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Discovery of thiadiazoles as a novel structural class of potent and selective PDE7 inhibitors. Part 2: Metabolism-directed optimization studies towards orally bioavailable derivatives

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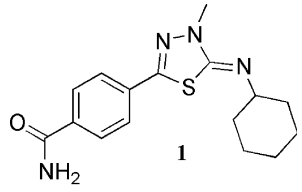
Abstract—The synthesis and optimization of pharmacokinetic parameters of structurally novel small PDE7 inhibitors is discussed.

1. Introduction

Phosphodiesterases (PDEs) are part of a family of enzymes, which play a role in signal transduction by regulating cellular concentrations of cAMP. Aberrant regulation of cAMP levels is implicated in many diseases like asthma, inflammation, immuno-related disorders, allergy and cancer.[1] And, it has been shown that inhibition of cAMP-specific PDE activity (e.g. with PDE4 inhibitors) causing an increase in intracellular concentrations of cAMP could be beneficial for the treatment of several diseases.[2] PDE7 is a recently described high affinity cAMP-specific PDE ($K_m = 200$ nM) whose functional role in T-cells[3] has been demonstrated. Recent findings on tissue distribution support the hypothesis that PDE7 could be a good target for the treatment of airway diseases,[4] T-cell related diseases,[3] CNS disorders,[5] leukemia,[6] cardiovascular diseases[7] and fertility disorders.[8] Therefore, the identification of selective inhibitors targeted against PDE7 enzyme has become an attractive area of research.[9] In this context, we have decided to design bioavailable PDE7 inhibitors to pursue our studies in animal models.



1

$IC_{50} = 61$ nM

Figure 1. Schematic representation of **1**.

In our previous publication,[10] we described the discovery of highly potent and selective PDE7 inhibitors. Among them, **1** (Fig. 1) is the representative of one chemical sub-series. Herein, we would like to report our efforts directed towards the discovery of orally bioavailable PDE7 inhibitors starting from this compound (Fig. 1).

2. Chemistry

The thiadiazole derivatives exemplified in this report were prepared according to the routes described[11] in Scheme 1 (some of these compounds can also be synthesized by alternative pathways).[10] The common reaction conditions leading to the key intermediate **5** were first

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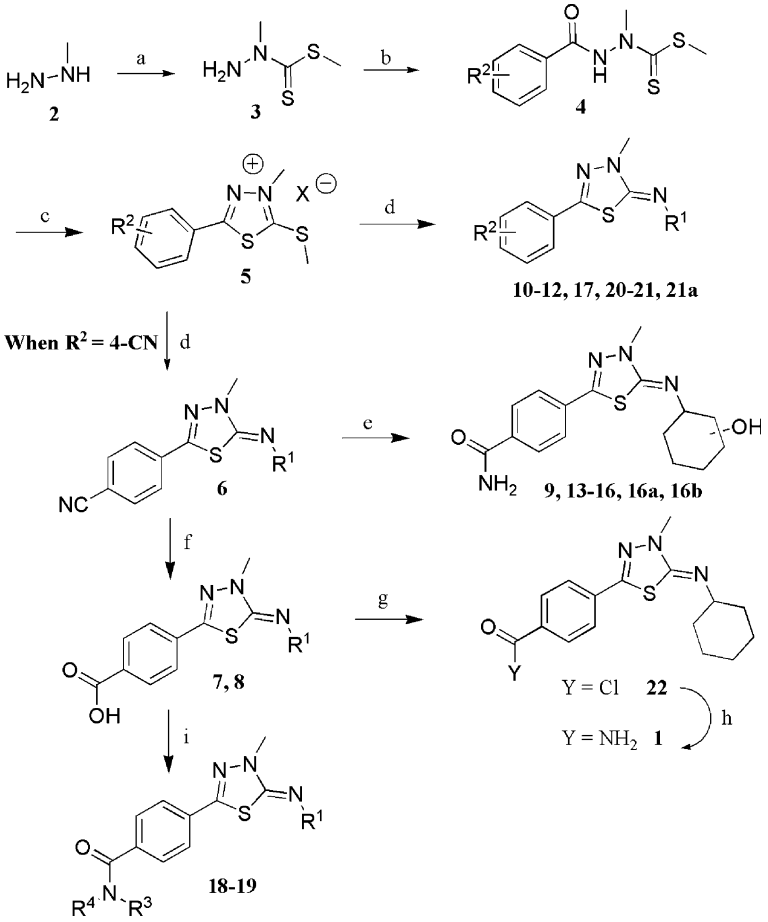


