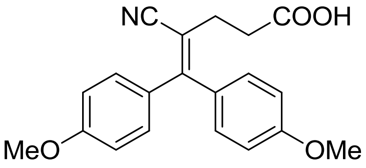
2. REVIEW OF LITERATURE

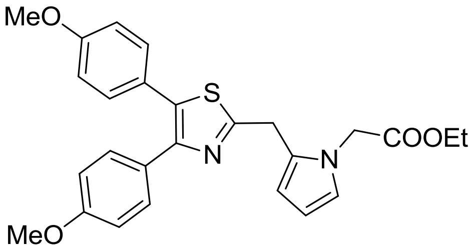
Syntheses of small molecules possessing the vicinal diaryl scaffold as a privileged substructure has received wide attention in the field of medicinal chemistry.[1] Molecules incorporating this scaffold have demonstrated biological activity of varying nature, especially as antiplatelet agents[3] and COX inhibitors.[2]

2.1. Substituted diaryl heterocycles as antiplatelet agents

There are several reviews that focus mainly on the molecular and functional basis of the inhibition of COX enzymes by non-selective and selective COX-2 inhibitors. Some compounds such as E-5510 **(2.1)**, KBT-3022 **(2.2)** and itazigrel **(2.3)** have been reported to inhibit cyclooxygenase reversibly.[4] Structural analysis of these compounds have shown that the bis(4-methoxyphenyl) moiety is essential for potent cyclooxygenase inhibition.



(2.1)



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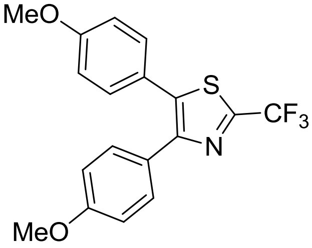
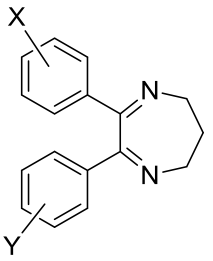


(2.3)

2.1.1. Substituted 1,4-diazepine derivatives

Previous findings from our laboratory[5] indicated that substituted 1,4-diazepine derivatives (**2.4**) exhibited antiplatelet activity comparable to aspirin. Various substituents like amino, nitro, methyl and chloro were introduced into one of the aryl groups of the diaryl system on 1,4-diazepine ring.

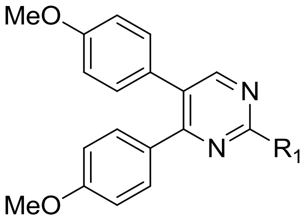


(2.4)

Among these compounds, it was found that 4-chloro and 4-fluoro groups as substituents on aryl rings imparted better activity than aspirin.

2.1.2. 2-Substituted 4,5-bis(4-methoxyphenyl)pyrimidines

In order to obtain novel aspirin-like antiplatelet agents, Tanaka and Motoyama synthesized a series of 2-substituted 4,5-bis(4-methoxyphenyl)pyrimidines.[4d] Among them, 4,5-bis(4-methoxyphenyl)-2-morpholinopyridines (**2.5e**) and 4,5-bis(4-methoxyphenyl)-2-(3,5-dimethylmorpholin-4-yl)pyrimidine (**2.5f**) showed potent inhibitory activity on malondialdehyde (MDA) produced *in vitro* (73.4 % inhibition at 10^{-8} M and $IC_{50} = 1.4 \times 10^{-8}$ M, respectively).



R_1 =

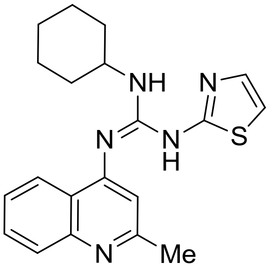
(a) CH_3,
(b) NH_2,
(c) NHCN,
(d) 4-Pyridyl,
(e) Morpholino,
(f) 3,5-Dimethylmorpholino,
(g) 1,2,3,6-Tetrahydro-1-methylpyridine

4,5-Bis(4-methoxyphenyl)pyrimidine (2.5)

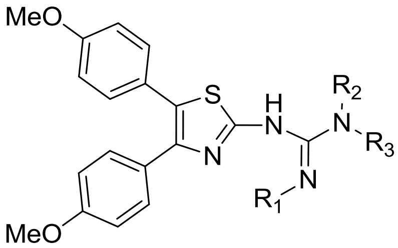
The *ex vivo* studies on these compounds showed that compounds (**2.5e** and **2.5g**) exhibited potent and long-lasting antiplatelet activity induced by arachidonic acid and collagen even after 6 hr of oral administration at 3.2 mg/kg in guinea pigs (100 and 97 % respectively). These results indicated that the *ex vivo* activity of (**2.5e** and **2.5g**) is more than three times that of aspirin. Aspirin showed 81 % and 5 % inhibitory activity on platelet aggregation induced by arachidonic acid and collagen respectively, 6 hr after oral administration of 10 mg/kg.

