inhibitory activity against recombinant human PTP1B using fluorescein diphosphate (FDP) as the substrate. Enzyme activity was assayed by measuring the fluorescence of the product, fluorescein monophosphate (FMT) at 485 nm (excitation) and 538 nm (emission).

Table 1. Inhibitory activity of 1,2-naphthoquinone derivatives against PTP1B



Compd	R_4 Substituents	IC_{50}, μM[a]
1	$-NH_2$	24.59
2	$-N(CH_3)C_6H_5$	34.88
3	$-N(CH_2)_4$	na[b]
4	–OCH3	29.11
5	$-OCH_2CH_2CH_2OH$	36.47
6	$-SO_3Na$	5.29
7	C_6H_5	0.86
8	$-C_6H_5$–2,5-Cl_2	5.05
9	$-C_6H_5OCH_3$[d]	5.24
10	$-C_6H_3$–2,5-F_2	0.50
11	$-C_6H_4COOCH_3$[d]	1.54
12	$-C_6H_4$–2-OCH_2CO_2Et	2.15
13	$-C_6H_4$–4-OCH_2CO_2Et	1.07
14	$-C_6H_4$–4-OH	0.44
15	$-C_6H_4$–2-OH	1.60
16	$-C_6H_2$-3,5-di-*t*-butyl-4-OH—	5. 73
17	C_6H_4-2-NO_2	1.17
18	–1-Naphthyl	2.15
19	–3-Indole	1.13
20	–3-Indole-5-carboxylic acid	3.00
21	–3-Indole-6-carboxylic acid	4.56
22	–3-Indole-1,2-$(CH_3)_2$	na
23	–3-Indole-2–C_6H_5	na
24	–Cyclohexyl	0.32[c]
25	–Benzyl	1.42[c]
26	$-(CH_2)_5CH_3$	3.30
27	–Cyclopentyl	4.20
28	–Biphenyl	5.40
29	–Isopropyl	10.13
30	–Butyl	na
31	–Decyl	na
	Sodium vanadate[16]	8.05

[a]IC_{50} values were determined from direct regression curve analysis.
[b]na, not active.
[c]The compound was obtained by Scheme 4 or Scheme 5.
[d]Regioisomers were not separated.

1,2-Naphthoquinone was identified as a hit through HTS (high throughput screening) with IC_{50} of 1.64 μM. Since this compound had a unique skeleton and showed a good in vitro activity against PTP1B, we used this compound as a starting point with the aim of making a potent and selective PTP1B inhibitor. Interestingly, 1,2-naphthoquinone structures have been reported to show inhibitory activity against phosphatases such as CD45, Cdc25B.[14,15] First, we decided to introduce substituents at R_4 position of 1,2-naphthoquinone to decrease structural instability owing to Michael type nucleophilic addition. The IC_{50} values are summarized in Table 1. Introduction of amino, alkyl or aryl amino groups at the R_4-position (**1**–**3**) showed a decrease of the in vitro activity compared with 1,2-naphthoquinone. Also substitutions of alkoxy group at R_4 position were detrimental to the inhibitory activity (**4** and **5**). Whereas, aryl substitution at R_4 exhibited enhanced potency, 4-phenyl-1,2-naphthoquinone (**7**) is the first of our compound to break the micromolar barrier with IC_{50} value of 0.86 μM and also showed better chemical and plasma stability (data not shown, determined by HPLC) than 1,2-naphthoquinone.

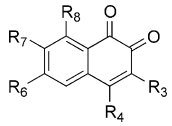
Chloro or methoxy substituted phenyl analogues (**8** and **9**) were weaker than unsubstituted 4-phenyl-1,2-naphthoquinone (**7**). 2,5-Difluorophenyl analogue (**10**) showed a good inhibitory activity (0.50 μM). Various ester analogues of phenyl group (**11**–**13**) exhibited IC_{50} values in the range of 1.07–2.15 μM. Compound **14** was another submicromolar inhibitor of PTP1B with an IC_{50} value of 0.44 μM. Further aryl modification at R_4 included the introduction of indole and its derivatives. Indole (**19**) at R_4 position demonstrated comparable potency with 4-phenyl-1,2-naphthoquinone (**7**). Acid substituted indoles (**20** and **21**) were less active than **19**. Masking of NH group (**22**) resulted in the loss of the in vitro activity. Introduction of alkyl groups at R_4 position was another possibility to increase inhibitory activity. Using the methodology through the reaction of 1,2-naphthoquinone with Grignard reagent in the presence of copper cyanide, several aryl or alkyl substituted compounds were presented. Among them, cyclohexyl analogue **24** was the best compound of this series with an IC_{50} value of 0.32 μM. Other alkyl substituents at R_4 position showed only weak activities (**26**–**31**).

