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

Jin Hee Ahn,[†] Sung Yun Cho,[†] Jae Du Ha,[†] So Young Chu, Sun Ho Jung, Yoon Sung Jung, Ji Yoen Baek, In Kyung Choi, Eun Young Shin, Seung Kyu Kang, Sung Soo Kim, Hyae Gyeong Cheon, Sung-Don Yang and Joong-Kwon Choi*

Medicinal Science Division, Korea Research Institute of Chemical Technology, Taejon, 305-600, Republic of Korea

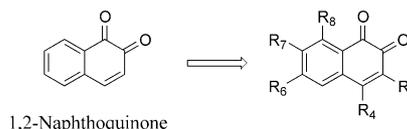
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Abstract—A new series of 1,2-naphthoquinone derivatives was synthesized by various synthetic methods and evaluated for their ability to inhibit protein tyrosine phosphatase 1B (PTP1B). 1,2-Naphthoquinone derivatives with substituent at R₄ position 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 R₃, R₆, R₇, or/and R₈ showed submicromolar inhibitory activity and good plasma stability. © 2002 Elsevier Science Ltd. All rights reserved.

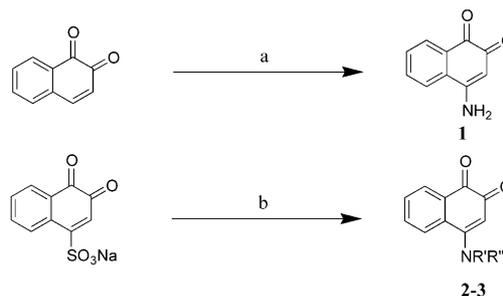
Protein tyrosine phosphatase 1B (PTP1B) plays a role in the negative regulation of insulin signaling and is involved in the insulin resistance associated with Type 2 diabetes.¹ Kennedy et al. have demonstrated that mice lacking the PTP1B gene showed enhanced insulin sensitivity.² Treatment of these mice 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.



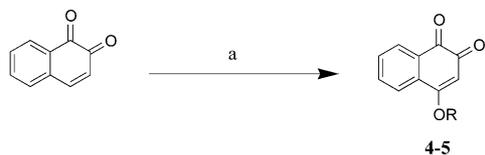
A series of 1,2-naphthoquinone derivatives was synthesized according to the synthetic Schemes 1–12. First, the preparation of 1,2-naphthoquinone with substituents at R₄ position was carried out as outlined in Schemes 1–6.



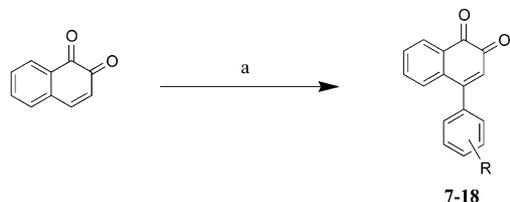
Scheme 1. (a) NaN₃, AcOH, 40 °C; (b) HNR'R'', K₂CO₃, H₂O, room temperature.

*Corresponding author. Tel.: +82-42-860-7070; fax: +82-42-860-7160; e-mail: jkchoi@kriict.re.kr

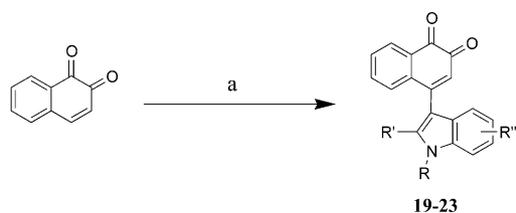
[†]Authors contributed equally.



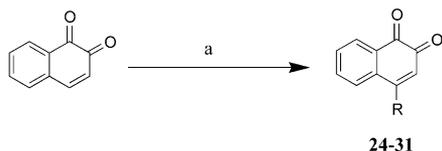
Scheme 2. (a) ROH, CeCl₃·7H₂O, NaIO₃.



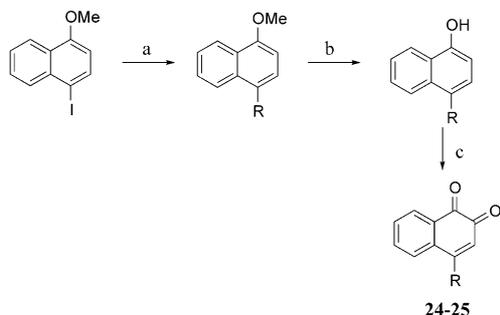
Scheme 3. (a) Pd(OAc)₂, acetic acid, arene, reflux.