2.1.3. 2-Guanidino-4,5-bis(4-methoxyphenyl)thiazole

Some of the diarylthiazoles were reported to be potent antiplatelet agents with vasodilatory action.[6] This study helped to conclude that guanidine moiety present in those structures had a major role in vasodilatation. *L*-Arginine, (*S*-2-amino-5-guanidinopentanoicacid), is a well-known essential amino acid which acts as a vasodilator through nitric oxide dependent pathway (NO donors).[7] Moreover, agamatine (4-aminobutyl guanidine)[8] and its derivatives like GYKI-14766 (*D*-methyl-phenylalanylprolylarginal)[9] were accessed as experimental medicines in anticoagulant and antithrombotic therapy. Timegadine a trisubstituted guanidine derivative and some other acyclic guanidines[10] possess potent vasodilatory actions.



(2.6)



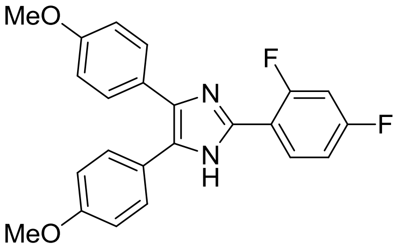
R_1 = H, Me
R_2 = Me, Morpholino
R_3 = Me

(2.7)

Aspirin (**1.1**) and itazigrel (**2.3**) provide antiplatelet activity by COX inhibition mechanism without causing vasodilation. Timegadine (**2.6**) showed inhibition of COX and vasodilation activity. Fusion of these two kinds of compounds (Itazigrel and Timegadine) has been attempted to obtain potent platelet aggregation inhibition through COX inhibition with vasodilatory activity offering 2-guanidino-4,5-bis(4-methoxyphenyl)thiazole (**2.7**). Introduction of a methyl group onto the guanidino moiety provided with an increase of the COX inhibition activity with moderate vasodilatory activity. Substitution with morpholine showed potent inhibition of COX with weak vasodilatory activity.

2.1.4. 2,4,5-Triaryl imidazole derivatives

Fenflumizole [2-(2,4-difluorophenyl)-4,5-bis(4-methoxyphenyl)-1*H*-imidazole] (**2.8**) has shown good antiplatelet activity. It was found to possess potent cyclooxygenase inhibitory activity. It is 170 times weaker as an inhibitor of PGI_2 generation in the rat stomach mucosa *ex vivo* as compared to indomethacin. Anti-aggregatory effect was found in patients of unstable angina. Fenflumizole effectively inhibited *in vitro* collagen-induced platelet aggregation and *ex vivo* ADP-induced platelet aggregation. Fenflumizole (**2.8**) possesses a potent antithrombotic activity and a relatively low gastro-ulcerogenicity in rats.[11]



(2.8)

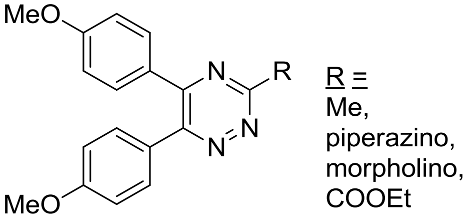
Fenflumizole was given to dogs in a single oral dose of 3 or 10 mg/kg. The plasma concentrations of fenflumizole and the two metabolites (mono and di-demethyl forms) attained the peak level within 1-2 hr after dosing of fenflumizole, returning to near the predose levels 8 hr after dosing. Fenflumizole (10 mg/kg) when given orally, significantly inhibited collagen and ADP-induced platelet aggregations *ex vivo* over 4 hr after the dosing. Fenflumizole effectively inhibited *in vitro* collagen-induced platelet aggregation, but failed to prevent ADP-induced aggregation. The mono-demethyl form of fenflumizole inhibited *in vitro* ADP and collagen-induced aggregations, but the di-demethyl form was found to be ineffective. However, fenflumizole seems to have retained therapeutic activities with reduced side effects, when compared to the actions of other non-steroidal anti-inflammatory drugs, particularly on the gastrointestinal tract.

