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Substituted indole-1-acetic acids as potent and selective CRTh2 antagonists—discovery of AZD1981

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ABSTRACT

Novel indole-3-thio-, 3-sulfonyl- and 3-oxy-aryl-1-acetic acids are reported which are potent, selective antagonists of the chemoattractant receptor-homologous expressed on Th2 lymphocytes receptor (CRTh2 or DP2). Optimization required maintenance of high CRTh2 potency whilst achieving a concomitant reduction in rates of metabolism, removal of cyp p450 inhibition and minimization of aldose reductase and aldehyde reductase activity. High quality compounds suitable for in vivo studies are highlighted, culminating in the discovery of AZD1981 (**22**).

The chemoattractant receptor homologous expressed on Th2 lymphocytes receptor (CRTh2 or DP2),[1] one of the receptors for prostaglandin D_2 (PGD_2), is highly expressed in humans on key cells implicated in the pathology of asthma and other allergic diseases.[1,2] Activation of CRTh2 elicits responses including chemotaxis[1] and mediator release.[3] These findings have stimulated considerable interest in the development of CRTh2 antagonists as novel treatments for asthma and other allergic diseases, such as allergic rhinitis.[4]

A variety of molecular frameworks have emerged as potent CRTh2 ligands and these have been recently reviewed.[5] Indole acids have emerged as one class of CRTh2 ligands, perhaps inspired by early reports of surprising CRTh2 activity from compounds such as Indomethacin[2] (**1**, Fig. 1) a non-selective cyclo-oxygenase inhibitor and Ramatroban (**2**),[6] originally developed as a thromboxane A_2 receptor (TP) antagonist. Compounds from the AstraZeneca collection with structural similarity to Indomethacin were screened to provide both agonists and antagonists of CRTh2, from which a series of 3-quinolinyl-indole-1-acetic acids (**3**) were identified.[7] Publications from other groups have disclosed alternative indole-derived CRTh2 series.[8]

An additional hit molecule **4** intriguingly highlighted the 3-thioaryl indole as a novel CRTh2 core template.

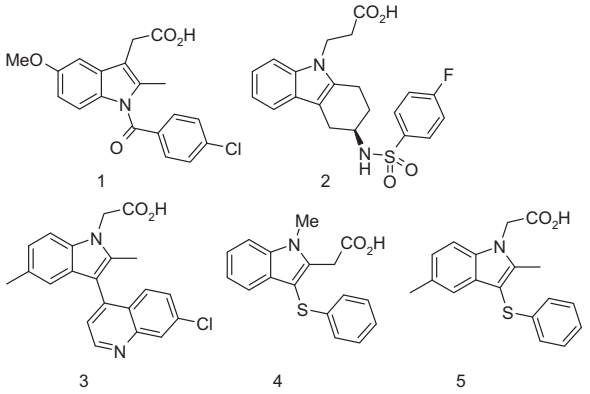

Figure 1. Known CRTh2 scaffolds **1**–**3** and AstraZeneca hits **4**–**5**.

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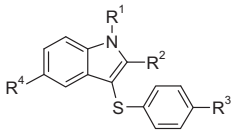
Table 1
Preliminary SAR



	R^1	R^2	R^3	R^4	CRTh2 binding IC_{50}[a] (nM)
5	CH_2CO_2H	Me	H	Me	20
6	CH_2CO_2H	Me	Cl	Me	15
7	CH_2CO_2H	Me	Cl	Cl	13
8	CH_2CO_2H	H	Cl	Cl	89
9	$CH(Me)CO_2H$	Me	Cl	Cl	501
10	CH_2 (1*H*-tetraz-5-yl)	Me	Cl	Cl	1468

[a] Radioligand binding assay (^{3}H-PGD_2), mean of n >2 measurements.

Compound **4** was of modest CRTh2 potency (binding[7] IC_{50} 794 nM), however by analogy to compounds **1** and **3**, the methyl and acetic acid side chain positions on the indole core were reversed and gratifyingly this resulted in a substantial increase in CRTh2 binding potency (Table 1, **5**: IC_{50} 20 nM). Compound **5** was also shown to behave as an antagonist in a functional assay, blocking PGD_2 mediated Ca^{2+} flux in HEK cells expressing human CRTh2[7] (IC_{50} 25 nM). The potency in this functional screen was similar to that observed from the radioligand binding assay. Given that the indole and acid components of the molecules are also present within the pharmacophores known for other related prostanoid targets (and as highlighted by structures **1** and **2**) it was unexpected that **5** was more than 100-fold selective over DP_1, TP and COX-1.