Scheme 4. (a) Indole derivatives, CeCl₃·7H₂O, NaIO₃, *t*-BuOH, 40 °C.

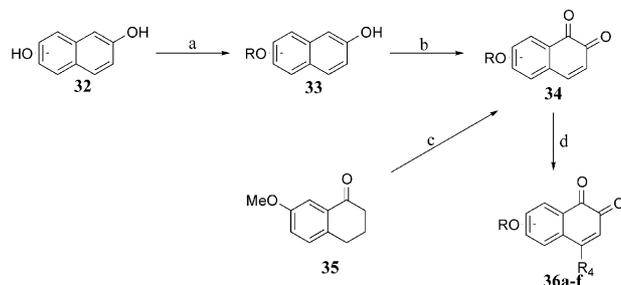


Scheme 5. (a) Copper(I) cyanide, alkyl or aryl Grignard reagents, -78 → -20 °C, THF.

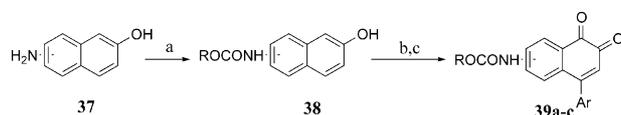


Scheme 6. (a) Benzyl or cyclohexylmagnesium halide, Ni(dppp)Cl₂, ether, reflux; (b) BBr₃, CH₂Cl₂, -78 °C; (c) benzene seleninic anhydride, THF, 50 °C.

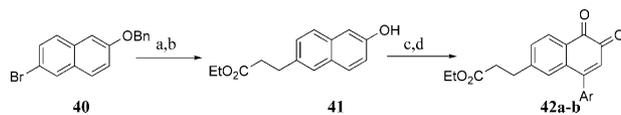
Commercially available 1,2-naphthoquinone was treated with sodium azide in glacial acetic acid to afford 4-amino-1,2-naphthoquinone (**1**).⁶ 1,2-Naphthoquinone-4-sulfonic acid sodium salt (from Aldrich, **6**) reacted with alkyl or aryl amines in the presence of K₂CO₃ to produce the corresponding 4-alkyl or arylamino substituted-1,2-naphthoquinones (**2** and **3**). Introduction of alkoxy group at R₄ position was achieved by Takuwa procedure using cerium chloride and sodium iodate in alcohol to give the corresponding compounds (**4-5**) (Scheme 2).⁷



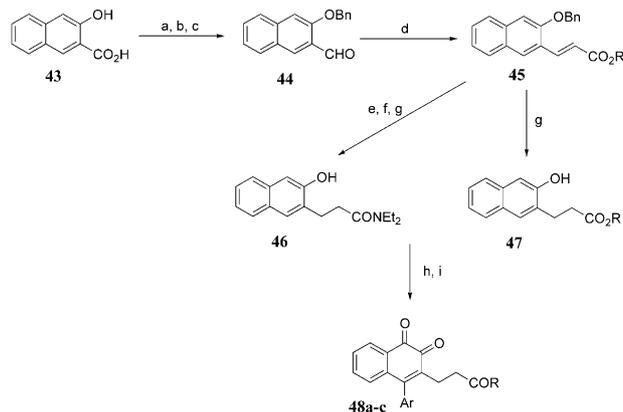
Scheme 7. (a) Bromopentane, K₂CO₃, acetone, reflux or methyl 2-hydroxy-3-phenylpropionate, DEAD, PPh₃, benzene, room temperature; (b) (PhSeO)₂O, THF, 50 °C; (c) SeO₂, AcOH, 60 °C; (d) Pd(OAc)₂, benzene, AcOH, reflux or indole, CeCl₃·7H₂O, NaIO₃, *t*-BuOH, 40 °C.



Scheme 8. (a) Benzyl chloroformate or ethyl chloroformate, Na₂CO₃, THF/H₂O, 0 °C → room temperature; (b) (PhSeO)₂O, THF, 50 °C; (c) Pd(OAc)₂, benzene, AcOH, reflux or indole, CeCl₃·7H₂O, NaIO₃, *t*-BuOH, 40 °C.



