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Design, synthesis and biological evaluation of substituted dioxodibenzothiazepines and dibenzocycloheptanes as farnesyltransferase inhibitors

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Abstract—A new series of FTase inhibitors containing a tricyclic moiety—dioxodibenzothiazepine or dibenzocycloheptane—has been designed and synthesized. Among them, dioxodibenzothiazepine **18d** displayed significant inhibitory FTase activity (IC_{50} = 17.3 nM) and antiproliferative properties.

The finding that 30% of human cancers are related to the presence of mutant ras genes, reaching as high as 90% for pancreas cancer and 50% for colon cancer,[1,2] has prompted many works to target Ras proteins with a view to developing new anticancer agents. Ras proteins (H-Ras, K-Ras4A, K-Ras4B and N-Ras) are small G proteins which have the crucial role of transducing intracellular signals from growth factor receptor to several signal transduction pathways, such as the MAP-kinases cascade and the PI3-K/Akt pathway.[3] Activation of these signal transduction pathways by Ras is critical for cell growth, proliferation and survival. Ras proteins require localization at the plasma membrane to exert their functions. However, as their primary structure has no anchorage residue, Ras proteins must be post-translationally modified by several sequential enzymatic steps.[4] The attachment of an isoprenoid residue to the cysteine of the C-terminal CA_1A_2X box (C = cysteine, A_1 and A_2 = aliphatic amino acid, X = C-terminal amino acid) of Ras proteins is the first and essential step. When X is serine, methionine, glutamine or alanine, the protein is recognized by zinc-metalloenzyme farnesyltransferase (FTase) which catalyzes the transfer of a 15 carbon isoprenoid chain from farnesyl pyrophosphate (FPP). Proteins with a C-terminal leucine or isoleucine are modified by the geranylgeranyltransferase-I (GGTase-I) enzyme with a 20 carbon isoprenoid motif from geranylgeranyl pyrophosphate (GGPP). Thus, farnesyltransferase inhibitors (FTIs) have been developed to inhibit Ras processing and to design new anticancer agents.[5,6] Recent studies have however suggested that the cytotoxic actions of FTIs are not exclusively due to the inhibition of Ras proteins and have indicated that other farnesylated protein targets, other than Ras, have to be considered.[7–9] These candidate targets include Ras-family GTPases such as RhoB[10] and Rheb,[11] the centromere-binding proteins CENP-E and CENP-F,[12,13] the phosphatases PRL-1, -2 and -3,[14] or an unidentified protein that functions as an activator of the PI3-K/Akt pathway.[15]

Knowledge of precise details about the structure and the reaction mechanism of FTase has resulted in three general approaches for the rational design of FTIs: a peptidomimetic design that competes for FTase with the CA_1A_2X sequence of the protein; a design of FPP analogs that competes for FTase with the substrate FPP; a design of bisubstrate analogs that combines the features

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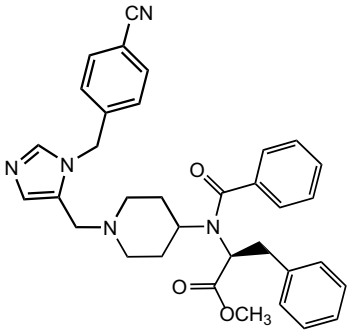
of both peptidomimetics and FPP analogs, mimicking a transition state. A number of natural products have also been identified as FTIs, and the screening of chemical libraries backed up by structure-directed medicinal chemistry optimization has led to the successful identification of tricyclic FTIs.[16,17]

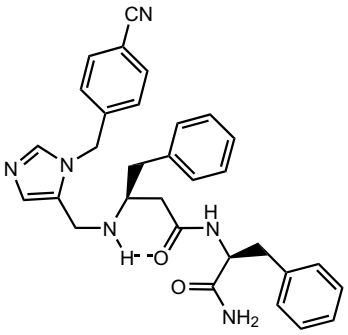
We recently described the design and the synthesis of FTase peptidomimetic inhibitors. The most interesting molecules **1**[18] and **2**,[19] with a piperidinyl or a β-homo-Phe linker, had IC_{50} values of 22 and 28.5 nM, respectively, on an isolated FTase enzyme (Chart 1).