2.1.5. 3-Substituted 5,6-bis(4-methoxyphenyl)-1,2,4-triazines

1,2,4-Triazine scaffold has been associated with diversified pharmacological activities, such as antiplatelet,[12] anticancer,[13] thromboxane synthetase inhibition,[14] anti-inflammatory[15] and antimalarial.[16] Further, the diaryl system attached to 1,2,4-triazine heterocycle has been reported to be a potent anticytokine, mediating through the inhibition of p38 MAPK signaling pathway.[17] Recent studies on 5,6-diaryl triazines showed neuropharmacological applications of this moiety, such as adenosine A_{2A} antagonism in Parkinson’s disease,[18] anti-neuroinflammatory activity in Alzheimer’s disease[19] and as neuroprotectants.[20] More recently, potent neuroprotective action of some 1,2,4-triazines by activating Wnt/b-catenin signaling pathway has been demonstrated by our research group.[21]

Some patents have also disclosed the topical anti-inflammatory and antithrombotic activity of diaryltriazines.[22]

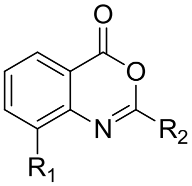
Tanaka *et al.* reported 3-substituted-5,6-bis(4-methoxyphenyl)-1,2,4-triazines (**2.9**) as antiplatelet agents.[12] Amongst these compounds, substituted piperazine compounds exhibited potent COX inhibition with vasodilatory activity. The *ex vivo* potency of substituted piperazine compounds was more than that of aspirin. Moreover, the reported triazines were found to be devoid of GI side effect which is the main drawback of aspirin.



(2.9)

2.2. Benzoxazinones as antiplatelet agents

2-Substituted benzoxazinones were reported as mechanism-based inhibitors of standard serine proteases of the chymotrypsin superfamily that inhibit the enzyme by formation of an acyl–enzyme complex through attack of the active site serine on the carbonyl group. Benzoxazinones showed significant inhibition of thrombin and tissue factor VIIa.[23] It is also mentioned in this study that they also prolonged thrombin-induced fibrinogen clotting times.



(2.10)

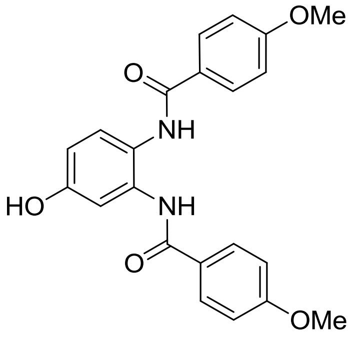
Some 2,8-disubstituted benzoxazinone derivatives (**2.10**) were reported having potent antiplatelet aggregation property. These derivatives were substituted with various groups like methoxy, methyl and chloro at C-8 position and 4'-bromophenyl, 2'-chlorophenyl, 2'-bromophenyl, 2'-fluorophenyl, 2'-methoxyphenyl and 2'-methylphenyl at C-2 positions.[24]

2.3. Vicinal diamides as antithrombotic agents

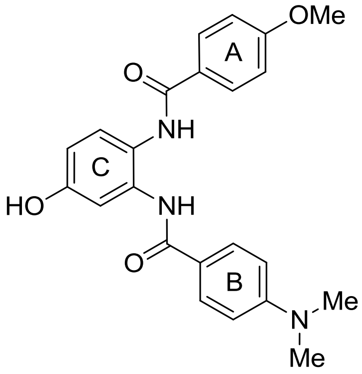
Various research groups have reported anthranilamides and diamidobenzenes to possess antithrombotic activity. Efforts in this area include contributions from Berlex and Lilly research groups.

2.3.1. 1,2-Dibenzamidobenzenes

Diamidobenzenes, the compounds structurally resembling anthranilamides were reported in literature with potent antiplatelet activity, particularly as FXa inhibitors. By high throughput screening of a library of compounds, compound (**2.11**) was identified as a potent FXa inhibitor with a K_i value of 1.6 µM.



