ORGANIC LETTERS

1999
Vol. 1, No. 9
1371−1373

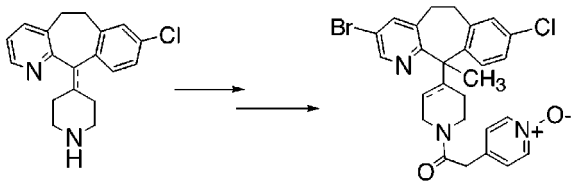
Synthesis of C-11 Methyl-Substituted Benzocycloheptapyridine Inhibitors of Farnesyl Protein Transferase

F. George Njoroge,* Bancha Vibulbhan, Jesse K. Wong, Steven K. White, Shing-Chun Wong, Nicholas I. Carruthers, James J. Kaminski, Ronald J. Doll, V. Girijavallabhan, and Ashit K. Ganguly

Schering-Plough Research Institute, Departments of Chemistry, 2015 Galloping Hill Road, Kenilworth, New Jersey 07033

Received August 9, 1999

ABSTRACT

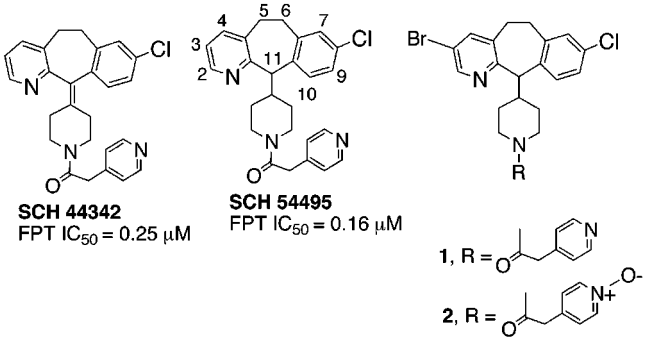


A B

Synthesis of C-11 methyl-substituted benzocycloheptylpyridine tricyclic compounds has been achieved via two different methods. Methylation of C-11 has been effected by treatment of amine 4 with BuLi followed by MeI quenching. In a similar procedure, introduction of a C-11 substituent with concomitant rearrangement of the exocyclic double bond has been carried out. Potent farnesyl protein transferase inhibitors have been synthesized using the above methodologies.

Farnesyl protein transferase (FPT) is a critical enzyme that facilitates signal transduction during cell proliferation.[1] Inhibition of FPT provides an attractive method for intercepting this mechanism, thereby presenting a potential method for arresting progression of tumor cells. Such inhibitors would be useful as antitumor agents, and a number of potential drugs have been advanced to clinical trials.[2]

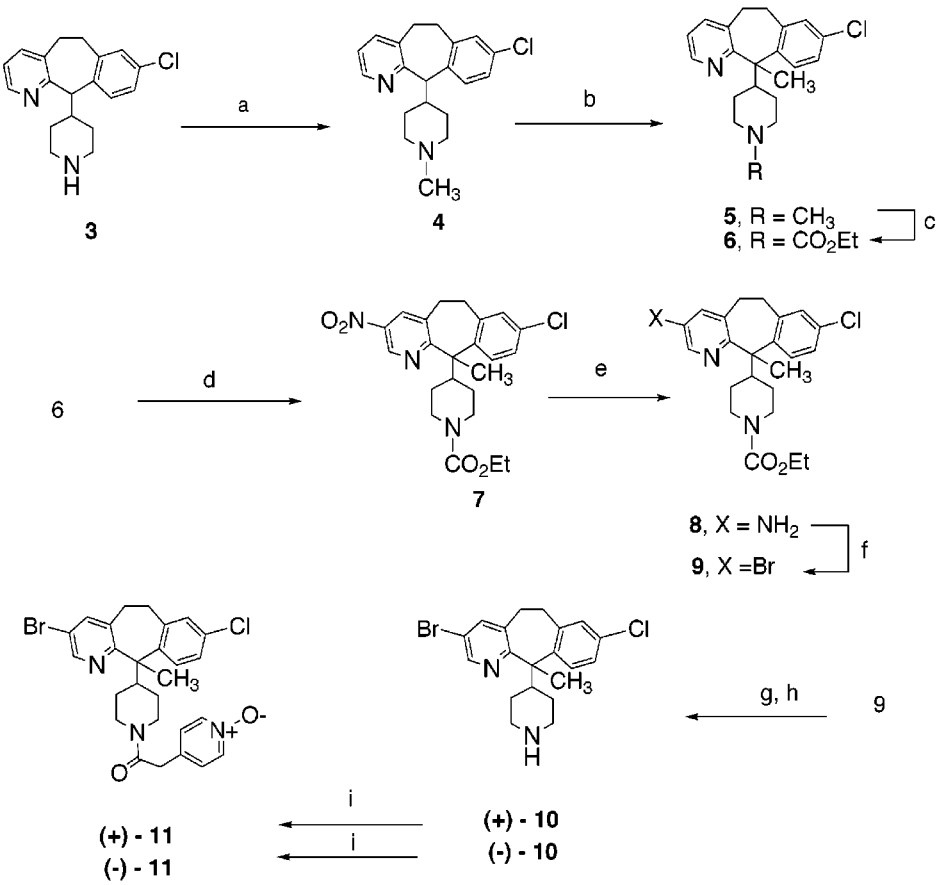
We recently showed that compounds with a benzocycloheptapyridine tricyclic ring nucleus, as exemplified by SCH 44342 and 55495, **1** and **2** (below), can provide potent FPT inhibitors with moderate cellular and in vivo activity.[3,4] We also established the following facts during these studies: (a) the presence of a bulkier halogen in the 3-position of the pyridine ring system enhanced FPT potency in these series of compounds;[4] (b) a pyridinylacetyl moiety attached to the piperidine gave compounds that had superior FPT activity;[4] (c) the C-11 single bond analogue, SCH 55495, gave better antitumor efficacy than the corresponding C-11 double bond counterpart SCH 44342.[3] Despite the fact that SCH 54595 demonstrated interesting in vivo activity, we were concerned that the C-11 hydrogen flanked by two aromatic groups would be highly acidic and possibly render that site amenable to enzymatic modifications.