Considering these structures and their interactions with the enzyme,[18,19] we designed new derivatives **18a–d**, **19**, **23a** and **25** including:

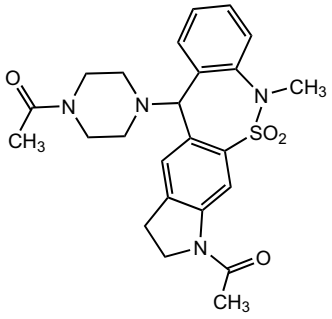
(i) a 4-cyanobenzylimidazole Zn-chelating group
(ii) a diazepane or a piperazine, making it possible to lay out correctly in a ring the two central N atoms of compounds **1** and **2**, so as to take into account the strong hydrogen bond between the secondary amine proton and amide oxygen of compound **2**. These new heterocyclic linkers combine the required features of **1** and **2** to obtain a correct



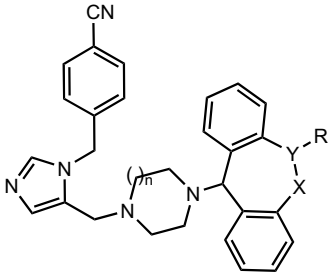
1 FTase IC_{50} = 22 nM



2 FTase IC_{50} = 28.5 nM



3 PC-3 IC_{50} = 0.19 μM



18a-d n = 2
23a n = 1
a X = SO_2, Y = N, R = CH_3
b X = SO_2, Y = N, R = C_3H_7
c X = SO_2, Y = N, R = C_4H_9
d X = SO_2, Y = N, R = C_3H_6-morpholine

19 n = 2
25 n = 1
X = Y = CH_2

Chart 1.

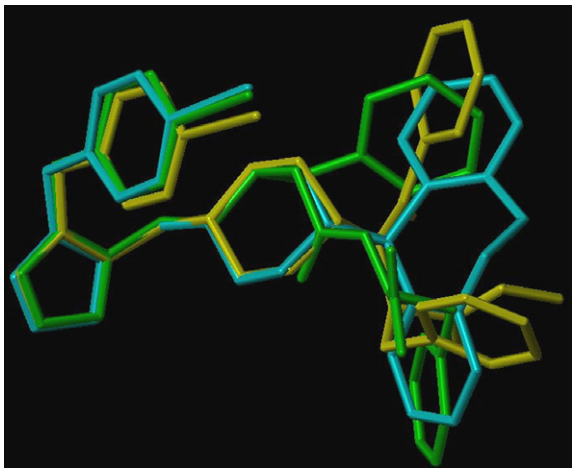
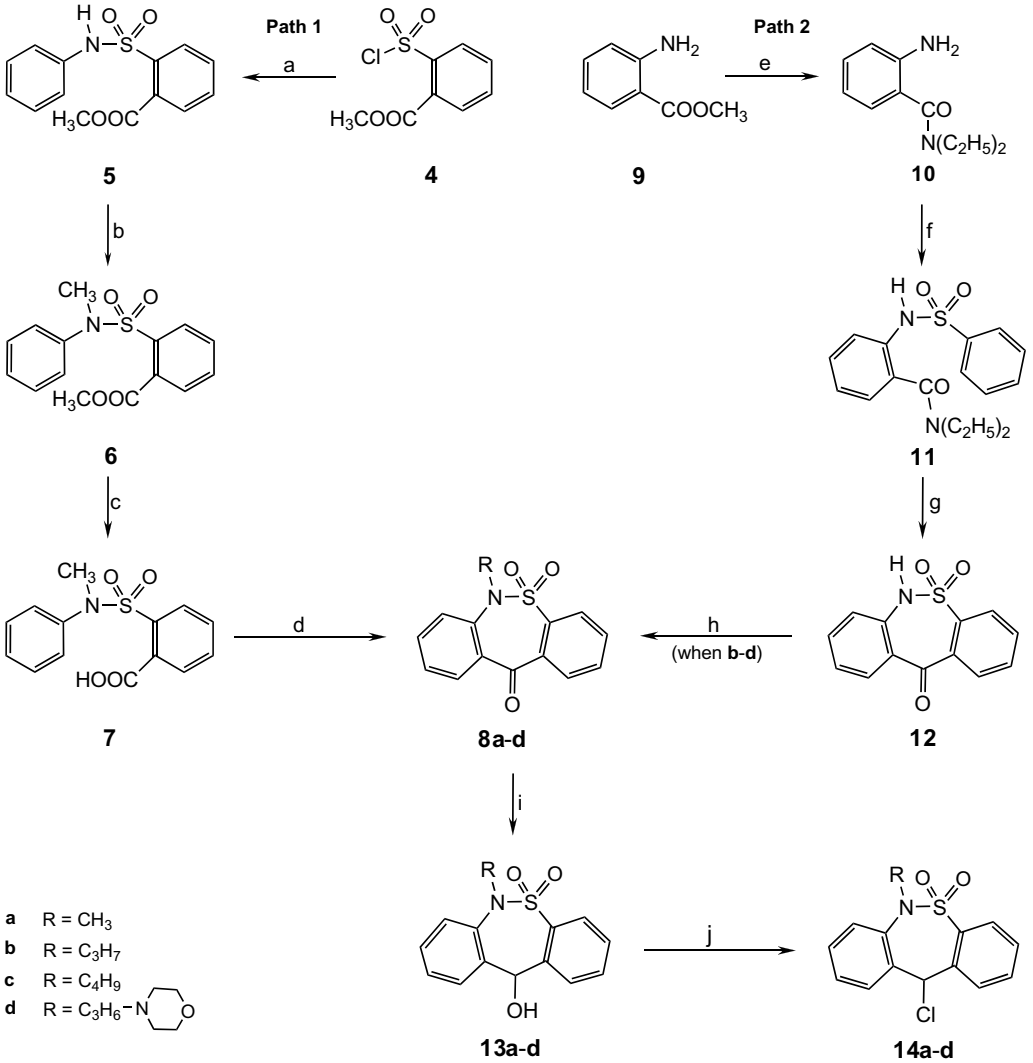