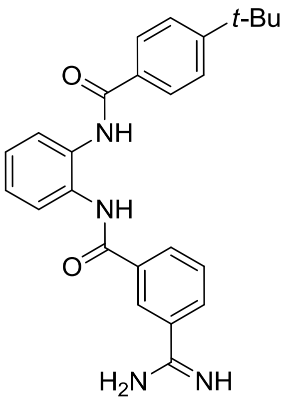
(2.11)



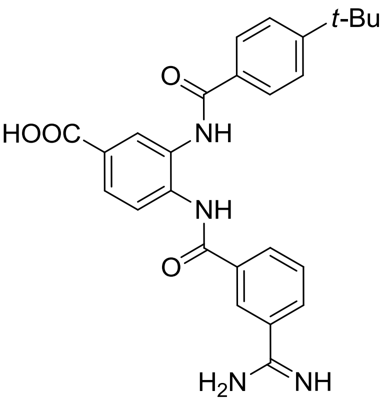
(2.12)

The best activity has been observed in substituted 1,2-dibenzamidobenzenes wherein the aromatic ring of one benzoyl group (A-ring) was substituted in the 4-position with a relatively small lipophilic group such as methoxy, vinyl or chloro and aromatic ring of the other benzoyl group (B-ring) was substituted in the 4-position with a larger lipophilic group such as *tert*-butyl or dimethylamino. The central phenyl ring (C-ring) tolerated a wide variety of substituents, but methoxy, methanesulfonamido, hydroxyl and carboxyl substituents produced slightly higher levels of activity than other substituents when present in combination with favourable B-ring substituents. Methylation of the amide nitrogen atoms was found to greatly decrease the activity. Compound (**2.12**) is the highest affinity FXa inhibitor in this group of compounds, having K_i value of 39 nM.[25]

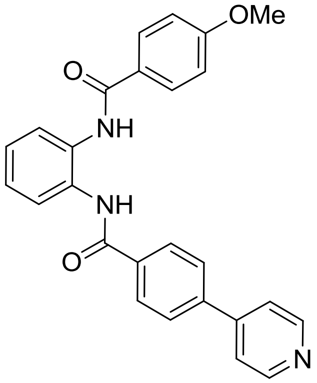
To increase the potency of 1,2-dibenzamidobenzenes, an amidine substituent was incorporated on one of the benzoyl side chains of compound (**2.12**) to obtain highly potent compounds (**2.13** and **2.14**).[26]



(2.13)



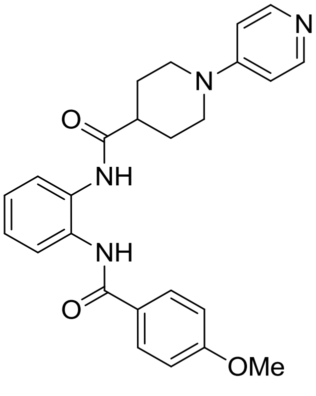
(2.14)



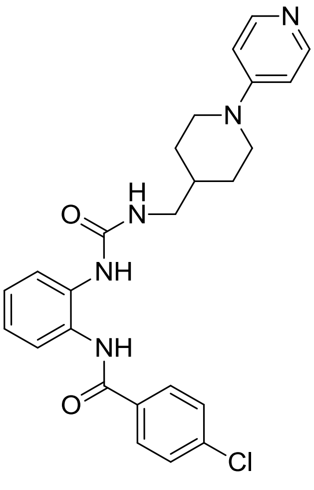
(2.15)

The amidine in compound (**2.13**) (FXa K_{ass} = 250 X 10^6 L/mol, FXa K_i = 4 nM) enhanced the potency by about 250-fold, and incorporation of carboxylic group in compound (**2.14**) (FXa K_{ass} = 470 X 10^6 L/mol, FXa K_i = 2.2 nM) further doubled the potency of compound (**2.13**). Both compounds demonstrated good *in vitro* clotting activity PT_{2x} = 0.96 μM and PT_{2x} = 0.83 μM respectively.