Wider screening across a range of receptors and enzymes revealed rat aldose reductase inhibition to be somewhat of a concern for **5** (MDS Pharma (now Ricerca), IC_{50} 157 nM). Indomethacin (**1**) and other structurally related acetic acids are known to inhibit human aldose reductase (ALR2).[9] ALR2 is a member of the aldo-keto superfamily of enzymes which includes the closely related aldehyde reductase (ALR1). Because both enzymes share a role in the removal of toxic aldehydes we tested **5** against human recombinant ALR2 and ALR1.[10] Gratifyingly the human activity at ALR2 (IC_{50} 31.6 μM) was weaker than rat, however the level of human ALR1 activity (IC_{50} 3.16 μM) was more concerning but still with ~150-fold separation from CRTh2. Interestingly, we are not aware of reports from other CRTh2 antagonist series highlighting this potential selectivity concern.

With this encouraging profile, compounds with close structural changes were prepared to unravel the CRTh2 potency SAR within this new series (Table 1). A chlorine atom in the 4-position of the S-aryl gave a small potency increase (**5** vs **6**), and a methyl group at the indole 2-position gave a substantial 6-fold potency increase (**8** vs **7**). Potent analogues were also shown to be antagonists in the functional Ca^{2+} assay (**6**: IC_{50} 87 nM, **7**: IC_{50} 35 nM). Attempts were also made to modify the structure around the carboxylic acid group, but unfortunately methyl substitution adjacent to the acid (**9**) and replacement of the carboxylate with a tetrazole (**10**) were poorly tolerated. Others have also reported poor results with α-Me acids in their indole derived series.[8d] Compound **6** was further profiled and had reasonable metabolic stability (rat hepatocyte (rat hep) CL_{int} 18, human microsomes (hum mic) CL_{int} <3), but was unfortunately found to be a relatively potent inhibitor of cytochrome p450 (cyp) 2C9 (IC_{50} 800 nM).

With the goals of increasing potency at CRTh2, minimizing the rate of metabolism and controlling selectivity over ALR1, ALR2 and cyp 2C9, a wider range of structural changes were investigated. Substituent changes on the indole core are summarized in Table 2.

This data set showed chloro substituents were more potent at CRTh2 at the indole 4- and 5-positions than at the 6- or 7-positions (**7**, **11–13**). Other small substituents were also potent, with 5-fluoro indole **14** having increased potency compared to the 5-chloro analogue (**7**). The larger electron withdrawing methylsulfone regio-isomers (**18–19**) had a stronger potency preference for the 4- over the 5-isomer, but interestingly the phenyl substituent was well tolerated at either position. As no closely related SAR has been published, it was inferred from these results that a mixture of size, lipophilicity and electronic factors were affecting CRTh2 potency.

A range of indoles containing polar amide and sulfonamide groups were prepared (**21–25**). Given the dramatic reduction of lipophilicity that these substituents produced, it was somewhat surprising that compounds **21** and **22** had such exceptional potency. Alkylating the amide lost considerable potency (**23** vs **22**) as did reversing the amide link (**24** vs **22**). Moving the acetamide group to the indole 5-position resulted in a loss of affinity at CRTh2 (**25** vs **22**). Finally, derivatives bearing heterocycles at the indole 4-position (**26, 29**) showed high affinity for CRTh2.

The more lipophilic compounds as a general trend had higher rates of metabolism (**11–12**, **27–28**) although this SAR was often compound specific and unpredictable (e.g., **22** and **29** have similar log D's but quite different rates of metabolism).

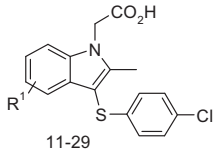
Representative compounds were screened against ALR2 and ALR1 and high selectivity was found across this set of 3-thioaryl analogues. Gratifyingly, some compounds also had improved selectivity over p450 enzymes (IC_{50} **21**: 2C9 10 μM; **22**: 1A2, 3A4, 2C9, 2D6 all >10 μM).