Figure 1. Superposition of the minimized conformation of compounds **1** (yellow), **2** (green) and **25** (cyan).

fitting with the imidazole zinc-chelator and with the "A_2 binding site"—delineated by Trp102β, Trp106β and Tyr361β—of the FTase

(iii) a dioxodibenzothiazepine or a dibenzocycloheptane residue corresponding to a constrained form of the peptidyl residue of **1** and **2**. Superposition of the minimized conformation[20] of compounds **1**, **2** and **25** (Fig. 1) suggested that the geometry of both aromatic terminal fragments could be included in a condensed structure. Furthermore, these fused tricyclic scaffolds are reminiscent of new benzoindolinothiazepine derivatives recently developed by us[21] and which contain a piperazine moiety, such as **3**, and which have shown potent antiproliferative activity against PC-3 tumor cell lines but no FTase activity. In addition, other tricyclic FTIs including a benzocycloheptapyridine have been described,[22] but they do not have the 4-cyanobenzylimidazole Zn-chelating group.

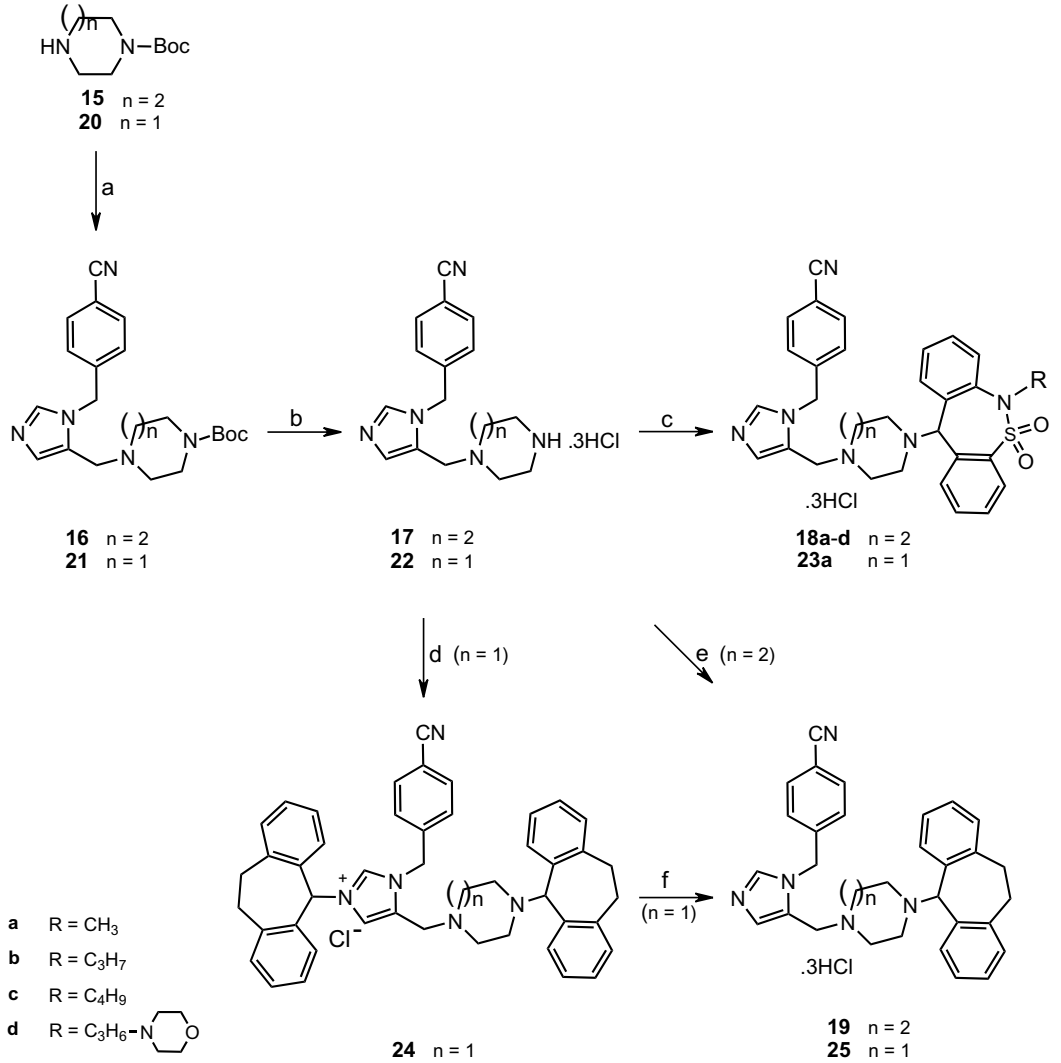


Scheme 1. Reagents and conditions: (a) $C_6H_5NH_2$, pyridine, DMF, 65 °C, 2 h, 45%; (b) i—NaH, DMF, rt, 3 h; ii—CH_3I, DMF, rt, 16 h, 89%; (c) NaOH, MeOH/H_2O, reflux, 2 h, 95%; (d) i—$SOCl_2$, CH_2Cl_2, rt, 16 h; ii—$AlCl_3$, $CHCl_3$, reflux, 1 h, 65%; (e) Et_2NH, *n*-BuLi, Et_2O, 0 °C, 4 h, 85%; (f) $C_6H_5SO_2Cl$, pyridine-THF, 60 °C, 1 h, 80%; (g) i—(*i*-Pr)$_2$NH, *n*-BuLi, THF, −10 °C, 45 min; ii—rt, 20 h, 25%; (h) i—NaH, DMF, rt, 3 h; ii—R–I, rt, 20 h or R–Cl, KI, 80 °C, 24 h, 36–45%; (i) $NaBH_4$, MeOH, rt, 3–4 h, 87–95%; (j) $SOCl_2$, CH_2Cl_2, rt, 3–4 h, 90–100%.

We report here the synthesis, the pharmacological evaluation and the docking of these novel tricyclic FTase inhibitors[23] with potent isolated enzymatic and cellular activities.