Other diaminobenzene analogs devoid of the amidine moiety, such as compounds (**2.15**) (FXa K_{ass} = 9.2 X 10^6 L/mol, FXa K_i = 108 nM), **(2.16)** (FXa K_{ass} = 2.3 X 10^6 L/mol, FXa K_i = 434 nM) and **(2.17)** (FXa K_{ass} = 100 X 10^6 L/mol, FXa K_i = 10 nM) were also reported to have moderate FXa inhibitory activity.[27]



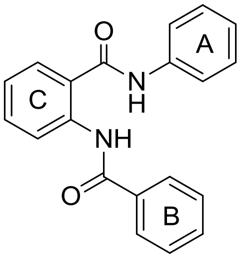
(2.16)



(2.17)

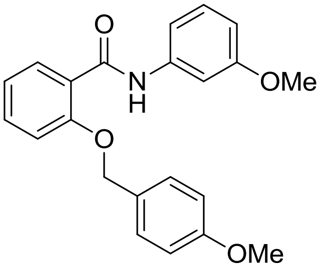
2.3.2. Anthranilamides

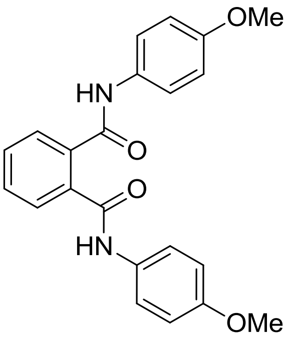
To improve oral absorption, researchers at Lilly discovered structurally more diverse leads which were proposed to serve as newer leads for the development of FXa inhibitors. These studies resulted into identification of compound (**2.18**) having a high affinity for FXa.

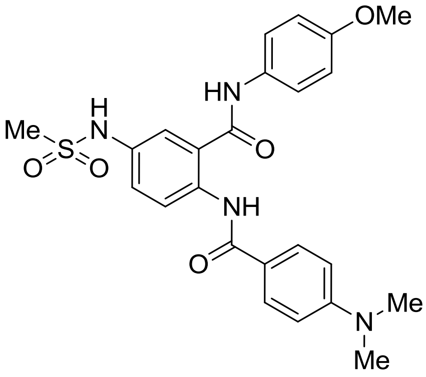


(2.18)

Replacement of one of the amide moieties with an ether linkage resulted into compound (**2.19**) with reduced activity (FXa K_i = 100 µM). Substitution of the scaffold of compound (**2.18**) with phthalamide in compound (**2.20**) led to complete loss of activity. Further Modifications of anthranilamides led to discovery of compound (**2.21**) [FXa K_{ass} (~1/K_i) = 57.9 × 10^6 L/mol, K_i =11.5 nM] as the most potent analog in the anthranilamide series.[28]

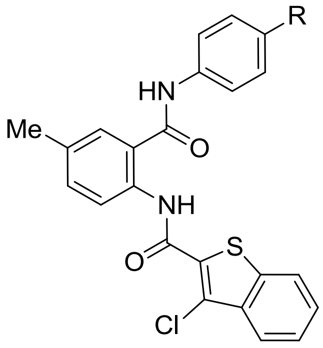




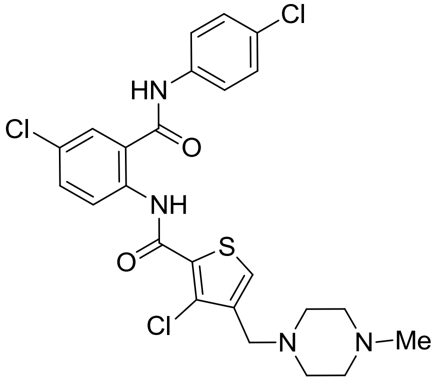


(2.19) **(2.20)** **(2.21)**

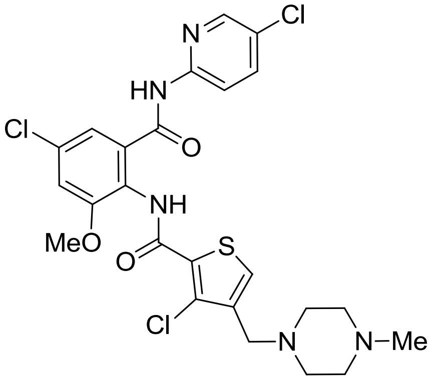
Researchers at Berlex identified compound (**2.22**) (FXa K_i = 11 nM) as a novel anthranilamide through high throughput screening. Replacement of the fluoroanilide with a chloroanilide moiety resulted into compound (**2.23**) with a 34-fold improvement in binding affinity toward FXa (K_i = 0.32 nM).[29] However, compound (**2.23**) showed poor *in vitro* anticoagulant activity due to its high lipophilicity. To improve the activity, further optimization led to the discovery of a series of compounds exemplified by compound (**2.24**) (FXa K_i = 1 nM, EC_{2xPT} = 12 μM).[30] Incorporation of methoxy group at C-3 position and replacement of chloroaniline with a chloroaminopyridine in compound (**2.24**) resulted into compound (**2.25**) (FXa K_i = 0.16 nM, EC_{2xPT} = 1.6 μM) with improved activity. Further modifications at P4 of compound (**2.25**) resulted into a series of compounds (**2.26-2.28**).[31]