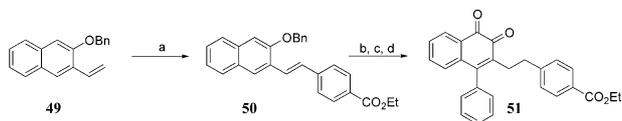
Scheme 9. (a) Methyl acrylate, Pd(OAc)₂, *n*-Bu₄NCl, KOAc, DMF, 150 °C; (b) 10% Pd/C, H₂, methanol, room temperature; (c) (PhSeO)₂O, THF, 50 °C; (d) Pd(OAc)₂, benzene, AcOH, reflux or indole, CeCl₃·7H₂O, NaIO₃, *t*-BuOH, 40 °C.



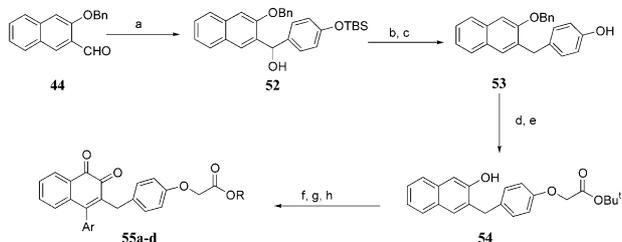
Scheme 10. (a) BnBr, K₂CO₃, acetone, reflux; (b) LiAlH₄, THF, 0 °C, (c) MnO₂, dioxane, room temperature; (d) PPh₃=CHCO₂R, THF; (e) NaOH, THF/H₂O; (f) Et₂NH, HOBt, EDCI; (g) 10% Pd/C, H₂, methanol, room temperature; (h) (PhSeO)₂O, THF, 50 °C; (i) Pd(OAc)₂, benzene, AcOH, reflux or indole, CeCl₃·7H₂O, NaIO₃, *t*-BuOH, 40 °C.

The 1,2-naphthoquinones with aryl substituent at R₄ position (**7-18**) were prepared by literature modification (Scheme 3) using Pd(OAc)₂ in arene and acetic acid under the reflux condition.⁸

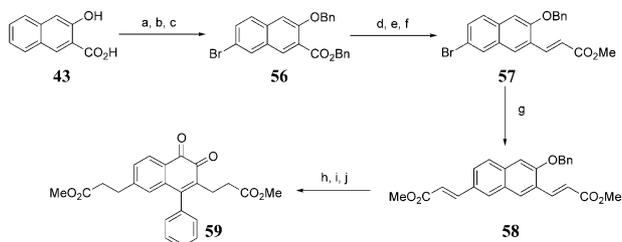
Another aryl substitution at R₄-position with indole was presented according to Scheme 4. 1,2-Naphthoquinone



Scheme 11. (a) Ethyl *p*-bromobenzoate, Pd(OAc)₂, *n*-Bu₄NCl, KOAc, DMF, 150 °C; (b) 10% Pd/C, H₂, methanol, room temperature; (c) (PhSeO)₂O, THF, 50 °C; (d) Pd(OAc)₂, benzene, AcOH, reflux.



Scheme 12. (a) (4-Bromophenoxy)-tert-butyltrimethylsilane, *n*-BuLi, THF, 0 °C then THF, -20 → 0 °C, THF; (b) Et₃SiH/TFA, CH₂Cl₂, 0 °C; (c) TBAF, THF, 0 °C; (d) BrCH₂CO₂Bu^t, K₂CO₃, KI, acetone, reflux; (e) 10% Pd/C, H₂, EtOH, room temperature; (f) (PhSeO)₂O, THF, 50 °C; (g) Pd(OAc)₂, benzene, AcOH, reflux or indole, CeCl₃ 7H₂O, NaIO₃, *t*-BuOH, 40 °C; (h) TFA, CH₂Cl₂, 0 °C.



