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Bridgehead modification of trihalocycloheptabenzopyridine lead to a potent farnesyl protein transferase inhibitor with improved oral metabolic stability

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Abstract—Modification of the ethano bridge of the core structure of the antitumor agent, **SARASAR®** (**SCH66336**) with concomitant introduction of a sulfonamide moiety off the distal piperidine afforded inhibitor **9**-(**S**-), a compound with greatly improved PK profile. Other compounds with enhanced FPTase inhibitory activity were obtained as exemplified by amide **10**-(**S**-) and urea **11**-(**S**-): these compounds demonstrated activity in picomolar range.

1. Introduction

A number of recent studies have reported farnesyl transferase inhibitors (FTIs) as successful agents in effecting tumor regression and promoting apoptosis (programmed cell death) in preclinical studies.[1] Use of these agents in clinical settings have successfully been translated to positive results in cancer patient.[2,3]

FTIs, normally interfere with the signal transduction pathway of tumorigenic cells by inhibiting the farnesylation process of the oncogenic proteins, thereby rendering the tumor cells less prone to activation for uncontrolled replication. These inhibitors have been found to be nontoxic, adequately tolerable, and therefore offer some advantages over traditional cytotoxic anticancer drugs currently used in treatment of cancer.[4]

In our effort to develop nonpeptidic FPTase inhibitors, we discovered **SARASAR®** (**SCH66336**), a potent trihalocycloheptabenzopyridine compound that is currently in phase III clinical trials for the treatment of tumors such as non-small cell lung carcinoma (NSCLC) and head and neck solid tumors (Fig. 1).[5] Preliminary

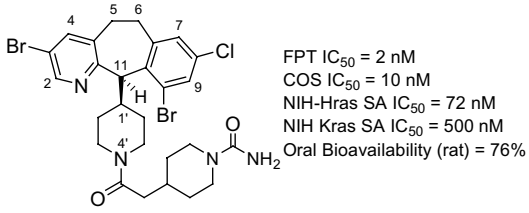

Figure 1. **SARASAR®**, **SCH66336**.

studies from phase I and II studies demonstrated **SARASAR®** to be well tolerated in patients and efficacy was observed in some of these studies.[6]

In an earlier publication by Piwinski et al.,[7] it was shown that Loratadine®, a tricyclic benzacycloheptapyridine closely related to **SARASAR®**, metabolized in rats to give, among other products, the hydroxylated compounds at positions 5 and 6 on the bridgehead (Fig. 2). We therefore, sought for ways to protect the bridgehead from similar metabolic fate and one way that looked attractive was introducing a double bond in this position with subsequent evaluation of the PK profile of the resulting targets. In this endeavor, various attempts were made to oxidize the 5,6-position using a variety of reagents without much success. However, chemistry that involved introduction of C-11 tertiary alcohol followed

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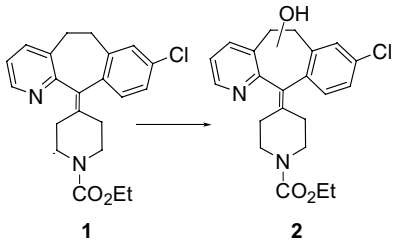
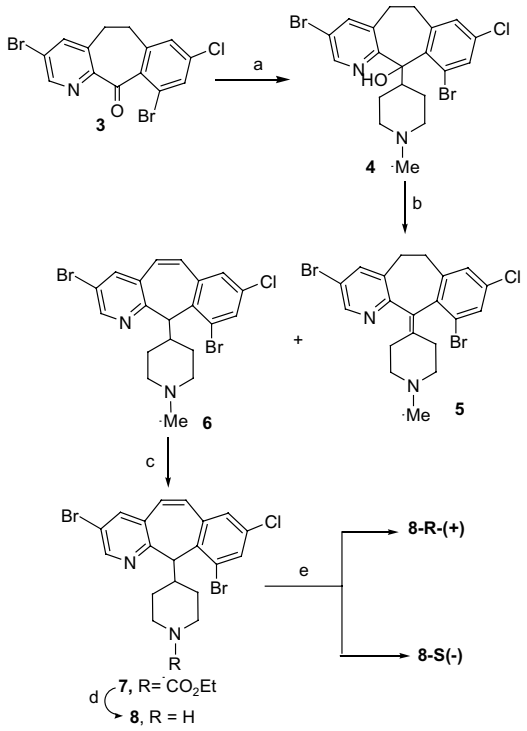