Scheme 1. Reagents and conditions: (a) CS_2, MeI, KOH, EtOH, 0–15 °C; (b) $R^2PhCOCl$, toluene, reflux; (c) Ac_2O, $HClO_4$, Et_2O, −5 to 5 °C or TMSOTf, CH_2Cl_2, rt (compounds **17** and **20**); (d) R^1NH_2, alcohol (EtOH), Et_3N, 40–80 °C; (e) H_2O_2 (30% in water), Na_2CO_3 (3 N), EtOH, rt; (f) KOH (6 N), isopropanol, reflux; (g) $SOCl_2$, toluene, reflux; (h) ammonia; (i) HNR^3R^4, BOP, *i*-Pr_2NEt, HOAt, DMF.

reported by Molina et al.[12] Methyl hydrazine (**2**) was reacted with carbon disulfide and with methyl iodide in presence of potassium hydroxide to form the hydrazine carbodithioate (**3**). Acylation of **3** followed by intramolecular cyclization in presence of acetic anhydride and perchloric acid in diethylether (or using TMSOTf in CH_2Cl_2) as reagents gives the corresponding intermediate 1,3,4-thiadiazolium salts **5** (ClO_4^- or OTf^-, respectively). Compound **5** is then reacted with suitable amines to yield the targeted thiadiazoles (**6**, **10**–**12**, **17**, **20**–**21** and **21a**). Reaction of the appropriate benzonitrile **6** with KOH (6 N) in isopropanol at reflux gave the carboxylic acid derivative **7** and **8**, respectively (**7**, when R^1 = cyclohexyl and **8**, when R^1 = *trans*-3-hydroxycyclohexyl). Compounds **9**, **13**–**16** and **16a**–**b** were prepared from **6** by transformation of the nitrile to the amide function with H_2O_2 (30% in water) as reagent in presence of a solution of sodium carbonate. The cyclohexyl derivative **7** is easily converted to compound **1** by transformation to the corresponding benzoyl chloride **22** with thionyl chloride, followed by a condensation with ammonia. **18** and **19** were, respectively, prepared by reaction of **7** and **8** with the corresponding primary amines in presence of the BOP coupling agent in dimethylformamide.

3. Biological results[13] and discussion

We have recently reported that the thiadiazole amide sub-series, represented by the general structure **23** (Fig. 2), show nanomolar inhibitory activities.[10] However, in rats, low bioavailabilities (<20%) and high clearances (>100 mL/min/kg) were observed for some of these derivatives. Additional data (not shown) suggested that the marginal bioavailabilities were not related to permeability, physicochemical properties (such as solubility or dissolution) or to transporters issues therefore suggesting a predominant role for a clearance route. Most of the in vivo clearances were much higher than the clearances predicted from in vitro rat microsomal stability studies (<46.3 mL/min/kg). Therefore, the high in vivo total clearance was suspected to be a combination of an extra-hepatic and hepatic metabolism. Consequently, we decided to identify the major in vivo metabolites in order to remove or alter the functionalities associated with the rapid rate of metabolism. The identification of the major metabolites after po and iv rat administration of **1** revealed two principal sites of metabolism: oxidation of the cyclohexyl ring to form **9** and hydrolysis of the amide function to give **7** (Fig. 2).