Table 2. Selectivity of 1,2-naphthoquinone derivatives against several phosphatases[a,b]

Entry	PTP1B IC_{50}, μM	CD45 IC_{50}, μM	LAR IC_{50}, μM	Yop IC_{50}, μM	PP1 IC_{50}, μM	Cdc 25B IC_{50}, μM
7	0.86	0.84	2.49	21.07	8.37	9.52
11	1.54	1.65	7.09	11.97	Not tested	2.13
19	1.13	3.07	10.2	25.61	3.19	1.95
24	0.32	3.27	8.99	17.88	8.06	3.00

[a]All phosphatases are human enzymes.
[b]IC_{50} values were determined from direct regression curve analysis.

Table 3. Inhibitory activity of 1,2-naphthoquinone derivatives against PTP 1B[a]



No	R3	R4	R6	R7	R8	IC_{50}
36a	$-O(CH_2)_4CH_3$	$-C_6H_5$				2.69
36b		$-C_6H_5$	$-O(CH_2)_4CH_3$			na[b]
36c		$-C_6H_5$		$-O(CH_2)_4CH_3$		0.92
36d		$-C_6H_5$		OMe		2.04
36e		$-C_6H_5$		$-OCH(Bn)-CO_2CH_3$		2.54
36f		Indole		$-OCH(Bn)-CO_2H$		2.07
39a		$-C_6H_5$		$NHCO_2Bn$		2.25
39b		$-C_6H_5$			$NHCO_2Bn$	1.34
39c		$-C_6H_5$			$NHCO_2Et$	0.65
42a		$-C_6H_5$	$-(CH_2)_2CO_2Me$			0.33
42b		Indole	$-(CH_2)_2CO_2Me$			0.92
48a	$-(CH_2)_2CO_2Et$	$-C_6H_5$				0.43
48b	$-(CH_2)_2CO_2Et$	Indole				0.27
48c	$-(CH_2)_2CONEt_2$	$-C_6H_5$				0.61
51	$-(CH_2)_2PhCO_2Et$	$-C_6H_5$				1.01
55a	$-CH_2Ph-4-O-CH_2CO_2Bu^t$	$-C_6H_5$				1.48
55b	$-CH_2Ph-4-O-CH_2CO_2Bu^t$	Indole				0.65
55c	$-CH_2Ph-4-O-CH_2CO_2H$	$-C_6H_5$				1.54
55d	$-CH_2Ph-4-O-CH_2CO_2H$	Indole				1.01
59	$-(CH_2)_2CO_2Me$	$-C_6H_5$	$-(CH_2)_2CO_2Me$			0.68
63	$-(CH_2)_2CO_2Me$	Indole		$-(CH_2)_2CO_2Me$		0.94
			Sodium vanadate[16]			7.85

[a]IC_{50} values were determined from direct regression curve analysis.
[b]na, not active.

The protein tyrosine phosphatase domains of receptor and nonreceptor PTPases are highly conserved with ~35% mean sequence identity between known phosphatase.[17] Therefore, it is essential that PTP1B inhibitors intended for chronic therapy demonstrate a high level of selectivity. The selectivity of several compounds was evaluated in vitro against several phosphatases as shown in Table 2. Compound **24** demonstrated 10- to 60-fold selectivity against the tested phosphatases.