Figure 2. Metabolic sites of tricyclic bridgehead.



Scheme 1. Reagents and conditions: (a) *N*-Me-4-piperidinylmagnesium bromide, THF; (b) $SOBr_2$; (c) EtCOCl, CH_2Cl_2; (d) HCl, reflux; (e) chiral separation on AD column.

by treatment with thionyl bromide provided, the 5,6-bridgehead unsaturation of the tricyclic molecule as shown in Scheme 1.

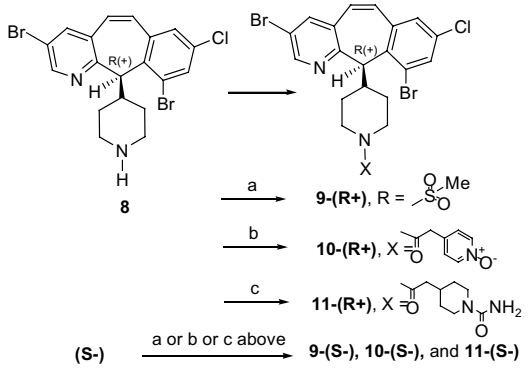
2. Chemistry

Compounds prepared for this study are shown in Table 1 and their synthetic schemes are outlined in Schemes 1 and 2. Thus, reaction of ketone **3**[8] with *N*-methyl-4-piperidinylmagnesium bromide in THF gave the C-11 tricyclic alcohol **4** in 64% yields. Treatment of **4** with thionyl bromide/dimethylacetamide in CH_2Cl_2, gave the dehydrocycloheptabenzopyridine compound **5** (44% yield) and 5,6-dehydro tricyclic compound **6** in 20% yields as a mixture. Conversion of the *N*-methyl-piperidine to the corresponding ethyl carbamate was effected using standard ethylchloroformate in refluxing toluene to provide the desired tricyclic carbamate **7** in 94% yield.[8] Hydrolysis of carbamate **7** to the corresponding amino **8** was efficiently carried out in refluxing concentrated HCl. Separation of the C-11 (+) and (−)-isomers were carried out on Chiralpack® AD column eluting with 20% isopropanol–80% hexane–0.2% diethylamine solvent system to give pure **8-R**-(+) and **8-S**-(−) (Scheme 1). The stereochemistry of the *S*-isomer was established from the X-ray structure of one of the inhibitors bound to the FPTase as will be described later.

Table 1. FT, soft agar activities and PK of **R**-(+) and **S**-(−) **8** derivatives

Compds	FPTase IC_{50}, nM	Soft agar Hras, IC_{50}, μM	PO AUC (h) μgh/mL (rat)
9-(R+)	45% @ 18	na	na
10-(R+)	44% @ 17	na	na
11-(R+)	16	na	na
9-(S-)	3.3	>0.50	45.4 (6)
10-(S-)	0.32	0.03	15.5 (6)
11-(S-)	0.40	0.05	7.0 (6)
SCH66336	2.0	0.07	24.1 (24)

na = not evaluated.



Scheme 2. Reagents and conditions: (a) Methanelsulfonyl chloride, CH_2Cl_2; (b) 4-pyridine acetic acid N-oxide–DEC-HOBT-NMM; (c) *N*-Boc piperidinyl acetic acid–DEC-HOBT-NMM, TFA, TMS-NCO.