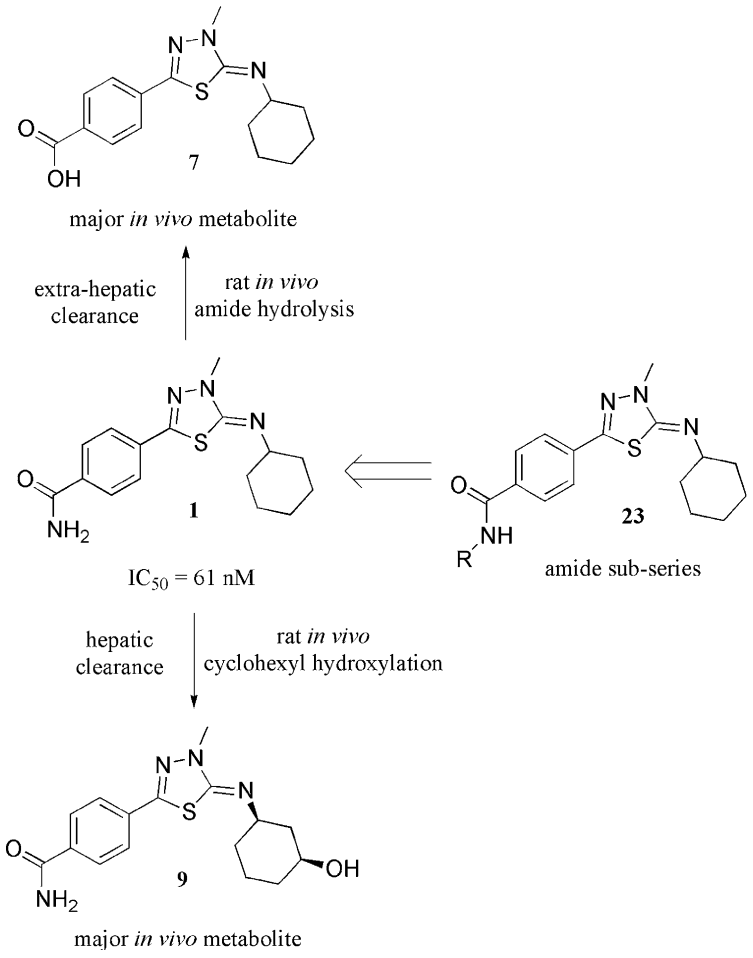


Figure 2. Schematic representation of the principle sites of metabolism.

Hydroxylation occurs mainly at the 3-position of the cyclohexyl ring to form the *cis*-stereoisomer with a marginal formation of 4-hydroxylated derivatives (stereochemistry not confirmed for the latter). This result was anticipated because this region of the molecule was highly hydrophobic and could be a good substrate for cytochrome P-450's, which have lipophilic binding sites. The extra-hepatic metabolic pathway was the hydrolysis of the amide function in rat whole blood, which gave the carboxylic acid derivative **7**, known to be a PDE7 inhibitor ($IC_{50} = 550\,nM$). It is worth noting that reduction of the global lipophilicity (decrease of $\log D$ by amino side chains as R groups (**23**), Fig. 2) resulted in an excellent in vitro metabolic stability (data not shown) but was without any effect on the in vivo total clearance.

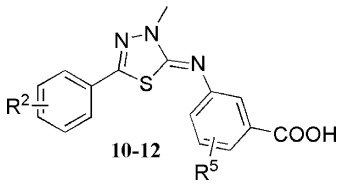
These results reflected that the extra-hepatic route was the primary contributor to the higher rat in vivo clearance.

To improve these pharmacokinetic parameters, the combined strategies adopted were to: (a) study and optimize the pharmacokinetics of the previously identified meta-benzoic acid sub-series (preceding publication)[10] which do not have these structural metabolism sites; (b) prepare hydroxylated cyclohexyl derivatives (which are potential metabolites of **1**) to assess their properties in terms of inhibitory activities and pharmacokinetics; (c) find stable amide bioisosteres without loss of inhibitory activity. These metabolism-directed optimization studies should lead to appropriate modifications of the metabolically labile structural parts to generate compounds with improved pharmacokinetics.

We first assessed the pharmacokinetic profile of some benzoic acid derivatives illustrated by representative examples **10**–**12** of this chemical sub-series (Table 1).