Modifications to the side chain at the 3-position of the indole were investigated (Table 3). These included changes to the linker atom between the two aromatic rings as well as variation of the ring substituents. For example, S-aryl substituents such as 3-Cl (**30**) and 2-Cl (**31**) as well as the 4-methylsulfone (**32**) and 4-methoxy (**33**) were highly potent CRTh2 ligands. The high potency of the alkoxy and methyl sulfone substituents was in contrast to some other reports.[8c,8g] For example, SAR now revealed by Novartis[8g] showed their 4-methoxyphenyl analogue to lose considerable activity, highlighting SAR divergence across series of indole/azaindole derived CRTh2 antagonists. Unfortunately, **32** was a reasonably potent cyp 2C9 inhibitor (IC_{50} 5.2 μM) despite its lower lipophilicity and the alkoxy substituent in **33** promoted unwanted ALR1 activity.

The sulfoxide linker (**34**) was significantly less potent than the original sulfide (**6**) at CRTh2, however the sulfone and oxygen linked compounds (**35–49**) had more encouraging levels of CRTh2 activity. Several of the indole and aryl substituents were potent across the different linkers. For example, the combination of a 5-F-indole core with a 4-Cl-phenyl side chain showed potency in excess of 10 nM across the S- (**14**), SO_2- (**36**) and O- (**43**) linkers. However this was not always the case and there were a number of surprises within the SAR across the individual linker types. For example, with the SO_2-linker, a 2-Cl-phenyl was poorly tolerated when compared to the S-linker (**40** vs **31**). 2,6-Di-chloro (**42**) was also poor as a sulfone link. These observations have subsequently been published by Novartis in a series of reverse azaindoles with a sulfone linker.[8g] This publication also highlighted the superiority of a 4-Cl over 3-Cl and 2-Cl isomers. However it is difficult in our data to rationalize why the 3-chloro isomer (**41**) was of modest CRTh2 potency in the sulfone series, but highly potent in the sulfides (**30**).

O-linked analogues (**46, 49**) were slightly less potent (~fivefold) than the S-linked analogues, but overall retained encouraging levels of CRTh2 activity. Some changes to the heterocyclic indole core were also prepared. The indole was successfully replaced with pyrrolopyridines (**50, 51**). These were slightly less potent at CRTh2 than their structurally-matched indoles (**6, 13**), but were of

Table 2
Modulation of indole substituents

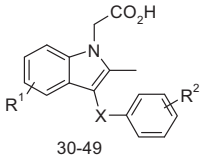


11-29

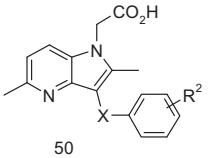
	R^1	CRTh2 binding IC_{50}[a] (nM)	hALR2 IC_{50} (nM)[b]	hALR1 IC_{50} (nM)[c]	Rat hep CL_{int}[d]	Hum mic CL_{int}[e]	Log $D_{7.4}$
11	7-Cl	60	11220	4467	75	<1	2.0
12	6-Cl	42	1995	1122	64	1	2.5
13	4-Cl	25	5012	1778	40	<1	2.2
14	5-F	1.6	>7943	3162	19	<3	1.8
15	4-Me, 5-F	1.3	3548	2239	17	<3	2.2
16	4-CN, 5-Cl	6.1	4732	2239	6	4	1.6
17	5-Cl, 6-CN	178	—	—	29	4	—
18	6-SO_2Me	159	—	—	<3	<3	0.8
19	5-SO_2Me	71	—	—	<6	—	0.5
20	4-SO_2Me	11	—	—	—	<3	0.6
21	4-MeSO_2NH	1.8	>5309	1000	6	13	0.2
22	4-MeC(O)NH	4.3	2512	794	1	<1	−0.2
23	4-MeC(=O)N(Et)	224	—	—	19	32	1.6
24	4-MeNHC(=O)	45	—	—	<3	<3	−0.9
25	5-MeC(O)NH	56	—	—	8	36	0.2
26	4-(2-Thiazolyl)	3.5	—	—	—	43	—
27	4-Ph	1.0	—	—	25	<1	2.6
28	5-Ph	3.5	4467	1778	—	16	3.7
29	4-(2-Pyrazinyl)	0.6	—	—	12	8	0.0

[a] Radioligand binding assay (^{3}H-PGD_2), n >2 measurements.
[b] Human aldose reductase, details in Ref. 10
[c] Human aldehyde reductase, details in Ref. 10
[d] Rat hepatocyte intrinsic clearance (μl/min/1 × 10^6 cells).
[e] Human liver microsomes intrinsic clearance (μl/min/mg).