Synthesis of chlorodioxodibenzothiazepines **14a–d** (Scheme 1) was performed in two different ways (paths 1 and 2) which both preclude the formation, at the cyclization step, of a central saccharin-like isothiazolone ring instead of the targeted thiazepinone cycle.[21] Chlorodioxodibenzothiazepine **14a** was prepared according to path 1, where alkylation of the sulfonamido nitrogen was completed before creating the mid heterocycle. Phenylsulfonamide **5** was obtained by nucleophilic substitution of methyl 2-chlorosulfonylbenzoate **4** with aniline (pyridine, DMF).[21] Alkylation of sulfonamide **5** (sodium hydride, methyl iodide) yielded *N*-methylsulfonamide **6**. After saponification of the ester group (sodium hydroxide), carboxylic acid **7** was cyclized, via its non-isolated acid chloride (Friedel–Crafts conditions) into dibenzothiazepinone **8a**. Chlorodibenzothiazepine **14a** was obtained by reducing dibenzothiazepinone **8a** (sodium borohydride) followed by the halogenation of the secondary alcohol **13a** with thionyl chloride.

The second method (Scheme 1, path 2) was used to prepare chlorodioxodibenzothiazepines **14b–d**. In this case, *N*-substituted dibenzothiazepinones **8b–d** were easily obtained from the unsubstituted parent tricycle **12**. Carboxylic ester of methyl anthranilate **9** was converted into diethylcarboxamide **10** (*n*-butyllithium, *N*,*N*-diethylamine)[24] before creating the sulfonamide function with benzenesulfonyl chloride. An intramolecular anionic Friedel–Crafts equivalent annulation[25] of **11** (lithium diisopropylamide prepared in situ, −10 °C), favored by the nucleophilicity of the transient carbanion and by the sensitivity of the *N*,*N*-diethylcarboxamide to such a nucleophilic attack, resulted in dibenzothiazepinone **12**. Appropriate *N*-alkylation of the sulfonamido group (sodium hydride, alkyl halide) gave dibenzothiazepinones