Our initial assessment indicated that 1,2-naphthoquinone derivatives with substituent at R_4 position showed better inhibitory activity and stability than 1,2-naphthoquinone, so we further modified this structure (4-substituted-1,2-naphthoquinone) by more substitution at R_3, R_6, R_7 and/or R_8. Although cyclohexyl showed most active in vitro inhibitory activity and selectivity as the R_4-substituent, we used phenyl or indolyl group as the R_4-substituents due to synthetic convenience. IC_{50} values are summarized in Table 3. Alkoxy-linked 4-aryl-1,2-naphthoquinones (**36a**–**f**) showed moderate or no inhibitory activity against PTP1B. Amino-linked 1,2-naphthoquinones (**39a**–**c**) exhibited inhibitory activity with the range of 0.64–2.25 μM. Compound **39a** and **39b** showed similar activities to alkoxy-linked 1,2-naphthoquinones. While, compound **39c** (0.65 μM) resulted in 2-fold better than **39b**. Carbon-linked 4-aryl-1,2-naphthoquinones were found to be more potent than alkoxy or amino-linked 1,2-quinones. Introduction of propionate at R_6 with phenyl at R_4 (**42a**) resulted in an increase of the in vitro activity (0.33 μM), while compound **42b** with indole at R_4 resulted in a 3-fold loss of activity. Propionate analogue at R_3 with phenyl at R_4 (**48a**) also exhibited a good activity similar to **42a**. During the synthesis of 4-aryl-1,2-naphthoqinones with carbon-linked substituent at diverse position, 3-substituted-4-aryl-1,2-naphthoquinone was more stable in plasma than other 4-aryl-1,2-naphthoquinone with substituent at R_6, R_7 or R_8 as well as 4-aryl-1,2-naphthoquinone (95% of the initially incorporated 3,4-disubstituted-1,2-naphthoquinone was remained in plasma after 1 h, determined by HPLC), so we focused on the synthesis of 1,2-naphthoquinone with substituents at R_3 and R_4 to find out the candidate of showing good in vivo stability and efficacy. Compound **48b** also showed a submicromolar in vitro activity (0.27 μM). Propionamide analogue (**48c**) was weaker than ester (**48a** or **48b**). Several other derivatives (**51**–**55**) were suggested and inhibited PTP1B with in vitro activities with the range of 0.6–1.5 μM.

Furthermore, 3-propionate-4-aryl-1,2-naphthoquinones with substituent at R_6 or R_7 (**59** and **63**) were synthesized and showed nanomolar range in vitro activity (0.68 and 0.94 μM, respectively). As a proof-of-concept, the compounds were also evaluated in vivo for their ability to reduce plasma glucose levels in the *ob*/*ob* mice. Compound **55b** was most active at an oral dose of 25 mg/kg/day for 5 days. More robust in vivo tests, such as biological stability, absorption and metabolism, are required for confirmation of the activity and elucidation of biological mechanism. Also modeling and X-ray co-crystal studies with PTP1B and inhibitor are in progress to understand how to increase the biological response.

In conclusion, a new series of 1,2-naphthoquinone derivatives was synthesized and evaluated for their ability to inhibit protein tyrosine phosphatase 1B. The 1,2-naphthoquinone derivatives with nitrogen or oxygen substituent at R_4 position showed weak in vitro activities. Aryls such as phenyl or indole derivatives showed better biological activity and stability than 1,2-naphthoquinone. The selectivity of several compounds was evaluated, and compound **24** demonstrated 10- to 60-fold selectivity against the tested phosphatase. Also, several 4-aryl-1,2-naphthoquinone derivatives with substituents at R_3, R_6, R_7, and/or R_8 showed submicromolar inhibitory activity and good plasma stability. Compound **55b** was active in vivo in *ob*/*ob* mice.

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10. To a suspension of copper cyanide (5 mmol) in dry THF under nitrogen was slowly added alkyl or aryl Grignard reagent (5 mmol) at −78 °C, then the mixtures were warmed to 0 °C. After recooling to −78 °C, to these mixtures was added 1,2-naphthoquinone (1 mmol) in THF. After stirring for 1 h at −78 °C and additional 1 h at −20 °C, the reaction mixture was quenched with aqueous NH_4Cl, and extracted with ethyl acetate. The organic layer was dried with $MgSO_4$. Evaporation of the volatiles and purification by chromatography on silica gel gave the corresponding products (entries **24**–**31**, yields 40–60%).
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