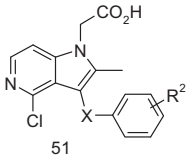
Table 3
SAR for modulation of side chain and core



30-49



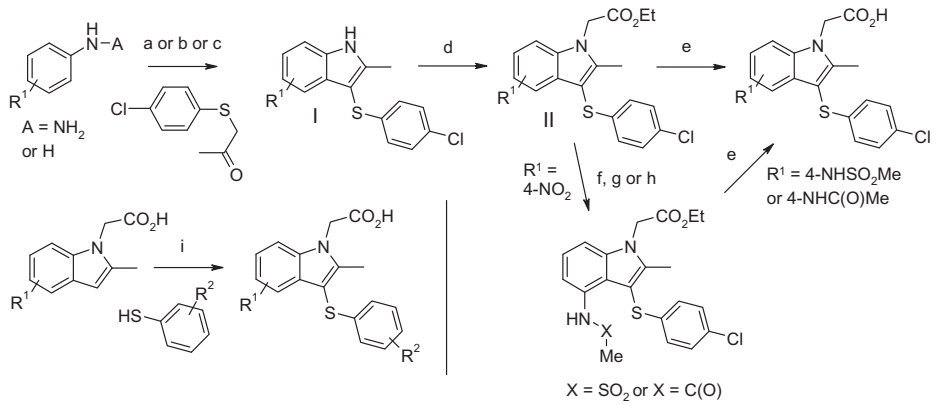
50



51

	X	R^1	R^2	CRTh2 binding IC_{50}[a] (nM)	hALR2 IC_{50} (nM)[b]	hALR1 IC_{50} (nM)[c]	Rat hep CL_{int}[d]	Hum mic CL_{int}[e]	Log $D_{7.4}$
30	S	5-Me	3-Cl	3.0	3162	1778	31	12	1.9
31	S	5-Me	2-Cl	2.6	11220	5623	24	<3	1.7
32	S	5-Me	4-SO_2Me	1.4	>10000	7943	7	<3	−0.1
33	S	5-Me	4-MeO	7.1	251	282	24	<3	1.0
34	SO	5-Me	4-Cl	1000	—	—	<5	3	0.1
35	SO_2	5-Me	4-Cl	26	6310	411	—	7	0.1
36	SO_2	5-F	4-Cl	7.1	—	—	<3	<3	−0.2
37	SO_2	5-Me	3-MeO	71	724	115	14	3	−0.4
38	SO_2	4-MeC(O)NH	4-Cl	7.1	4467	708	<1	<3	0.4
39	SO_2	4-MeSO_2NH	4-Cl	7.9	>5843	63	5	<3	−0.8
40	SO_2	5-Me	2-Cl	178	—	—	21	<1	—
41	SO_2	5-Me	3-Cl	79	—	—	—	—	—
42	SO_2	5-Me	2,6-Di-Cl	126	—	—	—	—	—
43	O	5-F	4-Cl	5.0	—	—	<3	<3	1.3
44	O	5-CF_3	4-Cl	11	—	—	—	—	2.3
45	O	4-MeSO_2NH	4-Cl	3.5	—	—	8	<3	−1.0
46	O	4-MeC(O)NH	4-Cl	18	—	—	—	—	−1.4
47	O	5-CF_3	4-SO_2Et	3.5	>10000	3981	6	<7	0.3
48	O	4-EtSO_2NH	4-Cl	36	—	—	—	—	−0.2
49	O	4-Ph	4-Cl	4.0	—	—	14	<3	—
50	S	—	4-Cl	56	—	—	5	5	0.4
51	S	—	4-Cl	32	—	—	—	—	0.9

[a] Radioligand binding assay (^{3}H-PGD_2), mean of n >2 measurements.
[b] Human aldose reductase see Ref. 10
[c] Human aldehyde reductase, see Ref. 10
[d] Rat hepatocyte intrinsic clearance (μl/min/1 × 10^6 cells).
[e] Human liver microsomes intrinsic clearance (μl/min/mg).