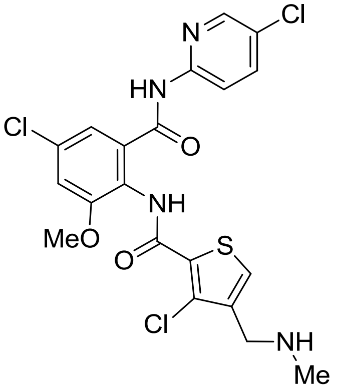
(2.22) R = F
(2.23) R = Cl



(**2.24**)

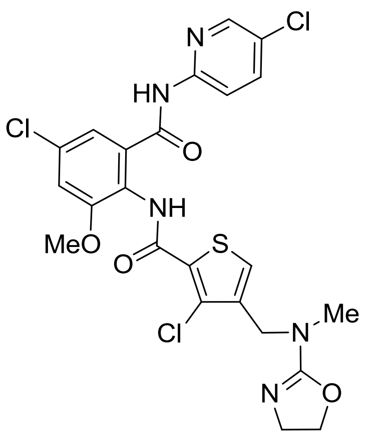


(2.25)



(2.26)

Researchers at Lilly reported anthranilamides using *t*-butylbenzoyl as P4 motif as represented by compound (**2.29**) (FXa K_{ass} ($\sim 1/K_i$) = 42 × 10^6 L/mol, K_i = 23.8 nM). Introduction of 3-aminopropanol at C-2 of the *t*-butylbenzoyl resulted into compound **(2.30**) (FXaK_{ass} ($\sim 1/K_i$) = 1,440 × 10^6 L/mol, K_i = 0.69 nM) with increased potency. Replacement of the *t*-butyl with a 1,4-diazepine resulted into highly active compound (**2.31**) (FXa K_{ass} ($\sim 1/K_i$) = 8970 × 10^6 L/mol, K_i = 0.11 nM).[32]



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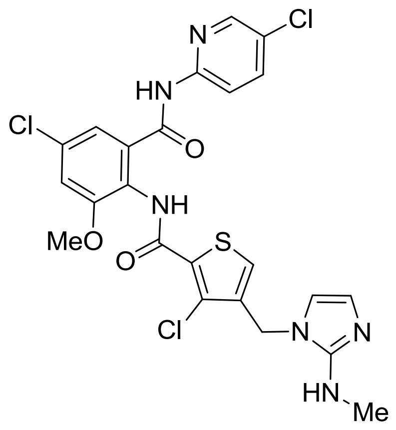

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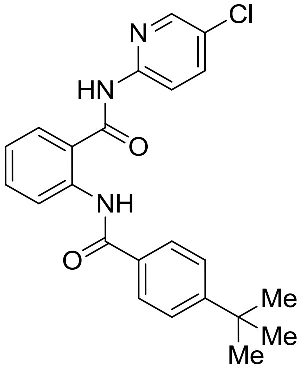
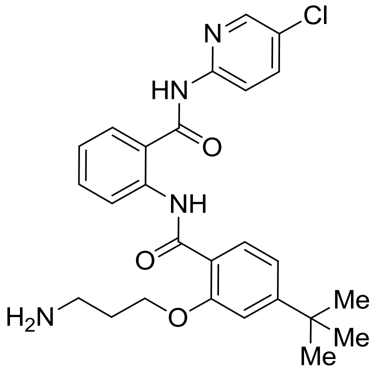


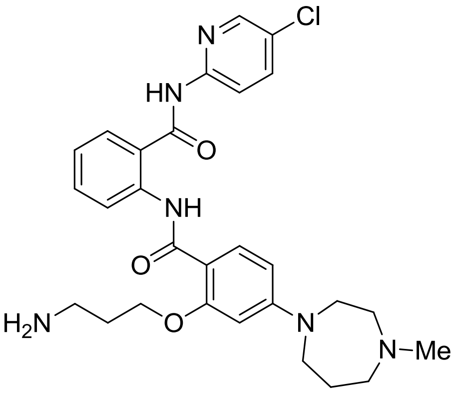
(2.29)