Scheme 2. Reagents and conditions: (a) $n = 2$: 1-(4-cyanobenzyl)-5-chloromethylimidazole, $(i\text{-Pr})_2NEt$, MeCN, 80 °C, 4 h, 72%; $n = 1$: 1-(4-cyanobenzyl)-5-formylimidazole, $NaBH_3CN$, MeOH, 50 °C, 40 h, 60%; (b) HCl/Et_2O, MeOH, rt, 4 h, 90–95%; (c) $n = 2$: **14a–d**, Et_3N, MeCN, rt, 4 h, 65–68%; $n = 1$: **14a**, Et_3N, MeCN, rt, 2 h, 68%; (d) $n = 1$: dibenzosuberyl chloride, Et_3N, MeCN, rt, 2 h, 40%; (e) $n = 2$: dibenzosuberyl chloride, Et_3N, MeCN, rt, 3 h, 63%; (f) MeOH, reflux, 6 h, 30%.

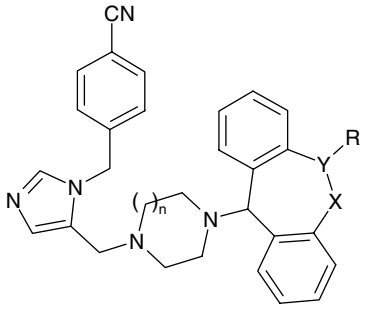
8b–d. Chloro tricycles **14b–d** resulted from a subsequent reduction of the ketone group (sodium borohydride) into alcohol (compounds **13b–d**) followed by halogenation (thionyl chloride).

The means adopted for the preparation of target compounds **18a–d** and **23a** (Scheme 2) involved a nucleophilic attack on chlorodioxodibenzothiazepines **14a–d** by the secondary amine of diazepane **17** or of piperazine **22**. Diazepane **16** and piperazine **21** were, respectively, obtained by substituting carbamate-monoprotected diazepane **15** or piperazine **20** by 1-(4-cyanobenzyl)-5-chloromethylimidazole,[26] or by reductive amination ($NaBH_3CN$) using 1-(4-cyanobenzyl)-5-formylimidazole.[18] If diazepane**19** was classically prepared by nucleophilic substitution of dibenzosuberyl chloride, piperazine **25** resulted from the unexpected dialkylation of piperazine **22** by dibenzosuberyl chloride (compound **24**) followed by the regioselective *N*-dealkylation in conditions used in classical *N*-detritylation (MeOH, reflux).[27]

Compounds **18a–d**, **19**, **23a**, and **25** were evaluated for their in vitro inhibitory activity against FTase using the continuous fluorescence spectrometry technique.[23] Several SARs may be deduced from the results (Table 1). A constrained structure such as the dibenzocycloheptane skeleton (compounds **19** and **25**) maintains moderate FTase inhibition whatever the size of the linker: diazepane for **19** (IC_{50} = 285 nM) or piperazine for **25** (IC_{50} = 310 nM).

When cycloheptane was replaced by dioxothiazepine as the central cycle and diazepane kept as the link (com-

Table 1. FTase activity of compounds **1**, **2**, **18a–d**, **19**, **23a** and **25**



Compound	*n*	X	Y	R	IC_{50}[a] (nM)
1	—	—	—	—	22
2	—	—	—	—	28.5
18a	2	SO_2	N	CH_3	44.8
18b	2	SO_2	N	C_3H_7	46.5
18c	2	SO_2	N	C_4H_9	43
18d	2	SO_2	N	C_3H_6-N⟨O⟩	17.3
19	2	CH_2	CH_2	—	285
23a	1	SO_2	N	CH_3	45
25	1	CH_2	CH_2	—	310

[a] Values are means of three determinations (standard deviation lower than 10%).

Table 2. Antiproliferative effects of compounds **1**, **2**, **18a–d**, **19**, **23a** and **25**

Compound	IC_{50}[a] (μM) or % inhibition			
	L1210	DU145	PC-3	MCF-7
1	4.95	nd[b]	nd[b]	nd[b]
2	41%	>100	>100	>100
18a	4.76	59.8	50.0	48.0
18b	4.0	38%[c]	34.1	nd[b]
18c	3.0	100	nd[b]	66.0
18d	4.57	47.4	27.3	33.0
19	34%[d]	51.3	nd[b]	41.0
23a	3.90	100	69.4	76.0
25	4.85	9.55	11.4	45.0

[a] Cell proliferation was measured from at least three independent determinations (standard deviation lower than 10%).
[b] Not determined.
[c] Compound tested at the concentration of 100 μM.
[d] Compound tested at the concentration of 10 μM.

pounds **18a–d**, **23a**), inhibition was significantly improved (more than 6-fold) when comparing **18a–c** to **19**. This observation validates our hypothesis assuming that the two lateral aromatic fragments of **1** and **2** may be advantageously combined through a rigid tricycle. The IC_{50} values for FTase in the series **18a–d** range from medium (46.5 nM for **18b**) to good (17.3 nM for **18d**). Substitution of the nitrogen in sultam by an alkyl chain did not modify the enzymatic activity, whereas substitution of the propyl chain by morpholine increased potency by about 2.5-fold, when considering **18d** (IC_{50} = 17.3 nM) and **18b**. This result suggests that a hydrogen bond acceptor could improve activity. Changing the linker size (diazepane for piperazine) did not modify the activity of **23a** versus **18a** (IC_{50} # 45 nM), as was already observed with **19** and **25**.

