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Synthetic chalcones as efficient inhibitors of *Mycobacterium tuberculosis* protein tyrosine phosphatase PtpA

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Hernán Terenzi dedicates this paper to the memory of his mentor, colleague and friend, Pr. Mario Zakin – Institut Pasteur – Paris.

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ABSTRACT

In the search for lead compounds for new drugs for tuberculosis, the activity of 38 synthetic chalcones were assayed for their potential inhibitory action towards a protein tyrosine phosphatase from *Mycobacterium tuberculosis* – PtpA. The compounds were obtained by aldolic condensation between aldehydes and acetophenones, under basic conditions. Five compounds presented moderate or good activity. The structure–activity analysis reveals that the predominant factor for the activity is the molecule planarity/hydrophobicity and the nature of the substituents.

Mycobacterium tuberculosis is responsible for tuberculosis infection, and the emergence in recent years of multi-resistant strains has made it a serious challenge in terms of international public health. Annually 10 million new cases of tuberculosis appear and about two million people die each year as a consequence of the disease.[1]

As generally described for intracellular pathogens, mycobacterial infection promotes the secretion of proteins by the pathogen, especially phosphatases, which contribute to the disease installation. For instance, *M. tuberculosis* secretes PI3P-phosphatase which inhibits phagosomal maturation[2]; *Yersinia pseudotuberculosis*, once in the host cell, releases phosphatase YopH, which inhibits bacterial phagocytosis by dephosphorylation of Cas and other focal adhesion proteins.[3,4] Similarly, the phosphatase SptP of *Salmonella enterica* serovar Typhimurium, is directly responsible for the reversal of the actin cytoskeletal changes induced after bacteria internalization into non-phagocytic cells.[5]

Tyrosine phosphatases (PTPs) constitute a family of closely related key regulatory enzymes that, in conjunction with protein-tyrosine kinases, control the state of tyrosine phosphorylation in a cellular context. Phosphotyrosine appears as a critical cell-signaling element and PTP activity is essential to control appropriate responses.[6] *M. tuberculosis* has two phosphotyrosine phosphatases (PTPs), PtpA and PtpB,[7] and has no tyrosine kinase genes annotated in its genome sequence database,[8] suggesting that the targets of these two phosphatases may be present in the host cell, and involved in host–pathogen interactions.

It was recently demonstrated that PtpA is secreted by *M. tuberculosis* in infected human macrophages,[9] and it was also very elegantly shown that VPS33B, a regulator of membrane fusion, is a PtpA substrate. This target, VPS33B, when dephosphorylated by PtpA inhibits phagosome–lysosome fusion, a process arrested in mycobacterial infections. Considered together, these data, demonstrate that PtpA is essential for mycobacterial intracellular persistence, emerging as a promising target for therapeutic intervention.

Chalcones are essential intermediate compounds in flavonoid biosynthesis in plants. Several reports have documented active biological properties of natural and synthetic chalcones.[10,11] Many studies have demonstrated antileukemic,[12,13] antitumoral,[14–20] antiinflammatory,[21,22] anti-ulcerogenic,[23] antioxidant,[14,24,25] antimalarial,[26] antileishmaniosis[26,27] and hypotensive[28] activities for chalcones, besides other pharmacological effects. Chalcones are also cited as being antibacterial,[29] including *M. tuberculosis*, by Lin et al.,[30] however, no information on the target of action of the com-

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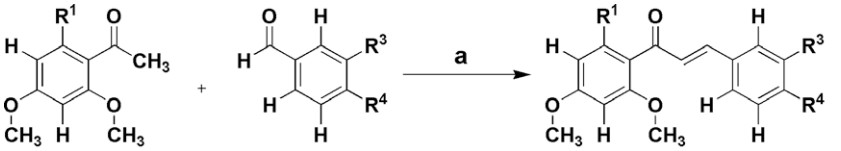
pounds is available. Nayyar and Jain (2005) cited chalcones as agents with chemotherapeutic potential against *M. tuberculosis*.[31]

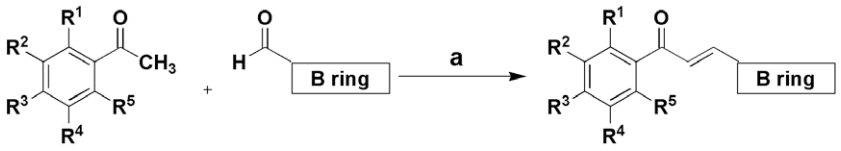
The main objective of this study is the search for a specific inhibitor of the protein tyrosine phosphatase PtpA. We synthesized and characterized 38 synthetic chalcones, which were assayed in vitro using a recombinant purified PtpA from *M. tuberculosis*.