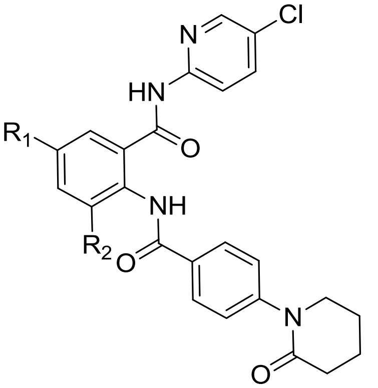
(2.30)

Inspired by the results obtained from apixaban, Bristol Meyers Squibb employed phenylpiperidinone and phenylpyridinone as P4 motifs in the anthranilamide scaffold, which led to the discovery of highly potent compounds (**2.32**) (FXa K_i = 1.2 nM, EC_{2xPT} = 4.6 µM) and (**2.34**) (FXa K_i = 0.14 nM, EC_{2xPT} = 2.6 µM). Installation of 3-methoxy and 5-chloro substituents on the anthranilamide scaffold resulted into compounds (**2.33**) (FXa K_i = 0.057 nM, EC_{2xPT} = 1.5 µM) and (**2.35**) (FXa K_i = 0.013nM, EC_{2xPT} = 1.4 µM) with greatly improved activity.[33]

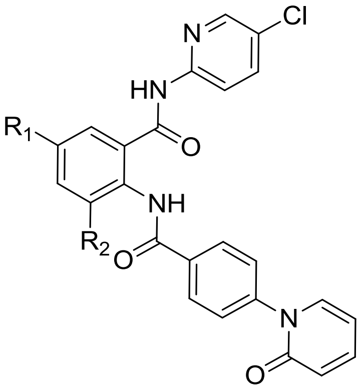
Researchers at Portola reported anthranilamide derivatives containing biaryl as P4 groups, e.g. compounds (**2.36** and **2.37**) (FXa K_i = 0.1 nM).[34] To overcome the issue of high lipophilicity and to lower the protein binding, compounds (**2.36** and **2.37**) were further modified by incorporating polar amino alkyl P4 motif to provide highly active compound (**2.38**) (FXa K_i = 1.3 nM).[35]



(2.31)

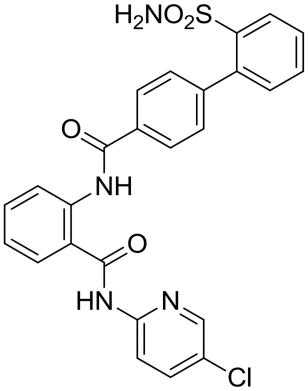


(2.32) R$_1$, R$_2$ = H
(2.34) R$_1$, R$_2$ = Cl



(2.33) R$_1$, R$_2$ = H
(2.35) R$_1$, R$_2$ = Cl

Replacement of dimethylamino group of compound (**2.38**) with 2-iminooxazolidine and acyclic amidine resulted into compounds (**2.39**) (FXa K$_i$ = 1.5 nM) and (**2.40**) (FXa K$_i$ = 0.6 nM) respectively. The SAR of this anthranilamide series was further extended by incorporating *N*,*N*-dialkylbenzamidine as P4 group in compound (**2.41**).[36]



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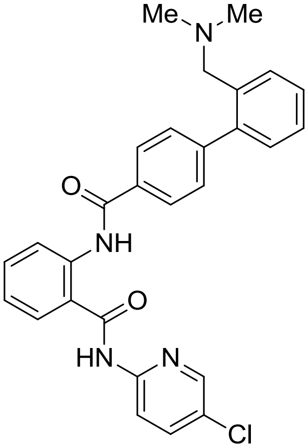
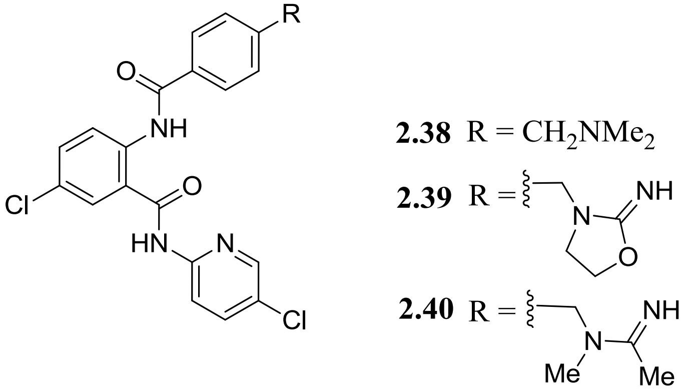
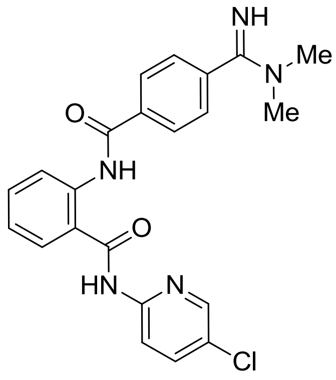