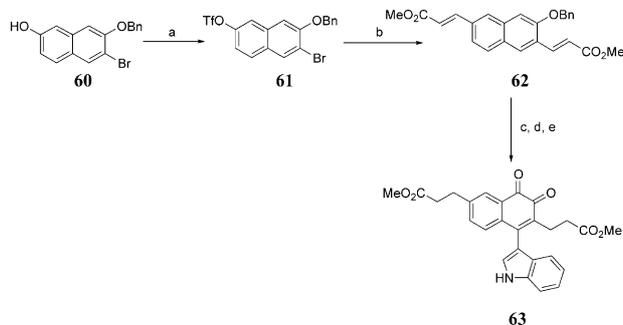
Scheme 13. (a) Br₂, AcOH, 0 °C → reflux; (b) Sn, 12 N HCl, AcOH, reflux; (c) BnBr, K₂CO₃, acetone reflux; (d) LiAlH₄, THF, 0 °C, (e) MnO₂, dioxane, room temperature; (f) PPh₃=CHCO₂R, THF; (g) methyl acrylate, Pd(OAc)₂, *n*-Bu₄NCl, KOAc, DMF, 150 °C; (h) 10% Pd/C, H₂, EtOH, room temperature; (i) (PhSeO)₂O, THF, 50 °C; (j) Pd(OAc)₂, benzene, AcOH, reflux.

reacted with indole or indole derivatives in the presence of CeCl₃·7H₂O and NaIO₃ to afford 4-(indol-3-yl)-1,2-naphthoquinones (entries 19–23).⁹

A methodology to introduce alkyl or aryl group at R₄ position from 1,2-naphthoquinone using Grignard reagent with copper cyanide was attempted as shown in Scheme 5.¹⁰

Cyclohexyl or benzyl group at R₄ 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)Cl₂ in ether under the reflux condition to produce the coupling product, followed by demethylation using BBr₃, and oxidation with benzene seleninic anhydride to afford the desired compounds (**24** and **25**).

4-Aryl-1,2-naphthoquinone derivatives with substituents at R₃, R₆, R₇, or/and R₈ 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, CH₂Cl₂, 0 °C → room temperature; (b) methyl acrylate, Pd(OAc)₂, *n*-Bu₄NCl, NaHCO₃, DMF, 120 °C; (c) 10% Pd/C, H₂, EtOH, room temperature; (d) (PhSeO)₂O, THF, 50 °C; (e) indole, CeCl₃ 7H₂O, NaIO₃, *t*-BuOH, 40 °C.

Alkylation of naphthalenediol (**32**) produced the mono substituted compound (**33**), which upon treatment with benzene seleninic anhydride¹¹ afforded 1,2-naphthoquinone (**34**). Substitution of 1,2-naphthoquinone at R₄ position with benzene⁸ or indole⁹ 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 SeO₂ oxidation.¹² The alkoxy-carbonylamino-linked 1,2-naphthoquinones were prepared by Scheme 8. Amino-2-naphthol (**37**) reacted with benzyl or ethyl chloroformate 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 H₂ atmosphere furnished **41**, and which was converted to **42** according to same oxidation and R₄ substitution procedure to Scheme 7.

Commercially available 3-hydroxy-2-naphthoic acid (**43**) was benzylation, and reduced by lithium aluminum hydride to produce alcohol, followed by oxidation (MnO₂) to afford benzoyloxynaphthylaldehyde (**44**). Introduction of α,β -unsaturated ester using PPh₃=CHCO₂R gave **45**.

Compound **45** was hydrogenated by Pd/C under H₂ 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/trifluoroacetic 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.

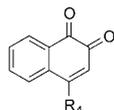
3-Hydroxy-2-naphthoic acid (**43**) was brominated by bromine and benzylated to produce **56**. Compound **56** was reduced by lithium aluminum hydride to produce alcohol, followed by oxidation (MnO_2) afforded benzyl-oxy-naphthylaldehyde. Introduction of α,β -unsaturated ester with $\text{PPh}_3=\text{CHCO}_2\text{R}$ gave **57**. Introduction of another α,β -unsaturated ester with methyl acrylate and $\text{Pd}(\text{OAc})_2$ 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 $\text{Pd}(\text{OAc})_2$ furnished di-unsaturated 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 fluores-

cence of the product, fluorescein monophosphate (FMT) at 485 nm (excitation) and 538 nm (emission).

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.