Scheme 1. Reagents and conditions: (a) A=NH_2, AcOH, MeCN, H_2O; (b) A=H, SO_2Cl_2, proton sponge, Et_3N, CH_2Cl_2; (c) A=H, *t*-BuOCl, CH_2Cl_2, Et_3N, 17% for product R^1 = 4-NO_2; (d) $BrCH_2CO_2Et$, NaHMDS or NaH, THF or K_2CO_3, DMF, 80% for R^1 = 4-NO2; (e) NaOH, H_2O, THF or THF/EtOH or MeOH, 44% for **21**, 55% for **22**; (f) Pt/C, EtOH, H_2, 83%; (g) AcCl, Et_3N, CH_2Cl_2, 94%; (h) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 73%; (i) I_2, DMF, 55% for **30**.

significantly lower log *D* and so provided interesting additional diversity.

A selection of additional compounds was screened against ALR2 and ALR1. Some of the more promising SO_2-linked compounds showed surprisingly reduced selectivity against ALR1 (**35**, **37**, **39** each <20-fold selective). One can speculate that these CRTh2 antagonists might mimic parts of the pharmacophore present within some known ALR2/1 inhibitors (e.g., Indomethacin, Zopolrestat), although other parts of these ligands appear quite different.[9b,9c] From the sulfones screened, only **38** had 100-fold selectivity over ALR1. It was also devoid of significant cyp liabilities. The high ALR1 selectivity of O-linked **47** was unexpected given that aryloxy side chains had diminished selectivity in other compounds (**37**, **33**).

Synthetic methods for the preparation of the CRTh2 antagonists are summarized in Scheme 1. Additional details have been reported elsewhere.[11] The 3-thioaryl indoles (I) were synthesized from 2-thioaryl-ketones using either Fisher (step a) or Gassmann[12a] (step b/c) methodology. The corresponding 3-oxyaryl indoles (not shown) were made from the analogous 2-oxyaryl ketones using a modified Fisher indole synthesis catalyzed by PCl_3.[12b] Additional transformations (steps d–h) afforded the desired acidic CRTh2 antagonists. A complimentary route (step i) allowed late stage introduction of substituted S-aryl side chains. SO_2-linked compounds could be prepared by S-oxidation chemistry (not shown).

Overall, there were no discernable trend of CRTh2 affinity with log *D*, however compounds that combined high metabolic stability and low cyp 2C9 activity tended to have log *D* <0.5 (Figs. 2a and b).

Unfortunately, for a given (low) log *D* value, a wide variety of compound performance was attained. For example at a log *D* of ~0.3 there is at least a 10-fold variation in both the cyp 2C9 po-

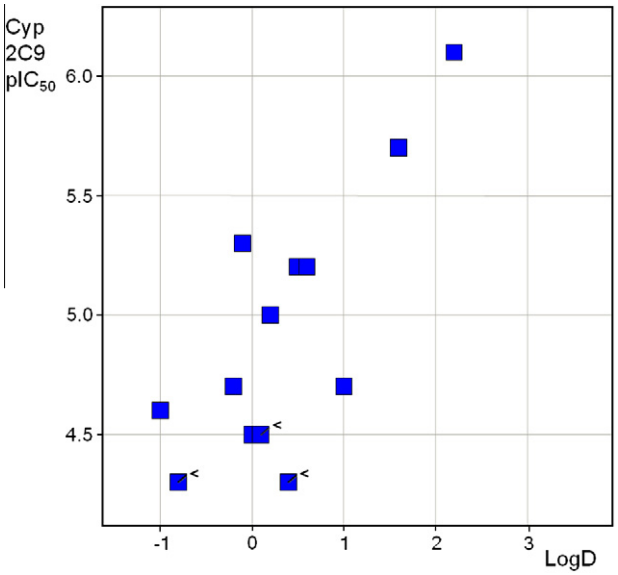


Figure 2a. cyp 2C9 pIC_{50} versus log *D*. Less than values are marked where appropriate.