The chalcones were prepared by aldolic condensation as shown in Figure 1. Chalcones **1** and **2** are derived from xanthoxyline; chalcones of the series **3** are derived from 2,4,6-trimethoxyacetophenone; chalcones of the series **4** are derived from 1-naphthaldehyde; chalcones of the series **5** are derived from 2-naphthaldehyde; and the chalcones of the series **6** are derived from 3,4-methylenedioxybenzaldehyde; the obtained yields were between 36% and 97% (Table 1).

The structures of all compounds, including those still not published (**4c**, **4f**, **4l**, **5c**, **5i**, **6i** and **6c**), were confirmed by chemical



	R^1	R^3	R^4
1	OH	NO_2	H
2	OH	Cl	H
3a	OCH_3	Cl	H
3b	OCH_3	NO_2	H
3c	OCH_3	Cl	Cl



		R^1	R^2	R^3	R^4	R^5
B ring:	**4a**	OCH_3	H	H	OCH_3	H
	4b	H	H	OCH_3	H	H
	4c	H	NO_2	H	H	H
	4d	OH	H	H	H	H
	4e	H	H	Br	H	H
	4f	H	H	NO_2	H	H
	4g	H	H	H	H	H
	4h	H	OCH_3	OCH_3	OCH_3	H
	4i	OCH_3	H	OCH_3	H	H
	4j	H	OH	H	H	H
	4l	OH	H	OCH_3	H	OCH_3
B ring:	**5a**	OCH_3	H	H	OCH_3	H
	5b	H	H	OCH_3	H	H
	5c	H	NO_2	H	H	H
	5d	OH	H	H	H	H
	5e	H	H	Br	H	H
	5f	H	H	NO_2	H	H
	5g	H	H	H	H	H
	5h	H	OCH_3	OCH_3	OCH_3	H
	5i	H	OCH_3	OH	H	H
	5j	H	OCH_3	OCH_3	H	H
	5l	OCH_3	H	OCH_3	H	OCH_3
B ring:	**6a**	OCH_3	H	H	OCH_3	H
	6b	H	H	OCH_3	H	H
	6c	H	NO_2	H	H	H
	6d	OH	H	H	H	H
	6e	H	H	Br	H	H
	6f	H	H	NO_2	H	H
	6g	H	H	H	H	H
	6h	H	OCH_3	OCH_3	OCH_3	H
	6i	H	OCH_3	OH	H	H
	6j	H	OCH_3	OCH_3	H	H
	6l	OCH_3	H	OCH_3	H	H

Figure 1. Synthesis of the chalcones. (a) Methanol, KOH 50%, rt, 24 h.

Table 1
Yields of the synthesis and activity of the *Mycobacterium tuberculosis* PtpA in the presence of 25 μM of the chalcones.

Chalcone	Yield (%)	Activity of the enzyme PtpA (% ± error)	Chalcone	Yield (%)	Activity of the enzyme PtpA (% ± error)
1	51	92 ± 15	**5d**	66	74.6 ± 7
2	36	87 ± 21	**5e**	88	89.2 ± 6
3a	91	98 ± 5	**5f**	73	89 ± 1
3b	43	100 ± 4	**5g**	95	88 ± 33
3c	89	99 ± 12	**5h**	97	109 ± 6
4a	65	54 ± 7	**5i**	39	61 ± 23
4b	58	82.4 ± 7	**5j**	96	31.5 ± 18
4c	54	88 ± 6	**5l**	88	104 ± 13
4d	57	24 ± 15	**6a**	74	91.3 ± 9
4e	63	75 ± 17	**6b**	77	94 ± 4
4f	57	82 ± 5	**6c**	40	74 ± 12
4g	65	62.7 ± 4	**6d**	62	103 ± 7
4h	70	102 ± 1	**6e**	76	86 ± 10
4i	59	80 ± 10	**6f**	85	80.5 ± 17
4j	51	79.5 ± 9	**6g**	66	103 ± 8
4l	58	84.4 ± 8	**6h**	88	82.4 ± 7
5[a]	83	42.5 ± 7	**6i**	47	80 ± 23
5b	90	81.5 ± 13	**6j**	72	99 ± 10
5c	71	84 ± 3	**6l**	95	91.9 ± 12

identification data using ^{1}H NMR, ^{13}C NMR, IR and elementary analysis.