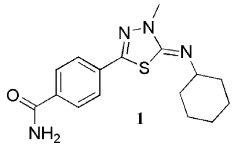
Upon oral dosing of these compounds to rats, compound **10** exhibited the highest bioavailability ($F = 49\%$) with a 2 h plasma half-life. As illustrated by **11** and **12**, the nature and the relative position of R^2 did not appear to affect the enzymatic activity, suggesting no or marginal favourable interactions with residues of the protein. The major contribution in terms of inhibitory activity probably resulted from interactions between the benzoic acid structural part and the enzyme. Then, in an attempt to increase the half-life of **10** the R^2 groups were modified (with $R^5 = H$) to reduce the plasma protein binding (PPB). Indeed, it is known that binding of acidic compounds to albumin is dependent on lipophilicity, hence lipophilic acids generally will tend to bind extensively and consequently will exhibit

Table 1. Rat pharmacokinetic parameters for compounds **1** and **10–12**



10-12

Compd			PDE7A1 IC_{50}, μM[a]	PDE4D3 IC_{50}, μM[a]	Cl (mL/min/kg)[b]	V_d (L/kg)[b]	$t_{1/2}$ (h)[c]	F (%)[c]	Solubility pH 7.4 (μg/mL)[d]
1			0.061	15.30	179.5	7.65	BLQ[e]	BLQ	4
	R^5	R^2							
10	4-F	4-Cl	0.16	39.66	3.9	0.187	1.96	49.3	145
11	H	4-SO_2Me	0.12	65.5	15.8	7.58	2.7	29.3	370
12	H	3-CN	0.19	35.67	2.65	0.994	4.75	37.0	295



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[a] Measured against the human full length enzyme produced in baculovirus infected sf9 cells. Values are means of three experiments.
[b] Dose 0.5 mg/kg iv.
[c] Dose 2.5 mg/kg po.
[d] Determined by stirring in pH 7.4 Na_2HPO_4/NaH_2PO_4 buffer for 24 h.
[e] BLQ = Below limit of quantification.

volumes of distribution close to plasma or blood volume (0.1–0.2 L/kg).[14] The highly hydrophobic compound **10** is a perfect representative example of this effect. As, the half-life is a function of the clearance and volume of distribution (according to the following equation: half-life = $0.693 \times V_d$/Cl), half-life of these related compounds can be improved by increasing the volume of distribution or reducing the plasma clearance.[15] Since **10** displayed low clearance, we decided to increase the V_d by reducing the plasma protein binding of related analogues. The approach was to decrease the global lipophilicity by introduction of polar groups (R^2) on the phenyl part of the molecule. These modifications illustrated by compounds **11** and **12** resulted indeed in a decrease of plasma protein binding (respectively 7% and 2% less than the PPB for **10**). Consequently **11** and **12** exhibited a 40-fold and 5.3-fold increase respectively in the volume of distribution (V_d) compared to **10** and accordingly improved the corresponding half-lives. Only a slight decrease of bioavailability was observed compared to **10**. In conclusion from these first studies, the design of new benzoic acid derivatives allowed a significant improvement of the pharmacokinetic profiles ($t_{1/2} > 2$ h, $F > 29\%$) with good solubilities (>145 μg/mL at pH 7.4) compared to the reference compound **1**.

We next examined another approach (c) directed towards the assessment of hydroxylated cyclohexyl derivatives in terms of inhibitory activities and pharmacokinetics. The objective was to identify within these new derivatives, potent PDE7 inhibitors with a reduced rate of metabolism at the cyclohexyl site. Table 2 summarizes a broad survey around the effect of cyclohexyl hydroxylation on PDE7 inhibitory activity, selectivity versus PDE4 and pharmacokinetics. Interestingly, some of the preliminary modifications based on the racemic forms of the hydroxylated derivatives resulted in a only moderate decrease in inhibitory activity (3-fold) as exemplified by **15** and **16** compared to **1**.

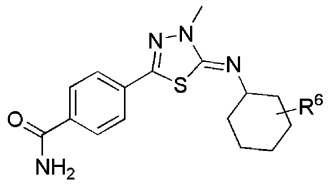
While a relatively more significant loss in activity was observed with compounds **13**, **14** and **9** versus **1**. It is worth noting that the position of the OH groups on the cyclohexyl ring and the stereochemistry modulate the level of inhibitory activity as exemplified by comparison of **13–14** (2-position) with **15** (4-position) or **16** (3-position) and by comparison of **9** (*cis*-isomer) with **16** (*trans*-isomer). The *trans*-isomer **16** displayed 190 nM IC_{50} while the *cis* analog **9** (major in vivo metabolite) is around 9-fold less potent.