Cellular proliferation was investigated on L1210 cells using numeration, and on DU145, PC-3 and MCF-7 cells by the colorimetric MTT assay.[23] These cellular models are representative of different tumoral conditions and were shown to be responsive to FTase inhibitors. For example, recent studies[28] have shown synergistic effects for the combination of ZOL (Zoledronic acid) with R115777 (Tipifarnib) in prostate adenocarcinoma models and, specifically, on androgen-independent (PC-3 and DU145) prostate cancer cell lines. These effects were paralleled by disruption of Ras → Erk and Akt survival pathways, a consequent decrease in phosphorylation of both mitochondrial bcl-2 and bad proteins, and a caspase activation. MCF-7 is one of the most currently used models in human breast cancer though Ras mutations are rare (less than 2%)[29] but Ras signaling is frequently upregulated in these tumors as a result of the activation of upstream growth factor signaling pathways. In leukemia, ras mutations are significant (6–40%) and cellular murine models (L1210) have indicated how extensive the antitumor activity is of many relevant inhibitors such as R115777 or SCH-66336 (Lonafarnib).[30,31]

The most potent inhibitor of FTase (**18d**) in the dibenzothiazepine series (**18a–d** and **23a**) also displays the best activity against DU145, PC-3 and MCF-7 (Table 2) and this is attributed to the presence of morpholine: the increase in FTase inhibition and the cytotoxic effect (in the micromolar range) may be induced by the creation of hydrogen bonds with Arg202β of the receptor (see the docking analysis) and by greater hydrophilicity in this region of the molecule. In addition, a direct comparison of mammalian antiproliferative effects showed that the diazepane core was more favorable than the piperazine spacer (**18a** vs **23a**); this requirement was not observed in the dibenzocycloheptane series (**19** vs **25**). The high sensitivity of the seven synthesized compounds towards L1210 cells could be connected to the significant efficacy of FTIs in myeloid leukemias[32] and to a weak resistance of L1210 cells.

Docking simulations, using GOLD software,[23] were carried out in order to clarify the binding mode of compound **18d** in the active site of FTase (Fig. 2). The pharmacological results concord with modelization and provide a reasonable explanation for its inhibitory activity. Besides the coordination between the distal imidazole nitrogen and the zinc ion, interaction was revealed between one aromatic ring of the tricycle and the hydrophobic pocket delineated by Trp102β, Trp106β and Tyr361β (the "A_2 binding site"). In addition, compound **18d** interacts via hydrogen bonds with Arg202β (between the two morpholinic oxygen doublets and side chain hydrogens of Arg) as it was observed for tetrapeptide substrates CVLS (H-Ras), CVIM (K-Ras4B) or CVIF (TC21).[33] The presence of a morpholine at the A_2 residue strengthens interactions in the binding site and may explain the better FTase inhibitory activity throughout this series.

To explain the improvement in potency of **18a–d** and **23a** over **19** and **25**, docking simulations of compounds **18a** and **19** were investigated. Studies established that the tricyclic moiety of compound **19** only displayed interaction in the hydrophobic pocket (data not shown) whereas the bridgehead modified compound **18a** interacted via hydrogen bonds between the sulfonamide oxygen and side chain hydrogens of Arg202β (Fig. 3).

In conclusion, we designed and synthesized a new series of FTase inhibitors in which hydrophobic residues were conformationally locked in a tricycle. These compounds were tested for their ability to inhibit metalloenzyme FTase activity and cellular proliferation; the presence of an additional morpholine as hydrogen bond acceptor resulted in enhanced binding to the enzyme. The broad anticancer action of the compound **18d** merits further investigation as does the implication of other proteins targets (like CENP-E and CENP-F). The determination of other protein targets may also explain the potent anticancer action of compounds **19** and **25** although they

