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Supporting Information

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Predicting and Tuning Physicochemical Properties in Lead Optimization: Amine Basicities

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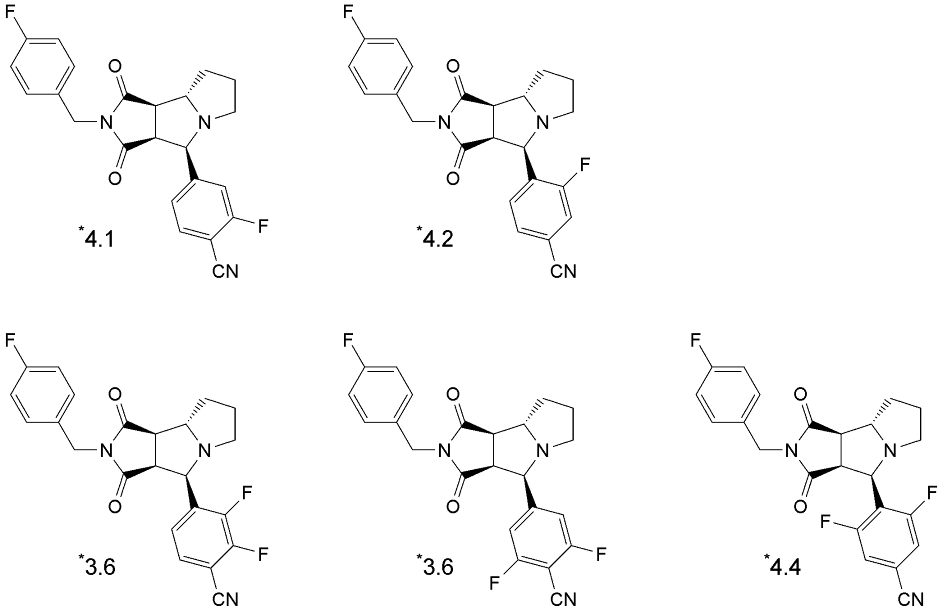


Figure 1SI Experimental pK_a values of the tertiary amine center in fluorinated precursors to tricyclic thrombin inhibitors.