All the derivatives exhibited a high selectivity against the PDE4 enzyme. In conclusion from these preliminary studies, two new potent PDE7 inhibitors **15** and **16** ($IC_{50} = 190$ nM) have been identified.

The in vivo rat pharmacokinetic profiles were determined for the selected racemic compounds **9** and **14–16** (Table 2). All the hydroxylated derivatives tested led to a significant decrease in the total clearances (range of reduction between 62–81% compared to **1**).

The optimal compounds combining good half-lives and bioavailabilities were the 3-hydroxy derivatives **9** and **16** with $F = 61.2\%$ and 38.5%, respectively ($t_{1/2} = 1.42$ and 1.80 h, respectively). These studies clearly demonstrated that the rat in vivo clearance could be considerably reduced by introduction of an OH group at the 3-position. In addition, compound **16** was identified as a tool for in vivo experiments. Considering the real benefit of the 3-hydroxylation (**16**) in terms of pharmacokinetics and considering the importance of the stereochemistry (*trans*

Table 2. In vitro data and in vivo rat pharmacokinetic parameters for compounds **1**, **9** and **13–16(a,b)**



Compd	R^6	Stereochemistry	PDE7A1 IC_{50}, μM[a]	PDE4D3 IC_{50}, μM[a]	Cl (mL/min/kg)[b]	Reduction in clearance versus **1** (%)	V_d (L/kg)[b]	$t_{1/2}$ (h)[c]	F (%)[c]
1	H	—	0.061	15.30	179.5	0	7.65	BLQ	BLQ
13	2-OH	*cis*	0.61	28.50	ND	ND	ND	ND	ND
14	2-OH	*trans*	0.55	>101	38.2	79	1.47	0.31	24.7
15	4-OH	*trans*	0.19	46.33	66.9	62	0.98	0.27	7
9	3-OH	*cis*	1.65	>101	34.4	81	1.39	1.42	61.2
16	3-OH	*trans*	0.19	71.64	59.9	67	1.78	1.8	38.5
16a	3-OH	(*R*,*R*)	0.088	61.62	ND	ND	ND	ND	ND
16b	3-OH	(*S*,*S*)	1.74	>101	ND	ND	ND	ND	ND

[a] Measured against the human full length enzyme produced in baculovirus infected sf9 cells. Values are means of three experiments.
[b] Dose 0.5 mg/kg iv.
[c] Dose 2.5 mg/kg po.

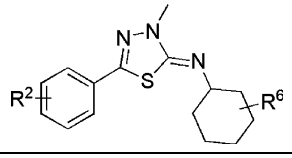
vs *cis*) in terms of potency, we decided to assess the inhibitory activity of both enantiomers of **16**. These compounds **16a** and **16b** were evaluated and the results are indicated in Table 2. This study allowed to identify the potent enantiomer **16a** (eutomer) with an IC_{50} of 88 nM (2-fold increase compared to **16**).

These new results led us to direct our efforts towards the discovery of hybrid structures combining stable amide bioisosteric groups with the novel (*R*)-hydroxy cyclohexyl part, to reduce more significantly the clearances and accordingly to increase again the half-lives and the bioavailabilities. Table 3 lists the structures, the inhibitory activities and the pharmacokinetics of some selected analogs from this study.

Simple modifications of the amide function without changes at the cyclohexyl site, exemplified by **17** (reverse amide) and **18** (increased steric hindrance) showed better metabolic stability compared to **1** (clearance reduced by 58 % and 75 %, respectively). Interestingly, **17** displayed the same level of inhibitory activity compared to **1**.