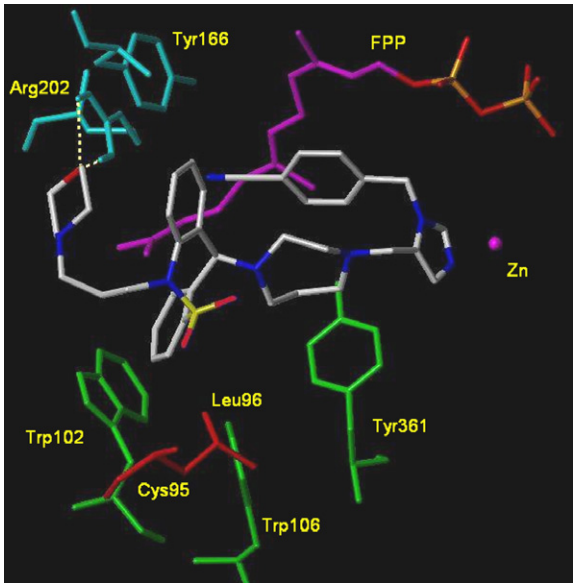


Figure 2. Docking of compound **18d** in the FTase binding site. The farnesyl group (FPP) is colored magenta. Arg202β and Tyr166α are shown in cyan, and the aromatic residue side chains that define a hydrophobic pocket (Trp102β, Trp106β, Tyr361β) are shown in green.

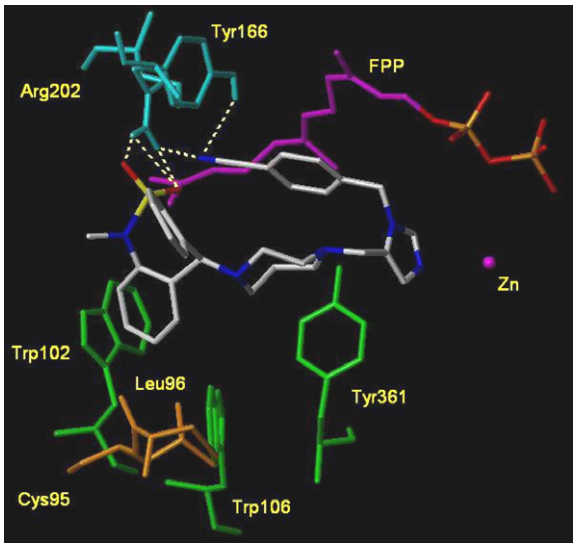


Figure 3. Docking of compound **18a** in the FTase binding site. The farnesyl group (FPP) is colored magenta. Arg202β and Tyr166α are shown in cyan, and the aromatic residue side chains that define a hydrophobic pocket (Trp102β, Trp106β, Tyr361β) are shown in green.

have no FTase enzymatic activity. Due to the role of CENP-E and CENP-F in the mitotic spindle function, inhibition of their farnesylation may contribute to the synergistic interaction observed between cytotoxic agents like taxanes and FTIs. This aspect is presently being studied and will come under further discussion.

Acknowledgments

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Supplementary data

Supplementary data associated with this article (including synthesis of compounds mentioned in Schemes 1 and 2) are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.07.002.