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 ₆ H ₅	34.88
3	–N(CH ₂) ₄	na ^b
4	–OCH ₃	29.11
5	–OCH ₂ CH ₂ CH ₂ OH	36.47
6	–SO ₃ Na	5.29
7	C ₆ H ₅	0.86
8	–C ₆ H ₅ –2,5-Cl ₂	5.05
9	–C ₆ H ₅ OCH ₃ ^d	5.24
10	–C ₆ H ₃ –2,5-F ₂	0.50
11	–C ₆ H ₄ COOCH ₃ ^d	1.54
12	–C ₆ H ₄ –2-OCH ₂ CO ₂ Et	2.15
13	–C ₆ H ₄ –4-OCH ₂ CO ₂ Et	1.07
14	–C ₆ H ₄ –4-OH	0.44
15	–C ₆ H ₄ –2-OH	1.60
16	–C ₆ H ₂ –3,5-di- <i>t</i> -butyl-4-OH—	5.73
17	C ₆ H 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 ₆ H ₅	na
24	–Cyclohexyl	0.32 ^c
25	–Benzyl	1.42 ^c
26	–(CH ₂) ₅ CH 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.

^bna, not active.

^cThe compound was obtained by Scheme 4 or Scheme 5.

^dRegioisomers were not separated.

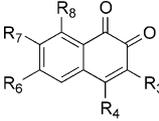
Chloro or methoxy substituted phenyl analogues (**8** and **9**) were weaker than unsubstituted 4-phenyl-1,2-naphthoquinone (**7**). 2,5-Difluorophenyl analogue (**10**) showed a good inhibitory activity (0.50 μM). Various ester analogues of phenyl group (**11–13**) exhibited IC_{50} values in the range 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

^aAll 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) ₄ CH ₃	-C ₆ H ₅				2.69
36b		-C ₆ H ₅	-O(CH ₂) ₄ CH ₃			na ^b
36c		-C ₆ H ₅		-O(CH ₂) ₄ CH ₃		0.92
36d		-C ₆ H ₅		OMe		2.04
36e		-C ₆ H ₅		-OCH(Bn)-CO ₂ CH ₃		2.54
36f		Indole		-OCH(Bn)-CO ₂ H		2.07
39a		-C ₆ H ₅		NHCO ₂ Bn		2.25
39b		-C ₆ H ₅			NHCO ₂ Bn	1.34
39c		-C ₆ H ₅			NHCO ₂ Et	0.65
42a		-C ₆ H ₅	-(CH ₂) ₂ CO ₂ Me			0.33
42b		Indole	-(CH ₂) ₂ CO ₂ Me			0.92
48a	-(CH ₂) ₂ CO ₂ Et	-C ₆ H ₅				0.43
48b	-(CH ₂) ₂ CO ₂ Et	Indole				0.27
48c	-(CH ₂) ₂ CONEt ₂	-C ₆ H ₅				0.61
51	-(CH ₂) ₂ PhCO ₂ Et	-C ₆ H ₅				1.01
55a	-CH ₂ Ph-4-O-CH ₂ CO ₂ Bu ^t	-C ₆ H ₅				1.48
55b	-CH ₂ Ph-4-O-CH ₂ CO ₂ Bu ^t	Indole				0.65
55c	-CH ₂ Ph-4-O-CH ₂ CO ₂ H	-C ₆ H ₅				1.54
55d	-CH ₂ Ph-4-O-CH ₂ CO ₂ H	Indole				1.01
59	-(CH ₂) ₂ CO ₂ Me	-C ₆ H ₅	-(CH ₂) ₂ CO ₂ Me			0.68
63	-(CH ₂) ₂ CO ₂ Me	Indole		-(CH ₂) ₂ CO ₂ Me		0.94
			Sodium vanadate ¹⁶			7.85

^aIC₅₀ values were determined from direct regression curve analysis.^bna, 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 R₄ 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 R₃, R₆, R₇ and/or R₈. Although cyclohexyl showed most active in vitro inhibitory activity and selectivity as the R₄-substituent, we used phenyl or indolyl group as the R₄-substituents due to synthetic convenience. IC₅₀ 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 R₆ with phenyl at R₄ (**42a**) resulted in an increase of the in vitro activity (0.33 μM), while compound **42b** with indole at R₄ resulted in a 3-fold loss of activity.

Propionate analogue at R₃ with phenyl at R₄ (**48a**) also exhibited a good activity similar to **42a**. During the synthesis of 4-aryl-1,2-naphthoquinones 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 R₆, R₇ or R₈ 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 R₃ and R₄ to find out the candidate of showing good in vivo stability and efficacy. Compound **48b** also showed a sub-micromolar 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 R₆ or R₇ (**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 R₄ 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 R₃, R₆, R₇, and/or R₈ showed submicromolar inhibitory activity and good plasma stability. Compound **55b** was active in vivo in *ob/ob* mice.

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- 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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