Treatment of **8-R**-(+) with methanesulfonyl chloride provided sulfonamide **9-R**-(+) in 99% yield. Similarly, DEC-mediated coupling of **8-R**-(+) with 4-pyridine acetic acid N-oxide provided **10-R**-(+) in 89% yield. Coupling of **8-R**-(+) with *N*-Boc piperidinyl acetic acid in presence of DEC-HOBT-NMM gave the *N*-Boc 4-piperidinyl acetamide intermediate, which after removal of the Boc group, followed by reaction of the resulting amine with trimethylsilylisocyanate and subsequent work-up with sodium bicarbonate provided the urea **11-R**-(+)[11] in 74% yield.

Compounds **9** to **11-S**-(−)[11] were prepared from the corresponding **S** (−)-**8** isomer in a similar way to their **R**-(+) counterparts described above.

3. Results and discussion

Compounds prepared in this study were tested for their ability to inhibit the FPT catalyzed transfer of [^{3}H]-

farnesyl moiety from farnesyl pyrophosphate to H-Ras-CVLS as previously described.[9] Potent compounds were evaluated in a cellular colony forming assay (soft agar assay) according to the method described by Bishop et al.[9] Biological and pharmacokinetic data for these compounds are summarized in Table 1.

As shown in Table 1, pairs of sulfonamides, amides, and ureas were prepared from the two enantiomeric amines **8-R-**(+) and **8-S-**(−). Analogs derived from the **R-**(+)-isomer were found to have poor FPTase inhibitory activity and were not further evaluated in the cellular assays (Table 1). On the other hand, inhibitors prepared from the **S-**(−)-isomer demonstrated activities ranging from low nanomolar to picomolar; thus, the sulfonamide analog, **9-S-**(−) had a FPTase inhibitory activity of 3.3 nM. However, this compound did not show cellular activity even at 500 nM range. Pyridine acetamide N-oxide compound **10-**(**S-**) had an FPTase inhibitory activity with an IC_{50} of 320 pM (~6 times more potent than **SCH66336**) and had soft agar cellular activity with IC_{50} = 50 nM. The piperidinyl urea analog, compound **11-**(**S-**) was also very potent (FPTase IC_{50} = 400 pM) and had soft agar cellular activity with IC_{50} = 50 nM. Absolute stereochemistry at C-11 of **11-**(**-S**) bound to FPTase[10] (Fig. 3) was established from the X-ray structure of the compound to FPTase. In structural terms, inhibitory activity observed with 5,6-dehydro tricyclic series was opposite to that observed in **SCH66336** series, whereby the more potent compounds were derived from the R-(+)-isomer. However, similar to structural orientation previously observed with **SCH66336** like structures, the piperidine moiety assumed a pseudo-axial position and the stereochemistry at the C-11 was **R**.

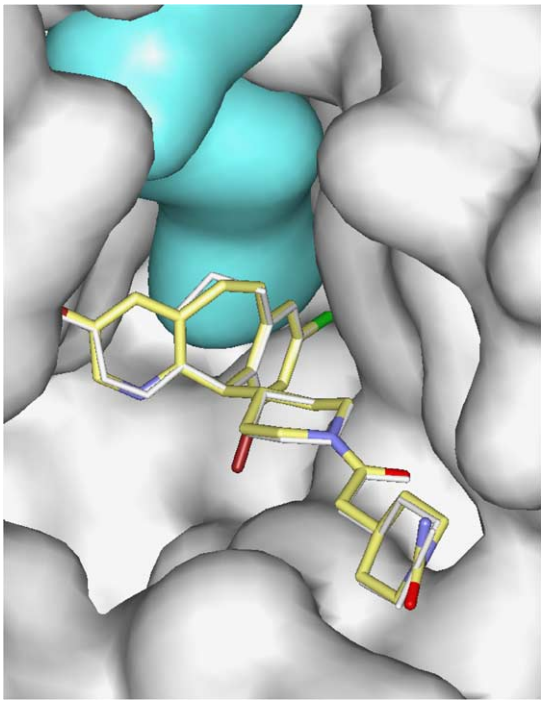


Figure 3. Structure of **11-**(**-S**) bound to FPT (blue surface—FPP, white surface—FPT, white sticks—**SARASAR®**, yellow sticks—**11-**(**-S**)).