References and notes

1. Bos, J. L. *Cancer Res.* **1989**, *49*, 4682.
2. Leonard, D. M. *J. Med. Chem.* **1997**, *40*, 2971.
3. Cho, K.-N.; Lee, K.-I. *Arch. Pharm. Res.* **2002**, *25*, 759.
4. Zhang, F. L.; Casey, P. J. *Annu. Rev. Biochem.* **1996**, *65*, 241.
5. Ohkanda, J.; Knowles, D. B.; Blaskovich, M. A.; Sebti, S. M.; Hamilton, A. D. *Curr. Top. Med. Chem.* **2002**, *2*, 303.
6. Russo, P.; Loprevite, M.; Cesario, A.; Ardizzoni, A. *Curr. Med. Chem.-Anti-Cancer Agents* **2004**, *4*, 123.
7. Sebti, S. M.; Der, C. J. *Nat. Rev. Cancer* **2003**, *3*, 945.
8. Margaritora, S.; Cesario, A.; Porziella, V.; Granone, P.; Catassi, A.; Russo, P. *Lett. Drug Des. Discov.* **2005**, *2*, 26.
9. Basso, A. D.; Kirschmeier, P.; Bishop, W. R. *J. Lipid Res.* **2006**, *47*, 15.
10. Wherlock, M.; Gampel, A.; Futter, C.; Mellor, H. *J. Cell Sci.* **2004**, *117*, 3221.
11. Gau, C. L.; Kato-Stankiewicz, J.; Jiang, C.; Miyamoto, S.; Guo, L.; Tamanoi, F. *Mol. Cancer Ther.* **2005**, *4*, 918.
12. Ashar, H. R.; James, L.; Gray, K.; Carr, D.; McGuirk, M.; Maxwell, E.; Black, S.; Armstrong, L.; Doll, R. J.; Taveras, A. G.; Bishop, W. R.; Kirschmeier, P. *Exp. Cell Res.* **2001**, *262*, 17.
13. Falugi, C.; Trombino, S.; Granone, P.; Margaritora, S.; Russo, P. *Curr. Cancer Drug Targets* **2003**, *3*, 109.
14. Zeng, Q.; Si, X.; Horstmann, H.; Xu, Y.; Hong, W.; Pallen, C. J. *J. Biol. Chem.* **2000**, *275*, 21444.
15. Jiang, K.; Coppola, D.; Crespo, N. C.; Nicosia, S. V.; Hamilton, A. D.; Sebti, S. M.; Cheng, J. Q. *Mol. Cell. Biol.* **2000**, *20*, 139.
16. Haluska, P.; Dy, G. K.; Adjei, A. A. *Eur. J. Cancer* **2002**, *38*, 1685.
17. Rokosz, L. L.; Huang, C.-Y.; Reader, J. C.; Stauffer, T. M.; Chelsky, D.; Sigal, N. H.; Ganguly, A. K.; Baldwin, J. J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5537.
18. Millet, R.; Domarkas, J.; Houssin, R.; Gilleron, P.; Goossens, J.-F.; Chavatte, P.; Logé, C.; Pommery, N.; Pommery, J.; Hénichart, J.-P. *J. Med. Chem.* **2004**, *47*, 6812.
19. Gilleron, P.; Millet, R.; Houssin, R.; Wlodarczyk, N.; Farce, A.; Lemoine, A.; Goossens, J.-F.; Chavatte, P.; Pommery, N.; Hénichart, J.-P. *Eur. J. Med. Chem.* **2006**, *41*, 745.
20. A representative sample of the conformational space was generated by a 200-cycle simulated annealing experiment. Computation began at 1000 K and the system was maintained at that temperature for 2000 fs. The temperature was then reduced with exponential ramping until 300 K was reached. At this point, the lowest energy conformation was selected and minimized.
21. Laconde, G.; Depreux, P.; Berthelot, P.; Pommery, N.; Hénichart, J.-P. *Eur. J. Med. Chem.* **2005**, *40*, 167.
22. Njoroge, F. G.; Vibulbhan, B.; Pinto, P.; Strickland, C.; Bishop, W. R.; Nomeir, A.; Girijavallabhan, V. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 984.
23. For details concerning evaluation of FTase, cellular activities and molecular modeling, see Refs. 18 and 26.
24. Lebègue, N.; Flouquet, N.; Berthelot, P.; Pfeiffer, B.; Renard, P. *Synth. Commun.* **2002**, *32*, 2877.
25. Iwema Bakker, W. I.; Familoni, O. B.; Padfield, J.; Snieckus, V. *Synlett* **1997**, *9*, 1079.
26. Wlodarczyk, N.; Gilleron, P.; Millet, R.; Houssin, R.; Goossens, J.-F.; Lemoine, A.; Pommery, N.; Wei, M. X.; Hénichart, J.-P. *Oncol. Res.* **2006**, *16*, 107.
27. Pless, J. *Helv. Chim. Acta* **1976**, *59*, 499.
28. Caraglia, M.; Marra, M.; Leonetti, C.; Meo, G.; D'Alessandro, A. M.; Baldi, A.; Santini, D.; Tonini, G.; Bertieri, R.; Zupi, G.; Budillon, A.; Abbruzzese, A. *J. Cell. Physiol.* **2007**, *211*, 533.
29. Sparano, J. A.; Moulder, S.; Kazi, A.; Vahdat, L.; Li, T.; Pellegrino, C.; Munster, P.; Malafa, M.; Lee, D.; Hoschander, S.; Hopkins, U.; Hershman, D.; Wright, J. J.; Sebti, S. M. *J. Clin. Oncol.* **2006**, *24*, 3013.
30. Liesveld, J. L.; Lancet, J. E.; Rosell, K. E.; Menon, A.; Lu, C.; McNair, C.; Abboud, C. N.; Rosenblatt, J. D. *Leukemia* **2003**, *17*, 1806.
31. O'Meara, S. J.; Kinsella, B. T. *Biochem. J.* **2005**, *386*, 177.
32. Gotlib, J. *Curr. Hematol. Rep.* **2005**, *4*, 77.
33. Reid, T. S.; Terry, K. L.; Casey, P. J.; Beese, L. S. *J. Mol. Biol.* **2004**, *343*, 417.