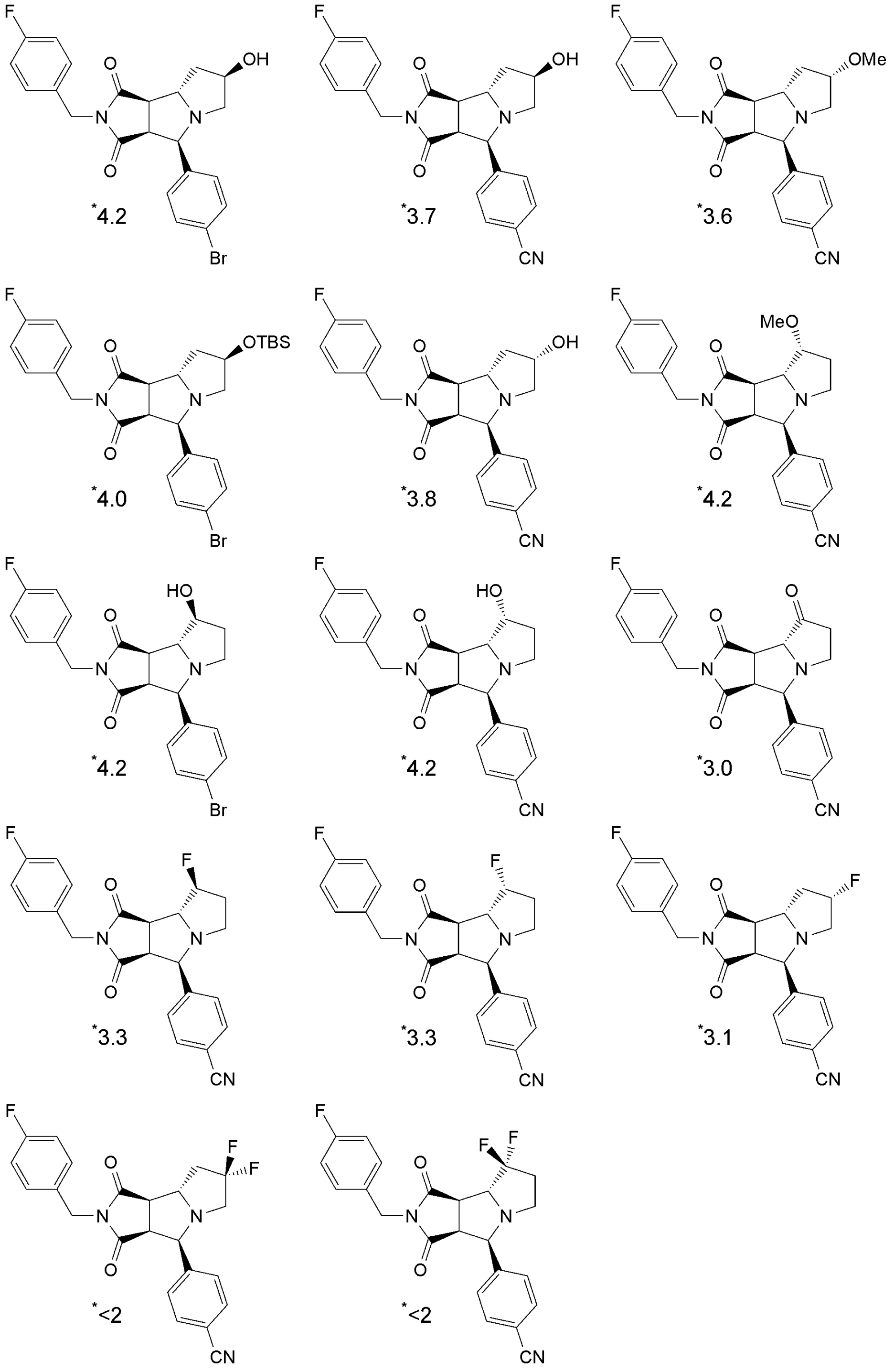


Figure 2SI Experimental p*K*a values of the tertiary amine center in precursors to tricyclic thrombin inhibitors bearing F, OH, and OMe substituents at the terminal pyrrolidine ring.

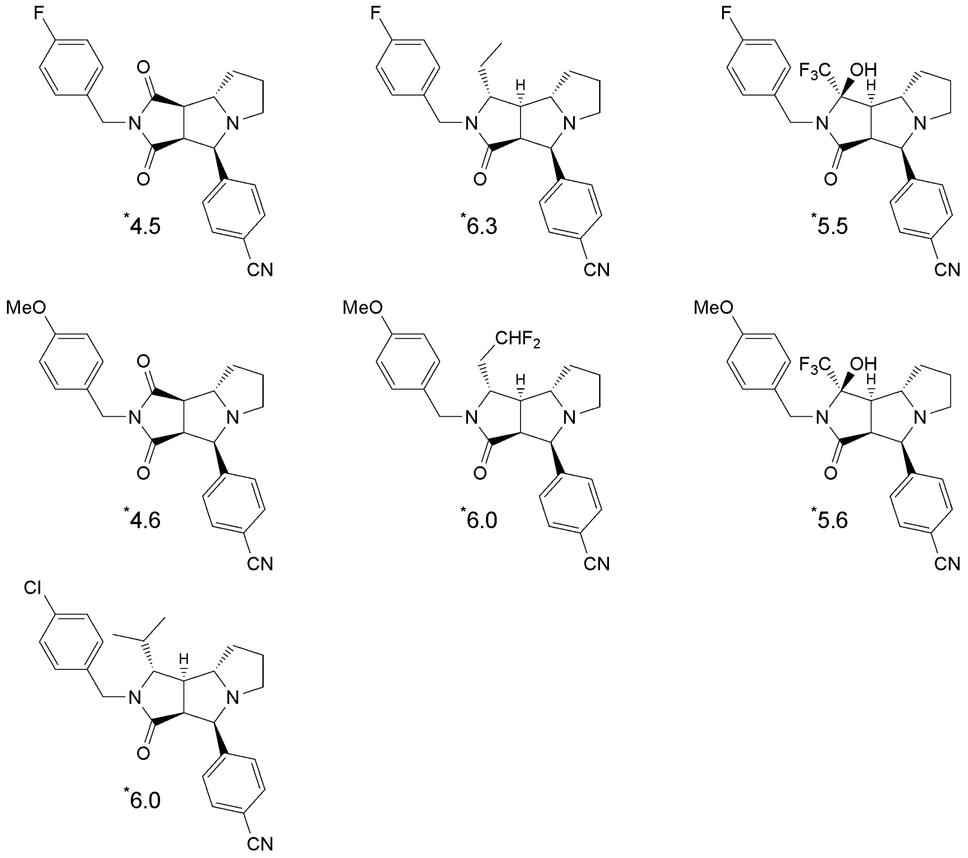
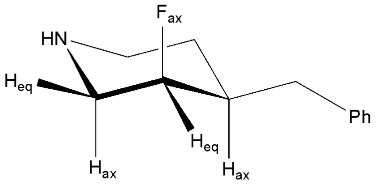


Figure 3SI Experimental pK_a values of the tertiary amine center in precursors to tricyclic thrombin inhibitors of the lactam type.

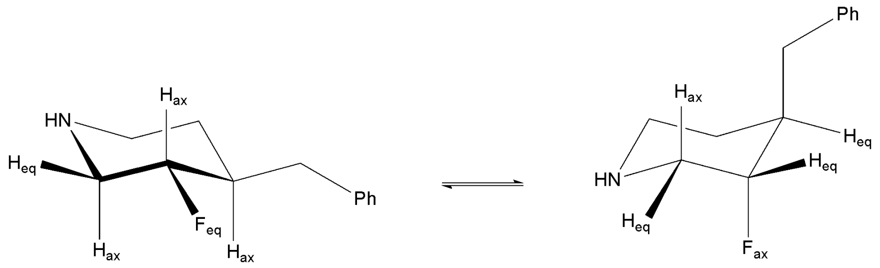


cis-**47**

cis-**47** adopts a chair conformation with F3 axial in both its neutral and protonated states