As illustrated by **18**, the high oral bioavailability (F = 85%) is likely to be the result of a lower clearance and a better solubility compared to compounds **1**, **17**

Table 3. In vitro data and in vivo rat pharmacokinetic parameters for compounds **1** and **16**, **17–21(a)**



Compd	R^6	Stereo-chemistry	R^2	PDE7A1 IC_{50}, μM[a]	PDE4D3 IC_{50}, μM[a]	Cl (mL/min/kg)[b]	Reduction in clearance versus **1** (%)	V_d (L/kg)[b]	$t_{1/2}$ (h)[c]	F (%)[c]	Solubility pH 7.4 (μg/mL)[d]
1	H	—	4-$CONH_2$	0.061	15.30	179.5	0	7.65	BLQ	BLQ	4
17	H	—	4-NHCOMe	0.068	34.25	74.7	58	3.3	0.74	19.6	8
16	3-OH	*trans*	4-$CONH_2$	0.19	71.64	59.9	67	1.78	1.8	38.5	40
18	H	—	4-CO(4-methyl-piperazin-1-yl)	0.42	>101	44.8	75	2.59	1.37	85	350
19	3-OH	*trans*	4-CONH(2-hydroxy-1,1-dimethylethyl)	0.38	>101	24.9	86	0.43	0.46	63	58
20	3-OH	*trans*	4-NHCOMe	0.085	40.80	13.3	92	2.02	2.3	76	350
21	3-OH	*trans*	4-SO_2Me	0.31	79.17	12.2	93	0.92	2	100	135
21a	3-OH	(*R*,*R*)	4-SO_2Me	0.052	20.0	15.1	91	0.62	2.5	100	160

[a] Measured against the human full length enzyme produced in baculovirus infected sf9 cells. Values are means of three experiments.
[b] Dose 0.5 mg/kg iv.
[c] Dose 2.5 mg/kg po.
[d] Determined by stirring in pH 7.4 Na_2HPO_4/NaH_2PO_4 buffer for 24 h.

and also **16**. This result reflects the benefit of amide modifications to optimize the pharmacokinetic profiles of thiadiazole derivatives. However, as mentioned in the preceding publication,[10] the loss of HBD properties (**18**) caused a decrease in inhibitory activity. Compound **19** was then designed to assess the importance of the combination of a novel hindered amide function (with HBD property) with the hydroxy cyclohexyl ring on the rate of metabolism. As expected, this modification resulted in a more pronounced reduction in clearance (86%) compared to **16** (67%), **17** (58%) and **18** (75%). This result confirmed the choice of a combined approach. However, the moderate volume of distribution for **19** resulted in a short half-life ($t_{1/2}=0.46$ h). Interestingly, the equivalent inhibitory activity displayed by **19** compared to **18**, suggested that steric bulk at the proximity of the amide H atom, is also detrimental to the HBD property and consequently to potency. It is worth noting that compounds **20** and **21** (**21a**) offered the appropriate structural combination resulting in a significant improvement of pharmacokinetic profiles compared to the starting point **1**. In addition, replacing the racemic form **21** by the enantiomer **21a** proved to be favourable for inhibitory activity (6-fold increase to reach 52 nM).

Compound **18** exhibited the higher V_d in contrast to some of the neutral compounds **16**, **19**–**21** and (**21a**). This is probably due to the basic property of the 4-methylpiperazine moiety, suggesting that the half-lives could be again optimized by incorporation of basic functions into the molecules. As anticipated, the V_d of neutral hydroxy compounds such as **16**, and **20** are lower compared, respectively, to **1** and **17** most probably reflecting a reduced lipophilicity (presence of polar functions) compared to compounds **1** and **17**. As expected, this effect is even more pronounced with **19** or **21** (**21a**). These results are in agreement with the overall trend for neutral compounds to display increased V_d with higher $\log D$,[14] with the risk also to increase the susceptibility to hepatic clearance as observed with **1** and **17**. The compounds **20**–**21** and **21a** displayed very high bioavailabilities (76–100%) with acceptable half-lives ($t_{1/2} > 2$ h) resulting not only from optimized low clearances but also due to the enhanced solubilities (>135 μg/mL) and to high permeabilities confirmed by measures across Caco-2 cells (Papp $>30\times10^{-6}$ cm/s).

4. Conclusion

In summary, we have rationally designed a structurally novel series of potent PDE7 inhibitors displaying good oral pharmacokinetics in rat. Compounds **20** and **21a** perfectly illustrated a successful metabolism-directed optimization approach that allowed to design derivatives with improved in vivo pharmacokinetics.

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