(2.37)

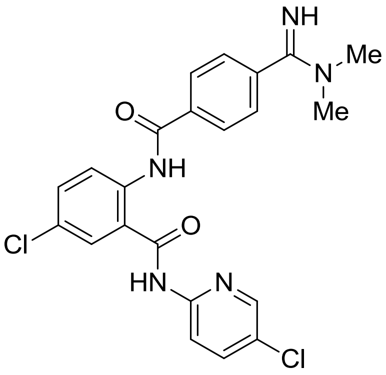


(2.38-2.40)

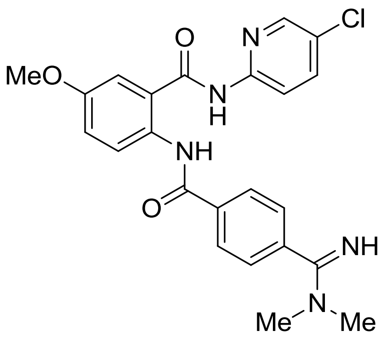


(2.41)

It was found that many of the benzamidine-containing compounds showed potent hERG inhibitory activity. Compounds (**2.41-2.43)** demonstrated good FXa inhibitory activity with some degree of hERG inhibitory activity. From this series, compound **1.10** (Betrixaban) showed good profile and was selected for clinical advancements.

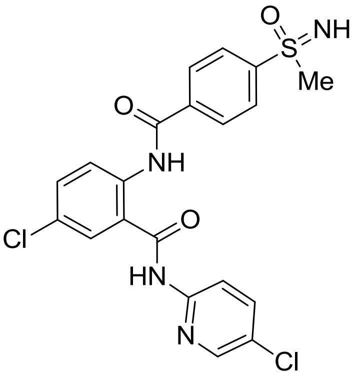


(2.42)

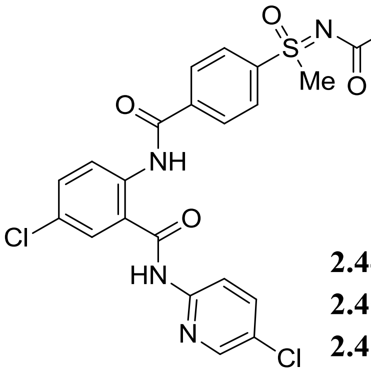


(1.10)

Researchers at Zydus Research Centre also reported some of the anthranilamide based compounds.[37] Replacement of highly basic amidine group (S4 ligand) of betrixaban (**1.10)** by a much less basic sulfoximine resulted into a series of active compounds. Compound **(2.43)** displayed 76 % inhibition of FXa at 0.1 µM. Effect of different substituents on nitrogen of sulfoximine group indicated that anticoagulant activity of any compound was a function of its hydrophilicity and plasma-protein binding. Compound **(2.44)** bearing methoxyacetyl group on the nitrogen of sulfoximine group has been observed with increased polarity, improved anticoagulant activity (PT_{CT2x} = 7.2 µM for compound **(2.43)** and 3 µM for compound **2.44**). Replacement of methoxy group of compound **(2.44)** with different acylimides resulted into identification of highly potent compound **(2.45)** (100 % inhibition at 0.1 μM and PT_{CT2x} = 0.68 μM).



(2.43)



2.44 R = OMe
2.45 R = NEt_2
2.46 R = NHEt

(2.44-2.46)

Compound **(2.45)** and its metabolite **(2.46)** were found to have higher selectivity (FXa K_i = 1.1 and 1.5 resp.) and lesser effect on CYP3A4. Compound **(2.45)** demonstrated good *in vivo* antithrombotic efficacy in thrombosis model.

2.4. References

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