exp *J* [Hz]	$^2J_{HH}$	$^3J_{HH}$	$^3J_{HH}$	$^3J_{HH}$	$^3J_{HF}$	$^3J_{HF}$	$^2J_{HF}$	$^3J_{HF}$	$^3J_{HH}$
	$H2_{eq}$-$H2_{ax}$	$H2_{eq}$-$H3_{eq}$	$H2_{ax}$-$H3_{eq}$	$H3_{eq}$-$H4_{ax}$	$H2_{eq}$-$F3_{ax}$	$H2_{ax}$-$F3_{ax}$	$H3_{eq}$-$F3_{ax}$	$H4_{ax}$-$F3_{ax}$	$H5_{ax}$-$H4_{ax}$
cis-**47** (neutral)	14.2	3.0	1.1	<1	11.0	41.6	46.2	36.6	n.d.
cis-**47** (DCl salt)	14.5	2.9	<1	<1	10.1	40.6	45.7	36.2	n.d.

Figure 4aSI NMR coupling constants for *cis*-**47** in D_2O in both neutral and protonated states. The NMR spectral data are given in Fig. 4cSI.



trans-**47**

trans-**47** adopts a chair conformation with F3 equatorial in its neutral state

exp *J* [Hz]	$^2J_{HH}$	$^3J_{HH}$	$^3J_{HH}$	$^3J_{HH}$	$^3J_{HF}$	$^3J_{HF}$	$^2J_{HF}$	$^3J_{HF}$	$^3J_{HH}$
	$H2_{eq}$-$H2_{ax}$	$H2_{eq}$-$H3_{ax}$	$H2_{ax}$-$H3_{ax}$	$H3_{ax}$-$H4_{ax}$	$H2_{eq}$-$F3_{eq}$	$H2_{ax}$-$F3_{eq}$	$H3_{ax}$-$F3_{eq}$	$H4_{ax}$-$F3_{eq}$	$H5_{ax}$-$H4_{ax}$
trans-**47** (neutral)	12.3	4.4	9.1	9.1	9.3	6.4	48.3	n.d.	10.9

protonated *trans*-**47** shows $^3J_{HH}$ and $^3J_{HF}$ pattern for rapidly interconverting chair conformations

exp *J* [Hz]	$^2J_{HH}$	$^3J_{HH}$	$^3J_{HH}$	$^3J_{HH}$	$^3J_{HF}$	$^3J_{HF}$	$^2J_{HF}$	$^3J_{HF}$	$^3J_{HH}$
	$H2_{eq}$-$H2_{ax}$	$H2_{eq}$-H3	$H2_{ax}$-H3	H3-H4	$H2_{eq}$-F3	$H2_{ax}$-F3	H3-F3	H4-F3	$H5_{ax}$-H4
trans-**47** (DCl salt)	13.3	2.9	6.5	6.5	24.0	n.d.	45.1	n.d.	7.0

estimated $^3J_{HH}$ and $^3J_{HF}$ [Hz] for protonated *trans*-**47** in chair conformations
with diequatorial and diaxial substituents
averaged $^3J_{HH}$ and $^3J_{HF}$ [Hz] assuming rapidly interconverting equally populated chair forms

est J *[Hz]*	$^2J_{HH}$	$^3J_{HH}$	$^3J_{HH}$	$^3J_{HH}$	$^3J_{HF}$	$^3J_{HF}$	$^2J_{HF}$	$^3J_{HF}$	$^3J_{HH}$
	$H2_{eq}$-$H2_{ax}$	$H2_{eq}$-$H3_{ax}$	$H2_{ax}$-$H3_{ax}$	$H3_{ax}$-$H4_{ax}$	$H2_{eq}$-$F3_{eq}$	$H2_{ax}$-$F3_{eq}$	$H3_{ax}$-$F3_{eq}$	$H4_{ax}$-$F3_{eq}$	$H5_{ax}$-$H4_{ax}$
chair model 3,4-dieq		4.4	9.1	9.1	9.3	6.4		n.d.	9.1
	$H2_{ax}$-$H2_{eq}$	$H2_{ax}$-$H3_{eq}$	$H2_{eq}$-$H3_{eq}$	$H3_{eq}$-$H4_{eq}$	$H2_{ax}$-$F3_{ax}$	$H2_{eq}$-$F3_{ax}$	$H3_{eq}$-$F3_{ax}$	$H4_{eq}$-$F3_{ax}$	$H5_{eq}$-$H4_{eq}$
chair model 3,4-diax		1.1	3.0	3.0	41.6	11.0		n.d.	3.0
(1:1) (dieq):(diax)		(4.4+1.1)/2 = 2.8	(9.1+3.0)/2 = 6.1	(9.1+3.0)/2 = 6.1	(9.3+41.6)/2 = 25.5	(6.4+11.0)/2 = 8.7			(9.1+3.0)/2 = 6.1

Figure 4bSI NMR coupling constants for *trans*-**47** in D_2O in both neutral and protonated states. The NMR spectral data are given in Fig. 4cSI.

cis-3-Fluoro-4-benzyl-piperidine (*cis*-**47**)