The PtpA coding region was subcloned from *M. tuberculosis* genomic DNA, and the expression vector pET28a-PtpA was used to produce recombinant His-tagged protein as previously described.[32]

Initial assays were performed with a single compound concentration (25 μM) to assess the potential of the compounds as inhibitors.[33] The activity of PtpA in vitro in the presence of the compounds was determined as previously described [34] and is shown in Table 1.

It can be observed from Table 1 that compounds **4a**,[37] **4d**,[36] **5a**,[39] **5i**[35] and **5j**[38] show important inhibitory activity towards PtpA. The data given in Table 1 indicate that the change in the substituent of the phenyl A ring affects the activity of the enzyme. When the B ring is substituted for 1 or 2-naphthyl groups, the compounds generally show potential bioactivity, such as **5i**, **4a**, **5a**, **5j** and **4d**, decreasing the relative activity of the enzyme to 61.0%, 54.0%, 42.5%, 31.5% and 24.0%, respectively, at a chalcone final concentration of 25 μM. We can observe a relationship, between the substituents that increase the electronic density of the A ring, such as methoxyl, and a 1 or 2-naphthyl group in the B ring. To assess the activity of these compounds, further assays were carried out and their IC_{50} values in relation to mycobacterial PtpA (5–60 μM of compound) were established and are given in Table 2.

Chalcones where the B ring is 3,4-methylenedioxy (all series **6**) and chalcones with electron acceptor substituents in the B ring (**1**, **2**, **3a**, **3b** and **3c**), or groups that decrease the electronic density of the A ring, such as bromo, chloro and nitro (compounds **1**, **2**, **3a**, **3b**, **3c**, **4c**, **4e**, **4f**, **5c**, **5e**, **5f**, **6c**, **6e** and **6f**), present a low inhibition of PtpA activity.

The compounds with the phenyl B-ring substituted for naphthyl groups and with three methoxyl groups (**4h**, **5l** and **5h**), without substituents (**4g** and **5g**) or with only one methoxyl or hydroxyl group in the A ring (**4b**, **4j**, **5b** and **5d**), did not show satisfactory reduction of the activity of PtpA, with the exception of **4d**. Compounds that exhibit similar changes in the molecule due to the substituents in position 2 and 6 of the A ring (**4l** and **5l**) also exhibit low PtpA inhibitory activity.

In Table 2 the activity of chalcones when the B ring is a naphthyl group and two electron-donors substituents are present in the A ring is depicted. We now observed that the inhibitory effect is considerably increased. Highest inhibitory activity was achieved when

Table 2
IC_{50} of the compounds more actives against *Mycobacterium tuberculosis* PtpA, assayed in concentrations of 5–60 μM.

Chalcone	Ring A	Ring B	IC_{50} (μM ± error)
5i	2-OCH_3-4-OH	2-Naphtyl	53.7 ± 1.3
4d	2-OH	1-Naphtyl	50.2 ± 2.1
4[a]	2,5-OCH_3	1-Naphtyl	39.5 ± 1.1
5j	3,4-OCH_3	2-Naphtyl	23.1 ± 1.6
5a	2,5-OCH_3	2-Naphtyl	8.4 ± 0.9

the substituents were 2,5-dimethoxy in the A ring and 2-naphthyl in the B ring, with an excellent IC_{50} of 8.4 μM (compound **5a**). Compound **5j** also with two methoxy groups in the A ring (3,4-dimethoxy) and a 2-naphthyl group in the B ring, had an IC_{50} value of 23.1 μM. These results permit us to observe that the substitution of the phenyl group for 2-naphthyl group in the B ring, seems to be a predominant factor to reduce the activity of PtpA, when associated with the ideal position of the methoxyl groups in the A ring. Compound **4a**, which has two methoxyl groups in A ring, and the phenyl group substituted by 1-naphtyl group as B ring, had relatively moderate activity against the enzyme, with an IC_{50} value of 39.5 μM. The moderate activity observed for compound **4d**, with an IC_{50} value of 50.2 μM, may be due to the presence of the hydroxyl group in the A ring that may eventually mediate hydrogen bonding with the enzyme.

On analyzing the relationships between structure and activity it was observed that the position and nature of the substituents in A ring, probably the hydrophobicity or planarity of the naphtyl groups in B rings are predominant factors to inhibition of PtpA. The presence of substituents that increase the electronic density of the A ring appear to be necessary for the activity of the chalcones.

In summary, from the 38 assayed chalcones, the synthetic compound, **5a** is highly effective against *M. tuberculosis* PtpA and **4a**, **4d**, **5i** and **5j** are moderately effective. These results encourage us to elucidate the possible binding mode of these compounds to PtpA.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.09.105.

