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BMCL Digest

The successful quest for oral factor Xa inhibitors; learnings for all of medicinal chemistry?

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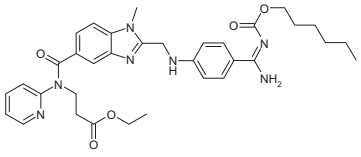
ABSTRACT

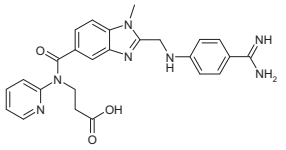
The medicinal chemistry of oral small molecule factor Xa inhibitors is discussed, highlighting key advances that led to clinical candidates and the first licensed medicines. Identification of neutral ligands for the primary specificity pocket was a key discovery; capitalised upon by structure based design and combinatorial methods to deliver many variations on the theme; but it was good medicinal chemistry practice, in the optimisation of physical properties, which ultimately delivered efficacious compounds with adequate oral exposure. As a retrospective appraisal, representative compounds were profiled using the more contemporary concepts of Ligand Efficiency and Property Forecast Indices; which gave clear indications of the value of these principles.

The search for new small molecules to prevent thrombosis has been of the most intensively researched areas of drug discovery over the past two decades.[1] Notwithstanding the potential for commercial rewards, the positive impact on patient care of an orally administered agent addressing the shortcomings of current therapies is highly desirable.[2] This would remove the need for supervised injections and unpleasant blood sampling to monitor efficacy, in addition to reducing the limiting drug–drug interactions and inter-patient variability.[3] The rationales and proofs of concept for directly targeting specific protease enzymes in the coagulation cascade have been well described;[4] Thrombin, factor IIa (fIIa), was the first target heavily pursued,[5] but, with time the emphasis shifted in particular to factor Xa (the Stuart-Prower factor, fXa) when ongoing studies indicated potential advantages for selective fXa inhibitors.[6] Extensive reviews of both the many patents[7] and the progression of leading compounds targeting fXa have followed.[8]

The purpose of this review is not to recover the well trodden ground, or be comprehensive in describing all compounds, but to critically examine the successful strategies employed to differentiate the few fXa inhibitors that progressed in the clinic from the very many that didn't make it. In particular, the exacting demands of identifying a selective, safe and efficacious oral compound are explored. To date, the particular success stories are the licensing of the oral inhibitors dabigatran etexilate[9] (fIIa) **1a** and rivaroxaban[10] (fXa) **2**, which should soon be joined by apixaban[11] (fXa) **3**. Others remain in the clinic at various stages, whilst more have contributed to the attrition statistics of the industry—be that due to scientific shortcomings or strategic decision making.[8a]



Dabigatranetexilate **1a**



Dabigatran **1**

Table 1 includes rivaroxaban **2** and apixaban **3** plus seven other representative fXa inhibitors **4**–**10**, which have reached various stages of clinical development, used to illustrate concepts developed in the review. Additionally, a download of available fXa inhibitory data from the ChEMBL database[12] gave 773 compounds with K_i values that allowed meaningful comparison, covering most of the series that led to the molecules in Table 1 and other related compounds.

The impact and influence of new methods in drug discovery can often be traced through particular targets; the story of fXa is intertwined with progress in protein crystallography and combinatorial chemistry. The first fXa crystal structure was solved in 1993,[13] but nearly ten years elapsed before the process of solving inhibitor bound structures became routine. This enabled better computational structure based design, which was complemented by the heavy investment in combinatorial chemistry methods around the millennium, leading to the rapid expansion of SAR in particular series. It is probably no coincidence that most published fXa inhib-

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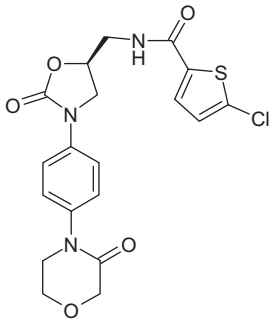
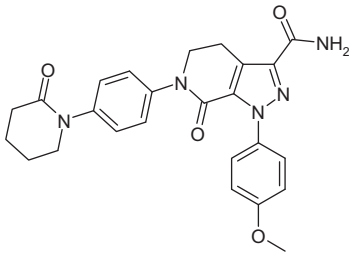
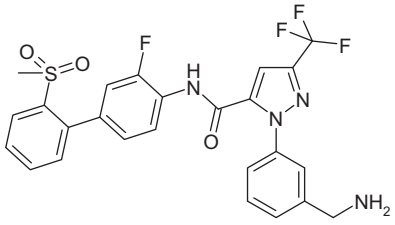
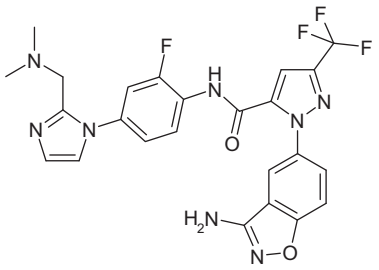
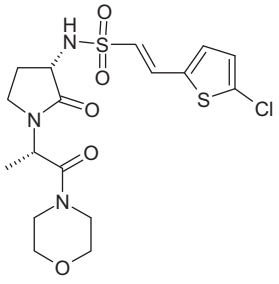
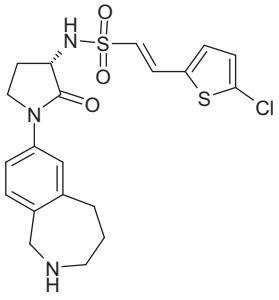
Table 1
Structures of representative fXa inhibitors used in this review; note the curved 'L-shaped' structures—the P1 motif is on the right of each structure drawn

	Rivaroxaban **2** — K_i (fXa) 0.4 nM; PT 0.23 μM; PT/K_i ~575. *C*log*P* 2.39; *i*PFI 4.89; cChrom log$D_{pH7.4}$4.35; PFI 6.35. LE 0.44, LLE_{At} 0.4; MW 435.9; HAC 29
	Apixaban **3** — K_i (fXa) 0.08 nM; PT 3.8 μM; PT/K_i = 47,500. Clog*P* 1.89; iPFI 4.89; cChrom log$D_{pH7.4}$ 4.79; PFI 7.79. LE 0.41; LLE_{At} 0.44; MW 459.5; HAC 34.
	DPC423 **4** — K_i (fXa) 0.15 nM; aPTT 4.86 μM; aPPT/K_i = 32,400. Clog*P* 2.88; iPFI 6.88; cChrom log$D_{pH7.4}$ 2.86; PFI 6.86.m LE 0.36; LLE_{At} 0.36; MW 532.5; HAC 37.
	Razaxaban **5** — K_i (fXa) 0.19 nM; PT 3.8 μM; PT/K_i = 20,000. *C*log*P* 2.47; iPFI 7.47; cChrom log$D_{pH7.4}$ 3.11; PFI 8.11. LE 0.35; LLE_{At} 0.37; MW 528.5; HAC 38
	GW813893 **6** — K_i (fXa) 4 nM; PT 1.2 μM; PT/K_i = 300. *C*log*P* 1.99; *i*PFI 3.99; cChrom log$D_{pH7.4}$ 4.24; PFI 5.24. LE 0.41; LLE_{At} 0.42; MW 448.0; HAC 28
	GSK1023480 **7** — K_i (fXa) 1 nM; PT 0.9 μM; PT/K_i = 900. *C*log*P* 3.54; iPFI 5.54; cChrom log$D_{pH7.4}$ 3.16; PFI 5.16. LE 0.43; LLE_{At} 0.36; MW 452.0; HAC 29