^{1}H NMR (600 MHz, D$_2$O, 25 °C, d$_4$-TSP): *d* = 7.39 (*m*, 2H, meta CH); 7.31 (*m*, 3H, *ortho*/*para* CH); 4.68 (*d*br, ^2J(H,F) = 46.2 Hz, 1H, H3); 3.39 (*dddd*, ^2J(H,H) = 14.2 Hz, ^3J(H,H) = 3.0, 1.6 Hz, ^3J(H,F) = 11.0 Hz, 1H, H2); 3.21 (*dddd*, ^2J(H,H) = 12.8 Hz, ^3J(H,H) = 4.9, 2.2, 2.0 Hz, 1H, H6); 2.88 (*ddd*, ^2J(H,H) = 14.2 Hz, ^3J(H,H) = 1.1 Hz, ^3J(H,F) = 41.6 Hz, 1H, H2); 2.78 (*dd*, ^2J(H,H) = 13.7 Hz, 1H, benzyl-CH$_2$); 2.75 (*dt*, ^2J(H,H) = 12.8 Hz, ^3J(H,H) = 12.8, 3.9 Hz, 1H, H6); 2.70 (*dd*, ^2J(H,H) = 13.7 Hz, ^3J(H,H) = 7.5 Hz, 1H, benzyl-CH$_2$); 2.02 (*dm*, ^3J(H,F) = 36.6 Hz, 1H, H4); 1.62-1.73 (*m*, 2H, H5) ppm.

N-protonated *cis*-**47**
^{1}H NMR (400 MHz, D$_2$O+DCl, 23 °C, d$_4$-TSP): *d* = 7.39 (*m*, 2H, meta CH); 7.31 (*m*, 3H, *ortho*/*para* CH); 4.82 (*d*br, ^2J(H,F) = 45.7 Hz, 1H, H3); 3.64 (*dddd*, ^2J(H,H) = 14.5 Hz, ^3J(H,H) = 2.9,1.8 Hz, ^3J(H,F) = 10.1 Hz, 1H, H2); 3.44 (*dm*, ^2J(H,H) = 12.7 Hz, 1H, H6); 3.18 (*dd*, ^2J(H,H) = 14.5 Hz, ^{3}H(H,F) = 40.6 Hz, 1H, H2); 3.03 (*ddd*, ^2J(H,H) = 12.7 Hz, ^3J(H,H) = 12.2, 5.4 Hz, 1H, H6); 2.83 (*dd*, ^2J(H,H) = 13.7 Hz, ^3J(H,H) = 8.3, 1H, benzyl-CH$_2$); 2.73 (*dd*, ^{2}J(H,H) = 13.7 Hz, ^3J(H,H) = 7.2 Hz, 1H, benzyl-CH$_2$); 2.12 (*dm*, ^3J(H,F) = 36.2 Hz, 1H, H4); 1.76-1.91 (*m*, 2H, H5) ppm.

trans-3-Fluoro-4-benzyl-piperidine (*trans*-**47**)
^{1}H NMR (400 MHz, D$_2$O, 23 °C, d$_4$-TSP): *d* = 7.39 (*m*, 2H, *meta* CH); 7.30 (*m*, 3H, *ortho*/*para* CH); 4.40 (*dtd*, ^2J(H,F) = 48.3 Hz, ^3J(H,H) = 9.1, 9.1, 4.4 Hz, 1H, H3); 3.24 (*dddd*, ^2J(H,H) = 12.3 Hz, ^3J(H,H) = 4.4, 1.1 Hz, ^3J(H,F) = 9.3 Hz, 1H, H2); 3.09 (*dd*, ^2J(H,H) = 13.5 Hz, ^3J(H,H) = 4.5 Hz, 1H, benzyl-CH$_2$); 2.86 (*m*, 1H, H6); 2.61 (*ddd*, ^2J(H,H) = 12.3 Hz, ^3J(H,H) = 9.1 Hz, ^3J(H,F) = 6.4 Hz, 1H, H2); 2.54 (*dd*, ^2J(H,H) = 13.5 Hz, ^3J(H,H) = 9.1 Hz, 1H, benzyl-CH$_2$); 2.43 (*ddd*, ^2J(H,H) = 12.8 Hz, ^3J(H,H) = 11.1, 3.1 Hz, H6); 1.99 (*m*, 1H, H4); 1.70 (*m*, 1H, H5); 1.21 (*dtdd*, ^2J(H,H) = 14.0 Hz, ^3J(H,H) = 10.9, 10.9, 4.2 Hz, ^4J(H,H) = 1.1 Hz, 1H, H5) ppm.