(1) Barbacid, M. *Annu. Rev. Biochem.* **1987**, *56*, 779.
(2) Leonard, D. M. *J. Med. Chem.* **1997**, *40*, 2971.
(3) Mallams, A. K.; Njoroge, F. G.; Doll, R. J.; Snow, M. E.; Kaminiski, J. J.; Rossman, R. R.; Vibulbhan, B.; Bishop, W. R.; Kirschmeier, P.; Liu, M.; Bryant, M. S.; Alvarez, C. S.; Carr, D.; James, L.; King, I.; Li, Z.; Lin, C.-C.; Petrin, J.; Remiszewski, S. R.; Taveras, A, G.; Wang, S.; Wong, J. K.; Catino, J.; Girijavallabhan, V.; Ganguly, A. K. *Bioorg. Med. Chem.* **1997**, *5*, 93.
(4) Njoroge, F. G.; Doll, R. J.; Vibulbhan, B.; Alvarez, C. S.; Bishop, W. R.; Petrin, J.; Kirschmeier, P.; Carruthers, N. I.; Wong, J. K.; Albanese, M. A.; Piwinski, J. J.; Catino, J.; Girijavallabhan, V.; Ganguly, A. K. *Bioorg. Med. Chem.* **1997**, *5*, 101.

10.1021/ol990218u CCC: $18.00
Published on Web 09/28/1999

Scheme 1. Preparation of 11-Methyl-Substituted Tricyclic Pyridinyl Acetamide *N*-Oxides



[a]a = 88% HCO_2H, 37% H_2CO, 80 °C; b = BuLi, MeI; c = EtOCl, Et_3N; d = Bu_4NNO_3-TFAA; e = Iron Filings-$CaCl_2$; f = conc. HCl-$NaNO_2$, Br_2-HBr; g = conc. HCl, Δ; (h) Chiral AD separation; i = DEC-HOBT-NMM, Pyridine aceticacid N-oxide

In the present work, we sought methods that would allow introduction of a methyl group at C-11 with the aim of blocking this potential metabolic site. We also utilized the nitration chemistry that was previously established in our laboratories, as a method to introduce bromine at the 3-position of the tricyclic ring system.[5,6]

As illustrated in Schemes 1 and 2, two methods of introducing a methyl group at the C-11 were employed. In the first approach (Scheme 1), previously prepared amine **3**[6] was *N*-methylated using formic acid−formaldehyde treatment according to the procedure of Carrera et al.[7] to give *N*-methylated amine **4** in 90% yield. A methyl group at C-11 was introduced by reacting amine **4** with n-BuLi and treating the resulting anion with methyl iodide to give desired C-11 alkylated product **5** in 71% yield. Conversion of **5** to desired carbamate **6** was achieved by reaction with ethyl chloroformate in refluxing toluene in 76% yield. Using a nitration protocol that we recently developed,[5,6] carbamate **6** was treated with trifluoacetic anhydride−tetrabutylammonium nitrate (TFAA−TBAN) to exclusively give 3-nitro carbamate **7** in 40% yield. There was no nitration observed on the phenyl ring, which was in agreement with our earlier observation in nitrations of similar benzocycloheptapyridine tricyclic ring systems.[6]