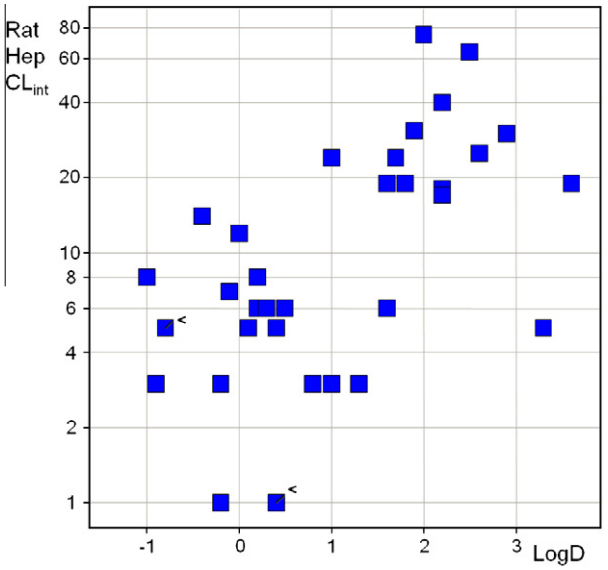


Figure 2b. Rat hepatocyte CL_{int} versus log *D*. Less than values are marked where appropriate.

Table 4
Rat[a] pharmacokinetic properties of key analogues

	Rat Cl (ml/min/kg)[b]	Rat V_{ss} (L/kg)[b]	Rat t½ (h)[b]	Rat F%[c]
21	11	1.1	1.7	42
22	4	0.5	1.9	63
38	4	0.2	0.9	<10
45	20	1.7	1.4	>46

[a] Male sprague dawley.
[b] IV dose 1 mg/kg.
[c] Oral dose 4 mg/kg (**21**, **22**) or 3 mg/kg (**38**, **45**).

tency and rate of metabolism (rat hep CL_{int}), rendering it challenging to predict the profile of individual compounds before synthesis.

Based on the optimal in vitro properties the best 4 compounds were progressed to in vivo profiling (Table 4). Highly polar compounds such as these are at theoretical risk of low levels of permeability and absorption.[13] For example, passive permeability drops considerably as log *D* falls below 1–2. The four compounds tested had low to moderate clearance as expected from the low in vitro rates of metabolism in rat hepatocytes, and low volumes of distribution in common with many strong acids. As hoped, this drove encouraging half-lives. Although compound **38** had very low oral bioavailability, interestingly, given their low lipophilicity, the other compounds (**21, 22, 45**) had much more promising oral PK profiles. Compound **22** was particularly noteworthy having the longest terminal half life coupled with high bioavailability.

Compound **22** successfully balanced a number of the desirable in vitro and in vivo properties. Additional profiling showed no discernable activity at related receptors and enzymes such as DP1 and arachidonic acid-mediated platelet aggregation (a marker of cyclooxygenase 1 and TP activity) at concentrations of 1 μM or above. Importantly, **22** was potent antagonist in a disease relevant cell system, inhibiting DK-PGD_2-induced CD11b expression in human eosinophils (IC_{50} 10 nM).

In summary, this lead optimization program generated a range of high quality compounds which met the aspirations of high CRTh2 potency, functional antagonism, low rates of metabolism, no significant cyp 2C9 inhibition and high selectivity against related receptors. It was challenging to balance these important drivers of quality given compounds of similar bulk properties often had very different metabolic and selectivity profiles and the finding that promising compounds often had low lipophilicity which suggested that in vivo DMPK properties could be compromised.

In conclusion, a novel series of CRTh2 antagonists was optimized from an initial hit via a variety of changes to the indole core, linker atom and substituents on the pendant aryl. Compound **22** was progressed into development by AstraZeneca as AZD1981 and is currently in clinical studies.

Acknowledgments

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10. Purified human recombinant aldehyde reductase (ALR1) and aldose reductase (ALR2) were kindly provided by Dr K. Bohren, Dept. of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas, USA. ALR1 and ALR2 activity was determined spectrophotometrically by monitoring the change in absorbance at 340 nM due to the oxidation of the co-factor NADPH. Assays were performed at 22 °C in U.V. clear polystyrene 96 well plates (Costar) and the change in absorbance monitored using a Spectramax 250 (Molecular Devices) spectrophotometer. For both assays, all reagents apart from NADPH were incubated for 15 min. at 22 °C and the reaction started by the addition of the co-factor. Absorbance readings were taken and the initial (linear) rate of reaction recorded. For calculation of enzyme inhibition IC_{50} values, the initial rates of reactions were corrected for non-enzymatic NADPH oxidation and the percent inhibition at any given compound concentration was calculated relative to the no-compound control. IC_{50} values are the mean of at least 2 separate determinations and were estimated from concentration effect curves fitted to a 4 parameter logistic function.
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