N-protonated *trans*-**47**
^{1}H NMR (600 MHz, D$_2$O+DCl, 25 °C, d$_4$-TSP): *d* = 7.40 (*m*, 2H, *meta* CH); 7.30 (*m*, 3H, *ortho*/*para* CH); 4.76 (*dtd*, ^2J(H,F) = 45.1 Hz, ^3J(H,H) = 6.5, 6.5, 3.2 Hz, 1H, H3); 3.59 (*ddd*, ^2J(H,H) = 13.3 Hz, ^3J(H,H) = 2.9 Hz, ^3J(H,F) = 24.0 Hz, 1H, H2); 3.32 (*m*, 2H, H2, H6); 3.11 (*ddd*, ^2J(H,H) = 11.9 Hz, ^3J(H,H) = 7.3, 4.0 Hz, 1H, H6); 2.99 (*dd*, ^2J(H,H) = 13.9 Hz, ^2J(H,H) = 5.9 Hz, 1H, benzyl-CH$_2$); 2.66 (*dd*, ^2J(H,H) = 13.9 Hz, ^2J(H,H) = 9.1 Hz, 1H, benzyl-CH$_2$); 2.37 (*m*, 1H, H4); 2.02 (*m*, 1H, H5); 1.56 (*dtd*, ^2J(H,H) = 14.6 Hz, ^3J(H,H) = 7.0, 7.0, 3.7 Hz, 1H, H5) ppm.

Figure 4cSI NMR spectral data for *cis*-**47** and *trans*-**47** in D$_2$O in both neutral and protonated states. d$_4$-TSP = 2,2,3,3-d$_4$-3-(Trimethylsilyl)propionic acid sodium salt.

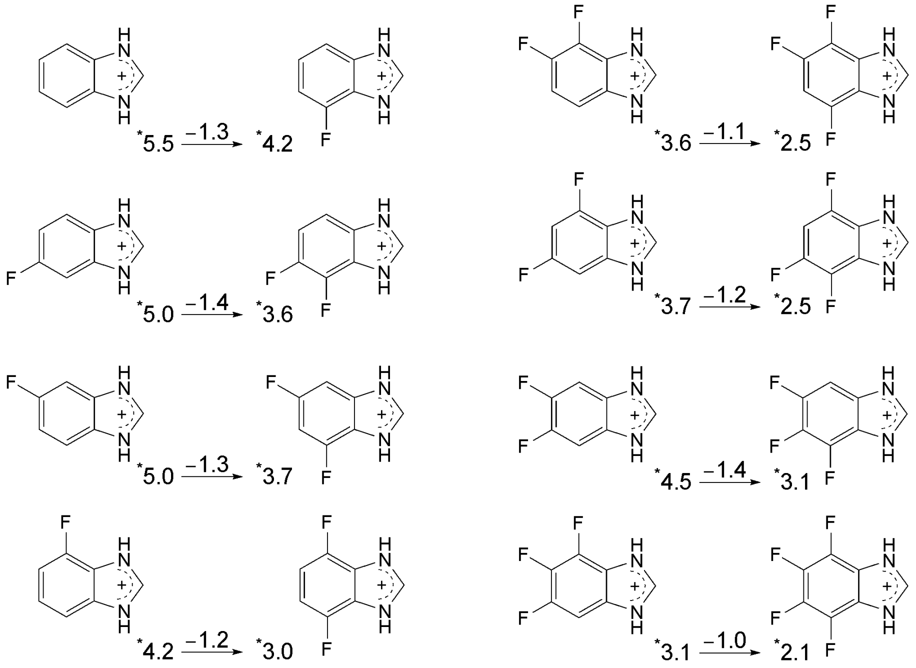


Figure 5SI ?pK_{a1} Effects observed upon the introduction of a fluorine substituent in *ortho* position to a nitrogen atom in substituted benzimidazoles.

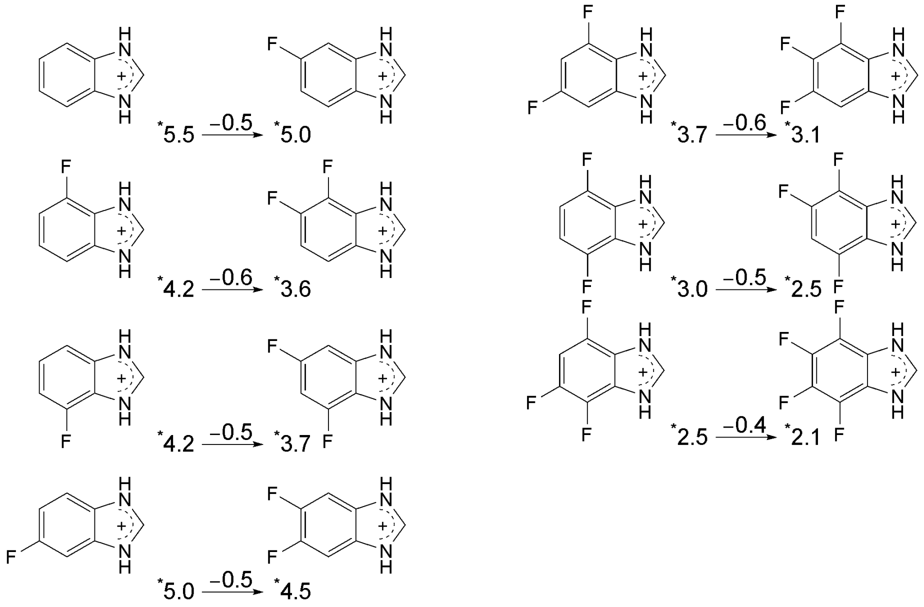


Figure 6SI ?pK_{a1} Effects observed upon the introduction of a fluorine substituent in *meta* position to a nitrogen atom in substituted benzimidazoles.