The bridgehead ethano bridge was found to be puckered and the tricyclic moiety adopted a 'butterfly' conformation. The bromine at C-10 firmly locked the piperidine in a pseudo-axial position as previously seen.[10]

Pharmacokinetic studies of the active compounds in rats showed the sulfonamide compound to be the most stable with an oral AUC of 45 μg h/mL after 6 h (twice the AUC of **SCH66336** after 24 h), the pyridine acetamide was the second best in stability with AUC of 15.5 μg h/mL Unexpectedly, the piperidinyl amide, which is similar to the moiety in **SCH66336** had AUC of 7.7 μg h/mL after 6 h (possibly lower than **SCH66336**).

4. Conclusion

Modification of the bridgehead of compounds with **SCH66336** core by introduction of double bond provided compounds with potency in picomolar range as exemplified by tricyclic amide **10-**(**S-**) and urea **11-S**(−). Binding of the **10-S-**(−) to the FPTase was similar to that of the other inhibitors with characteristic piperidinyl moiety assuming a pseudo-axial orientation facilitated by the bulky bromine at C-10 position. Unlike compounds in **SCH66336** series, where the potent compounds exhibited an R-(−) stereochemistry at C-11, the 5,6-dehydro analogs were found to have S-(−) at this position. One of the inhibitors, the sulfonamide **9-**(**S-**) had very good oral pharmacokinetic profile although it lacked the appropriate cellular activity desired. We are currently exploring various ways to modify compounds in the sulfonamide series in an attempt to achieve better cellular potency possibly retaining the metabolic stability observed with **9-S**(−) inhibitor.

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11. Preparation of intermediates **8**-**R**-(+) and **8**-**S**-(−): Ketone **1**[8] (20 g, 0.05 mmol) was dissolved in 1 L of dry THF. To this solution was added a solution of *N*-methylpiperidinylmagnesium bromide[7] (80 mL, 1.56 M, 0.13 mol, 2.5 equiv), cooled to −40 °C. The reaction mixture was stirred for 0.5 h and then quenched with NH_4Cl. THF was distilled off and 500 mL of CH_2Cl_2 was added. The pH of the resulting solution was adjusted to 5 with 10% HCl before further extraction with CH_2Cl_2. Combined CH_2Cl_2 extracts were washed with $NaHCO_3$ and dried before passing through a short pad of Celite. Acetonitrile (300 mL) was then added and CH_2Cl_2 was distilled off until only ∼300 mL remained. Crystals precipitated out and were collected and dried to give 15.9 g (64%) of the target alcohol **4**. To alcohol **4** (5.0 g, 9.97 mmol) was added dimethylacetamide (9.5 g 109 mmol, 10 mL) and the reaction mixture cooled 0 °C. To this reaction was added 35 mL of thionyl bromide (freshly prepared NaBr and $SOCl_2$. The reaction mixture was stirred for 4 h and then portioned between $NAHCO_3$ and CH_2Cl_2. The organic extracts were dried and concentrated and resulting crude product purified by flash silica gel chromatography eluting with 1% MeOH–NH_3–CH_2Cl_2) to give and 2.1 g (44%) of C-11 saturated olefin **5** and 0.8 g (17%) of **6** as a solid. The *N*-methyl amine **6** was converted, first to the ethyl carbamate **7** and then to amine **8** using previously reported procedures.[8] Separation of atropisomeric amine **8** by HPLC using Chiralpack AD column and eluting with 20% isopropanol–80% hexane–0.2% diethylamine gave the desired amines **8**-**R**-(+) and **8**-**S**-(−).