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34. *Measurement of phosphatase activity and inhibition*: The phosphatase assays were carried out in 96-well plates containing 5 μl of diluted compound or solvent (100% DMSO) in each well. After dilution in PtpA buffer (25 mM bis Tris–HCl [pH 8.0], 20 mM Imidazol [pH7.0], 40 mM DL-dithiothreitol, 40 mM *p*-nitrophenyl phosphate [pNPP]), 2 μl of recombinant PtpA (1.0 μg/μl) diluted in PtpA buffer was added in order to start the reaction. After 20 min at 37 °C, the absorbance was measured (at 410 nm with readings every 2 min) on an ELISA plate spectrophotometer (TECAN). Negative controls were performed in the absence of enzyme, and positive controls were carried out in the presence of enzyme with DMSO 100% in place of the compound. The percentage of activity was calculated by the average of two experiments carried out in triplicate, and also the IC_{50} values were determined in triplicate in two independent experiments.
35. *Compound* ***4a*** *– (2E)-1-(2′,5′-dimethoxyphenyl)-3-(1-naphthyl)-2-propen-1-one.* Yellow solid, mp 89–90 °C. ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.96 (d, 1H, *J* = 8.2 Hz, H4′), 7.06 (dd, *J* = 8.0 Hz, 1H, H4), 7.49–7.59 (m, 5H, H3, H5, H6, H7, H8), 7.85 (d, 1H, *J* = 7.2 Hz, H3′), 7.89 (d, 1H, *J* = 16.0 Hz, Hα), 7.89 (s, 1H, H6′), 8.24 (d, 1H, *J* = 8.0 Hz, H2), 8.50 (d, 1H, *J* = 16.0 Hz, Hβ). ^{13}C NMR ($CDCl_3$) δ 56.12 (OCH_3), 56.72 (OCH_3), 113.60 (C3′), 114.72 (C6′), 119.71 (C4′), 123.85 (Cα), 125.40 (C1′), 125.72 (C10), 126.45 (C3), 127.06 (C9), 128.96 (C5), 129.69 (C4), 129.86 (C8), 130,72 (C6), 132.01 (C2), 132.85 (C7), 133.96 (C1), 140.20 (Cβ), 152.97 (C5′), 153.90 (C2′), 192.45 (C=O). IR ν_{max}/cm^{-1} 1657 (C=O), 1588 (C=C), 1223, 1043 (C–O), 2947, 1493, 977, 807, 787 (KBr) Anal. Calcd for $C_{21}H_{18}O_3$: C, 79.23; H, 5.70. Found: C, 79.24; H, 6.11. Yield: 65%.
36. *Compound* ***4d*** *– (2E)-1-(2′-hydroxyphenyl)-3-(1-naphthyl)-2-propen-1-one:* Yellow solid, mp 106–108 °C. ^{1}H NMR ($CDCl_3$) δ 6.97 (dd, 1H, *J* = 7.4 Hz, H5′), 7.06 (d, 1H, *J* = 8.4 Hz, H3′), 7.51–7.62 (m, 4H, H3, H6, H7, H4′), 7.76 (d, 1H, *J* = 15.2 Hz, Hα), 7.90–7.99 (m, 4H, H6′, H4, H5, H8), 8.29 (d, 1H, *J* = 8.4 Hz, H2), 8.79 (d, 1H, *J* = 15.2 Hz, Hβ), 12.88 (s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ 118.93 (C3′), 119.17 (C5′), 122.99 (Cα), 123.67 (C2), 125.59 (C8), 125.68 (C1′), 126.67 (C3), 127.41 (C6), 129.07 (C4, C5), 130.00 (C9, C6′), 131.48 (C10), 136.74 (C1, C4′), 142.66 (Cβ), 163.93 (C2′), 194.12 (C=O). IR ν_{max}/cm^{-1} 3451, 1635, 1351, 1576, 1203, 1015, 3047, 1435, 1162, 972, 760 (KBr). Anal. Calcd for $C_{19}H_{14}O_2$: C, 83.19; H, 5.14. Found: C, 83.88; H, 5.18. Yield: 57%.