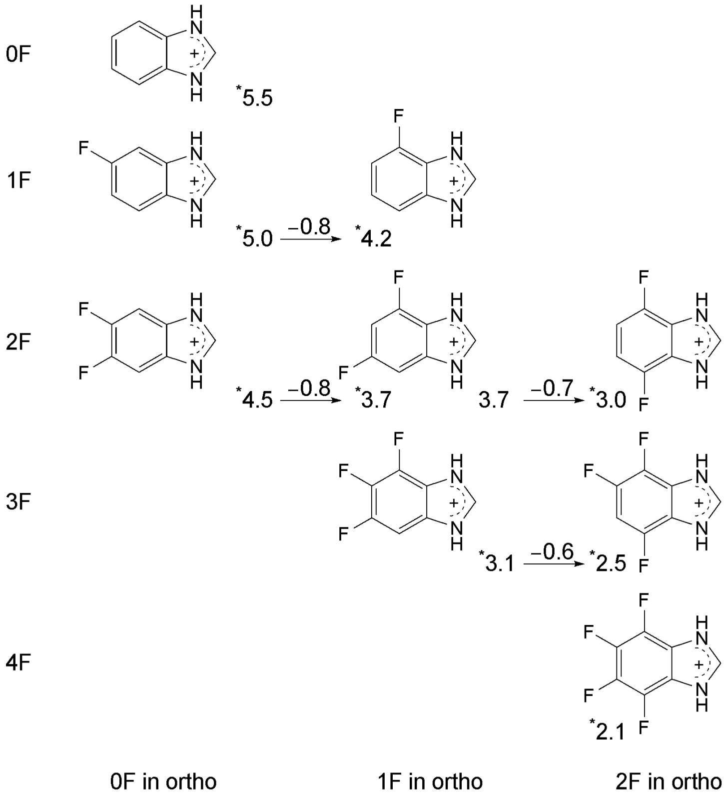


Figure 7SI ?pK_{a1} Effects observed for the shift of a fluorine substituent from a *meta* to an *ortho* position to a nitrogen atom in substituted benzimidazoles.

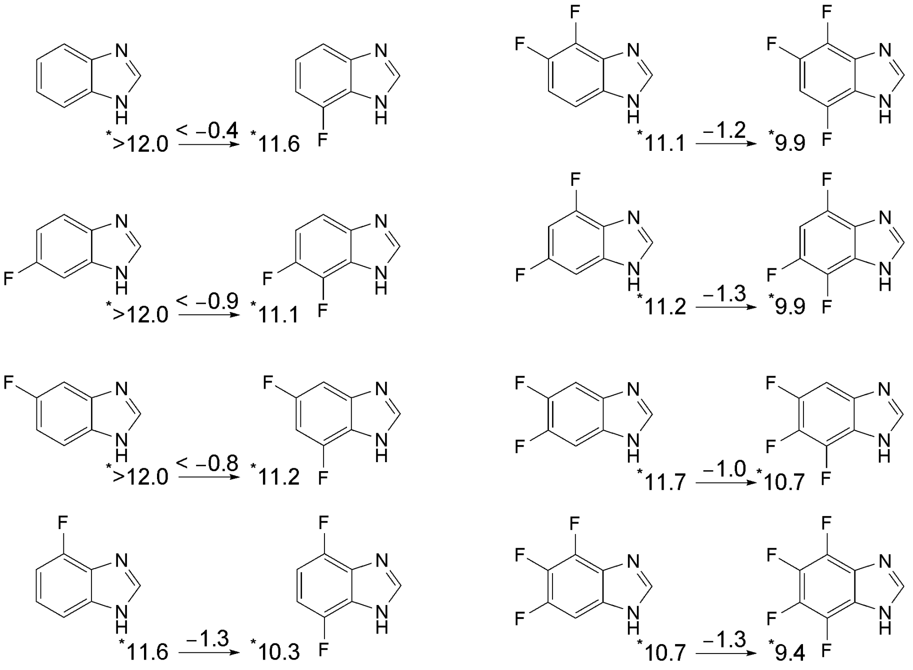


Figure 8SI ?pK_{a2} Effects (deprotonation of benzimidazole) observed upon the introduction of a fluorine substituent in *ortho* position to a nitrogen atom in substituted benzimidazoles.