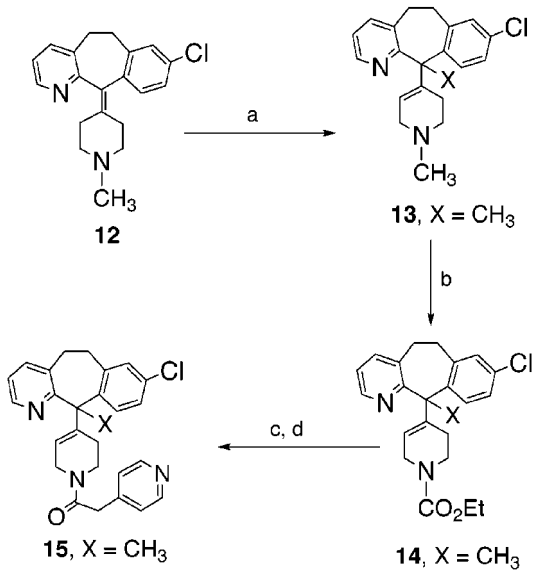
As we previously reported,[5] reduction of nitro carbamate **7** to amino compound **8** was carried out with iron filings−$CaCl_2$ in refluxing 85% aqueous EtOH. Diazotization of **8** with HBr−$NaNO_2$ followed by addition of molecular bromine provided bromo carbamate **9** in 63% yield. Hydrolysis of **9** in refluxing HCl gave racemic amine **10** in quantitative yield. The enantiomers of **10** were separated on a Chiral AD column to give **(+)-10** and **(−)-10** isomers which were then coupled with pyridine acetic acid *N*-oxide to provide pyridine acetamide *N*-oxides **(+)-11** and **(−)-11** in 54 and 97% yields, respectively. Whereas, **(+)-11** inhibited 50% of FPT activity at 98 nM, its corresponding (−)-isomer compound **(−)-11** was significantly less active exhibiting IC_{50} > 180 nM. The 3-desbromo analogue **16** prepared in a

(5) Njoroge, F. G.; Vibulbhan, B.; Rane, D. F.; Bishop, W. R.; Petrin, J.; Patton, R.; Bryant, M. S.; Chen, K.-J.: Nomeir, A. A.; Lin, C.-C.; Liu, M.; King, I.; Chen, J.; Lee, S.; Yaremko, B.; Dell, J.; Lipari, P.; Malkowski, M.; Li, Z.; Catino, J.; Doll, R. J.; Girijavallabhan, V.; Ganguly, A. K. *J. Med. Chem.* **1997**, *40*, 4290.

(6) Njoroge, F. G.; Vibulbhan, B.; Pinto, P.; Chan, T.-M.; Osterman, R.; Remiszewski, S.; Rosario, J. D.; Doll, R.; Girijavallabhan, V.; Ganguly, A. K. *J. Org. Chem* **1998**, *63*, 445.

(7) Carrera, G. M. Jr.; Garvey, D. S. *J. Heterocycl. Chem.* **1992**, *29*, 847.

Scheme 2. Preparation of 11-Methyl-Substituted Tricyclic Analogue **15**

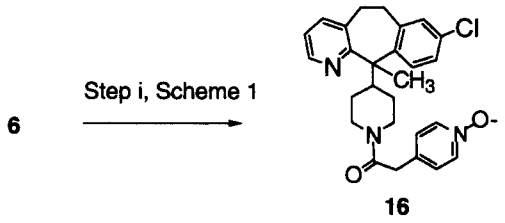


[a]a = BuLi, MeI; b = EtOCl, Et_3N; c = conc. HCl reflux ; d = DEC-HOBT-NMM, Pyridine aceticacid

similar manner (Scheme 3) was also less active than its 3-bromo analogues (IC_{50} = 1.8 μM).

Another method of introducing a methyl group at C-11 took advantage of the observation that upon treatment of amine **12** with n-BuLi, an anion was generated at C-11 with concomitant rearrangement of the double bond into the piperidine ring (Scheme 2). Subsequent quenching of the preformed anion of **12** with MeI gave C-11 methyl compound **13** in 32%. As described above, *N*-methyl compound **13** was converted to carbamate **14** by treatment with ethyl chloroformate. Hydrolysis of **14** in refluxing HCl followed by coupling with pyridine acetic acid gave the desired acetamide **15**. Compound **15** was found to have FPT inhibitory activity with IC_{50} = 2.2 μM. The activity of **15** was similar to that of the C-3,4-saturated compound **16** (Scheme 3).

Scheme 3. Preparation of 11-Methyl-Substituted Tricyclic **16**



In summary, our efforts to block C-11 of a benzocycloheptapyridine, a potential metabolic site, have resulted in synthesis of methyl-substituted compounds at this center via two different methods. Evaluation of these compounds as FPT inhibitors indicates that their activity is similar to that of the corresponding unsubstituted counterparts.

Supporting Information Available: Experimental procedures and characterization data of all new compounds. This material is available free of charge via the Internet at http:pubs.acs.org.

OL990218U