37. *Compound* ***5a*** *– (2E)-1-(2′,5′-dimethoxyphenyl)-3-(2-naphthyl)-2-propen-1-one.* Light yellow, mp 120–121 °C. ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H, *o*-OCH_3), 3.89 (s, 3H, *m*-OCH_3), 6.97 (d, 1H, *J* = 8.0 Hz, H4′), 7.06 (d, 1H, *J* = 8.0 Hz, H3′), 7.23 (s, 1H, H6′), 7.51–7.53 (m, 2H, H6, H7), 7.53 (d, 1H, *J* = 16.0 Hz, Hα), 7.75 (d, 1H, *J* = 8.0 Hz, H3), 7.81 (d, 1H, *J* = 16.0 Hz, Hβ), 7.83–7.88 (m, 3H, H4, H5, H8), 7.99 (s, 1H, H1). ^{13}C NMR ($CDCl_3$) δ 55.89 (*o*-OCH_3), 56.56 (*m*-OCH_3), 109.77 (C6′), 113.42 (C3′), 114.40 (C4′), 119.17 (C1′), 123.76 (Cα), 126.68 (C3), 127.07–127.23 (C6, C7), 127.78 (C5), 128.63 (C8), 129.73 (C1), 130.51 (C4), 132.66 (C10), 133.36 (C9), 134.27 (C2), 143.46 (Cβ), 152.58–153.64 (C2′, C5′), 192.48 (C=O). IR ν_{max}/cm^{-1} 1644 (C=O), 1570 (C=C), 1336, 1130 (C–O), 3012, 2946, 2837, 1508, 1227, 1005, 693 (Ar) (KBr). Anal. Calcd for $C_{21}H_{18}O_3$: C, 79.23; H, 5.70. Found: C, 79.69; H, 6.00. Yield: 83%.
38. *Compound* ***5i*** *– (2E)-1-(3′-methoxy-4′-hydroxyphenyl)-3-(2-naphthyl)-2-propen-1-one:* Light yellow solid, mp: 166–168 °C. ^{1}H NMR ($CDCl_3$) δ 4.01 (s, 3H, OCH_3), 6.10 (s, 1H, OH), 7.02 (d, 1H, *J* = 8.0 Hz, H5′), 7.29 (s, 1H, H2′), 7.52–7.54 (m, 1H, H6′), 7.66–7.72 (m, 3H, H3, H6, H7), 7.83 (d, 1H, *J* = 15.6 Hz, Hα), 7.80–7.87 (m, 3H, H4, H5, H8), 7.97 (d, 1H, *J* = 15.6 Hz, Hβ), 8.05 (s, 1H, H1). ^{13}C NMR (DMSO-d_6) δ 56.37 (*m*-OCH_3), 110.74 (C2′), 114.05 (C5′), 121.99 (C3), 123.96 (Cα), 126.97 (C6′), 127.51 (C6), 128.03 (C7), 128.85 (C1), 128.91 (C8), 130.68 (C4, C5), 131.33 (C1′), 132.81 (C10), 133.63 (C9), 134.54 (C2), 144.30 (Cβ), 147.15 (C4′), 150.64 (C3′), 188.74 (C=O). IR ν_{max}/cm^{-1} 3265 (OH), 1643, 1202 (C=O), 1280, 1025 (C–O), 1563 (C=C), 2950, 2835, 1522, 1445, 970, 844, 816, 779 (Ar) (KBr). Anal. Calcd for $C_{20}H_{16}O_3$: C, 78.93; H, 5.30. Found: C, 78.86; H, 5.76. Yield: 39%.
39. *Compound* ***5j*** *– (2E)-1-(3′,4′-dimethoxyphenyl)-3-(2-naphthyl)-2-propen-1-one:* Light yellow solid, mp 168–170 °C. ^{1}H NMR ($CDCl_3$) δ 3.97 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.94 (d, 1H, H6′), 7.50–7.53 (m, 2H, H6, H7), 7.65 (s, 1H, H1), 7.67 (d, 1H, *J* = 15.6 Hz, Hα), 7.73 (d, 1H, H5′), 7.81–7.87 (m, 4H, H3, H4, H5, H8), 7.95 (d, 1H, *J* = 15.6 Hz, Hβ), 8.02 (s, 1H, H2′). ^{13}C NMR ($CDCl_3$) δ 56.31 (*m*-e *p*-OCH_3), 110.23 (C5′), 111.04 (C2′), 121.99 (Cα), 123.30 (C6′), 123.93 (C3), 126.97 (C6), 127.52 (C5), 128.02 (C7), 128.90 (C4, C8), 130.70 (C1), 131.60 (C1′), 132.78 (C10), 133.61 (C9), 134.52 (C2), 144.29 (Cβ), 149.50 (C3′), 153.52 (C4′), 188.76 (C=O). IV ν_{max}/cm^{-1} 1652 (C=O), 1583 (C=C), 1261, 1021 (C–O), 3008, 2935, 2841, 1510, 1448, 1415, 975, 920, 844, 810 (Ar) (KBr). Anal. Calcd for $C_{21}H_{18}O_3$: C, 79.23; H, 5.70. Found: C, 79.06; H, 6.14. Yield: 96%.