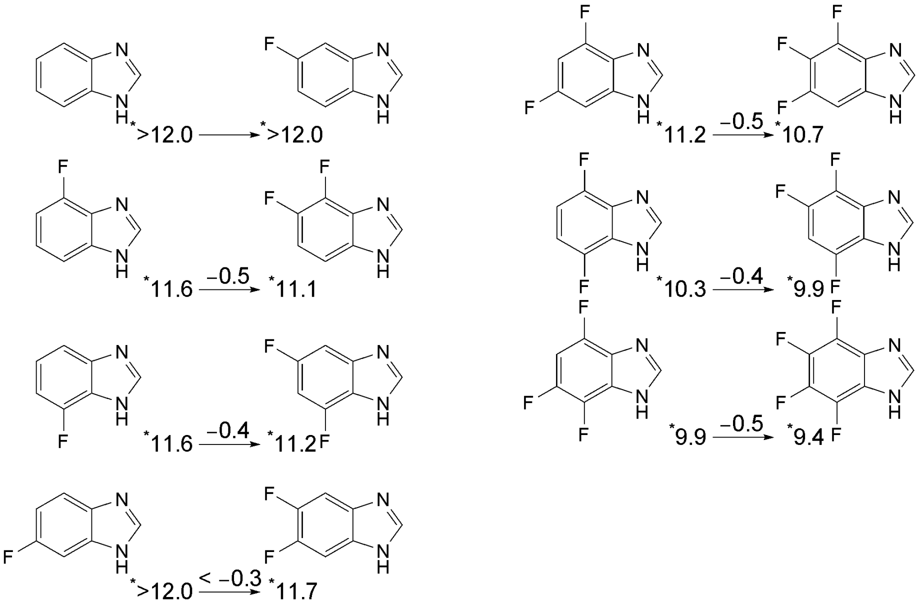


Figure 9SI ?pK_{a2} Effects observed upon the introduction of a fluorine substituent in *meta* position to a nitrogen atom in substituted benzimidazoles.

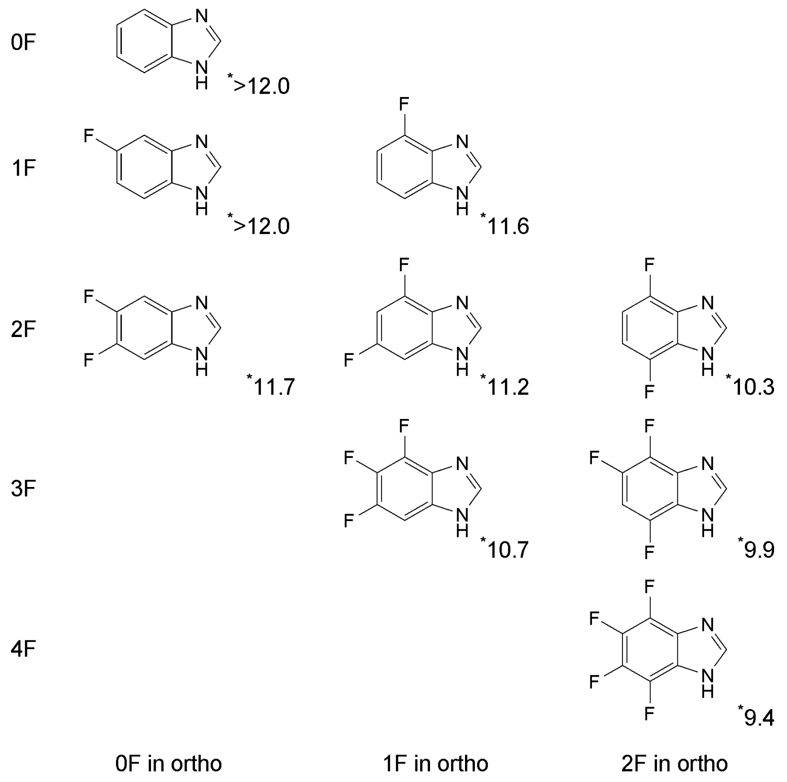


Figure 10SI Effects on pK_{a2} resulting from shifting fluorine atoms from *meta* to *ortho* positions in substituted benzimidazoles.

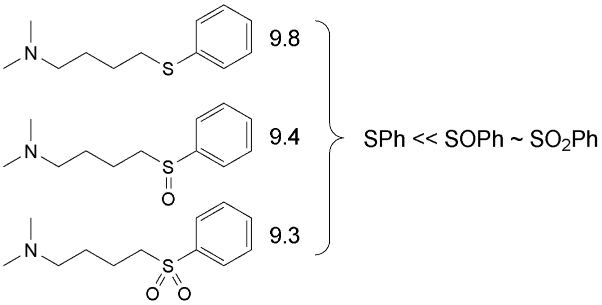


Figure 11SI Comparison of the experimental pK_a values of tertiary amines carrying a phenylthio, phenylsulfoxide, or a phenylsulfone unit in *d*-position, suggesting that the sulfoxide group exerts an effect similar to a sulfone unit.[31]

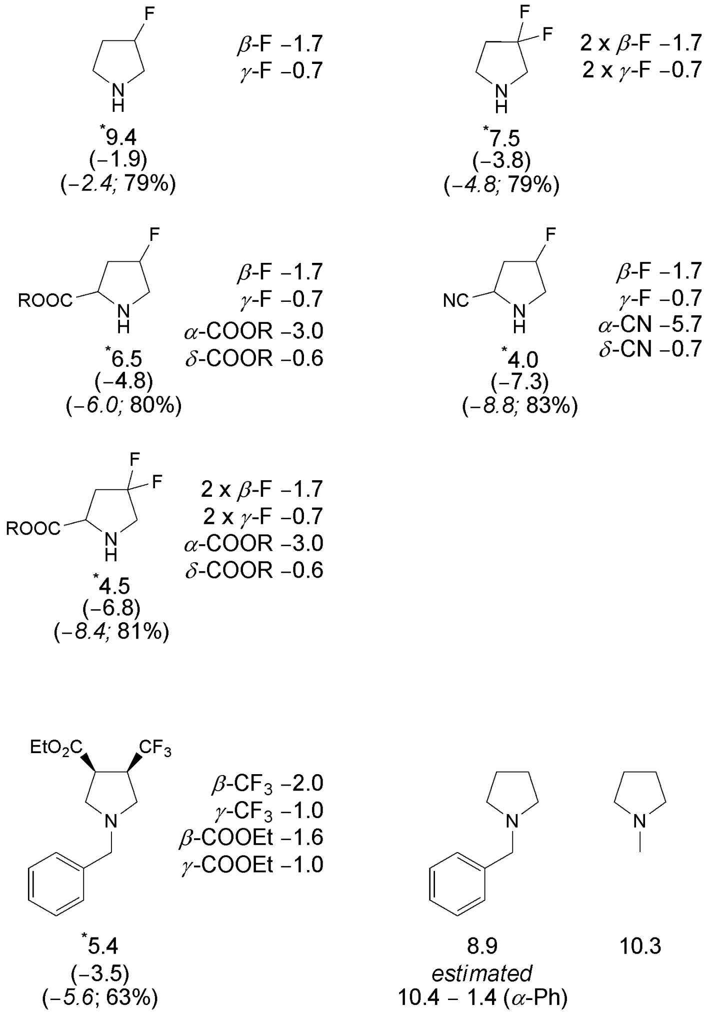
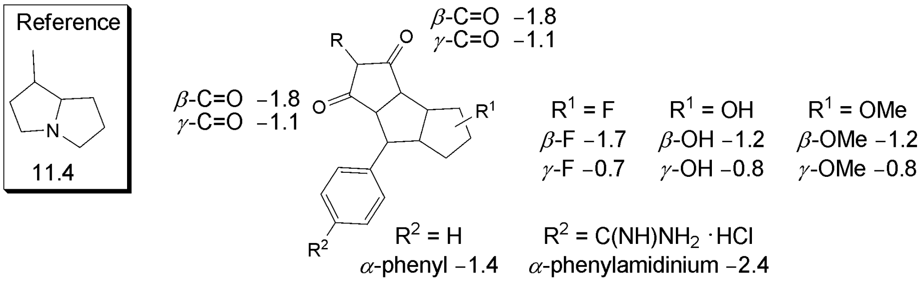


Figure 12SI Experimental pK_a values of substituted pyrrolidine derivatives. The first parenthetical value below the pK_a represents the total pK_a shift relative to unsubstituted pyrrolidine (11.3) or *N*-benzyl-pyrrolidine (9.9, estimated). The expected total downshifts based on the pK_a decrements from acyclic or 6-membered systems are given in italics below together with the correction factor (ca. 60% - 80%) that would have to be applied in order to match the observed ones; the pK_a decrement for *d*-COOEt is estimated by analogy to *d*-COR (see Fig.14a,b).



Compound	p$K_{\mathrm{a\,ref}}$	p$K_{\mathrm{a\,exper}}$	Δp$K_{\mathrm{a\,exper}}$	Δp$K_{\mathrm{a\,calc}}$	corr. factor
(±)-**3**	11.4	5.6	−5.8	−7.2	81%
(±)-**6**	11.4	4.5	−6.9	−8.2	84%
(±)-**26**	11.4	4.1	−7.3	−10.2	72%
(±)-**27**	11.4	3.7	−7.7	−10.2	75%
(±)-**28**	11.4	3.4	−8.0	−10.6	75%
(±)-**29**	11.4	4.2	−7.2	−10.2	71%
(±)-**30**	11.4	4.2	−7.2	−10.2	71%
(±)-**31**	11.4	3.3	−8.1	−10.6	76%
(±)-**32**	11.4	< 2.0	> −9.4	−13.0	72%
(±)-**33**	11.4	3.3	−8.1	−12.2	66%
(±)-**34**	11.4	3.9	−7.5	−10.2	74%
(±)-**35**	11.4	3.6	−7.8	−10.2	76%
(±)-**36**	11.4	3.3	−8.1	−10.6	76%
(±)-**37**	11.4	3.9	−7.5	−10.2	74%
(±)-**38**	11.4	3.7	−7.7	−10.2	75%
(±)-**39**	11.4	3.3	−8.1	−10.6	76%
(±)-**40**	11.4	< 2.0	> −9.4	−13.0	72%
(±)-**41**	11.4	3.2	−8.2	−12.2	67%

Figure 13SI Summary of pK_a-lowering substituent effects in tricyclic thrombin inhibitors. For each substituent the expected downshifts are given for its positions relative to the tertiary amine center. The table lists selected compounds with substitution at the terminal pyrrolidine ring. The experimental ΔpK_a values (relative to hexahydro-pyrrolizine) are compared to the calculated[39] ΔpK_a effects on the basis of the pK_a decrements from acyclic and 6-membered systems; the rightmost column gives the correction factors that would have to be applied in order to match the calculated values to the observed ones.