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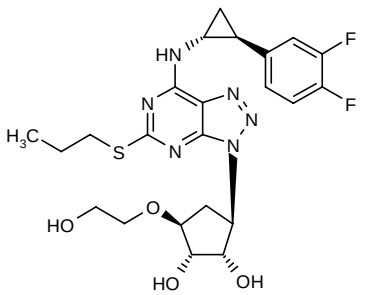
AZD6140

Antiplatelet Therapy
$P2Y_{12}$ (P2T) Receptor Antagonist

AR-C126532
Ticagrelor (Rec INN; USAN)

(1*S*,2*S*,3*R*,5*S*)-3-[7-[(1*R*,2*S*)-2-(3,4-Difluorophenyl)cyclopropylamino]-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol

InChI=1/C23H28F2N6O4S/c1-2-7-36-23-27-21(26-15-9-12(15)11-3-4-13(24)14(25)8-11)18-22(28-23)31(30-29-18)16-10-17(35-6-5-32)20(34)19(16)33/h3-4,8,12,15-17,19-20,32-34H,2,5-7,9-10H2,1H3,(H,26,27,28)/t12-,15+,16+,17-,19-,20+/m0/s1



$C_{23}H_{28}F_2N_6O_4S$
Mol wt: 522.5693

CAS: 274693-27-5

CAS: 377093-13-5 (hydrate)

EN: 283279

Abstract

AZD6140 is a novel, selective, orally active, reversible antiplatelet agent. The drug is a $P2Y_{12}$ purinoceptor antagonist that belongs to a novel class of compounds called cyclopentyltriazolopyrimidine inhibitors. Unlike thienopyridines, AZD6140 does not require conversion to an active metabolite. Compared with clopidogrel, AZD6140 produces a greater and more consistent inhibition of ADP-induced platelet aggregation. Its rapid onset of action has the potential to improve outcomes for patients with acute coronary syndromes, and its reversibility may offer advantages to patients needing surgery after initiating antiplatelet therapy. Two phase II trials have investigated the efficacy and safety of AZD6140 *versus* clopidogrel in atherosclerosis and non-ST segment elevation acute coronary syndrome (NSTE-ACS). If the positive results of these preliminary investigations are confirmed in large-scale, randomized trials, AZD6140 may provide a valuable option for the prevention of ischemic events.

Synthesis

AZD6140 can be prepared by two related methods, as follows:

1) 4(*R*)-Aminocyclopentane-(1*S*,2*R*,3*S*)-triol 2,3-acetonide (I) is condensed with 4,6-dichloro-5-nitro-2-propylthiopyrimidine (II) in the presence of diisopropylethylamine in THF to afford the aminopyrimidine adduct (III), which is reduced to the diamine (IV) by means of iron powder in acetic acid. Cyclization of diamine (IV) employing isoamyl nitrite in hot acetonitrile followed by displacement of the resulting 6-chloro-8-azapurine (V) with ammonia in THF gives the azaadenine (VI). The lithium alkoxide of cyclopentanol (VI) is then alkylated with methoxycarbonylmethyl triflate (VII), producing ether (VIII). After conversion of amine (VIII) to the corresponding bromide (IX) by diazotization with isoamyl nitrite in bromoform, bromide displacement with 2-(3,4-difluorophenyl)cyclopropylamine (X) gives adduct (XI). Finally, DIBAL reduction of the ester function of (XI) provides acetonide (XII), which is finally hydrolyzed under acidic conditions to furnish the title compound (1, 2). Scheme 1.

2) In an alternative method, 2-thiobarbituric acid (XIII) is alkylated with 1-iodopropane and NaOH in *N*-methylpyrrolidone to afford the 2-(propylsulfanyl)pyrimidine (XIV). Diazotization of *p*-toluidine (XV) with $NaNO_2$ and HCl, followed by coupling of the intermediate diazonium salt with pyrimidine (XIV) in the presence of NaOAc, produces the diazo adduct (XVI). After chlorination of (XVI) with $POCl_3$, reductive cleavage of the diazo compound (XVII) with H_2 and Pt/C gives 5-amino-4,6-dichloro-2-(propylsulfanyl)pyrimidine (XVIII). Subsequent condensation of (XVIII) with the cyclopentylamino compound (XIX) in ethanolic triethylamine at 120 °C in a pressure vessel provides the diaminopyrimidine (XX), which is further converted to the azapurine (XXI) by treatment with $NaNO_2$ in

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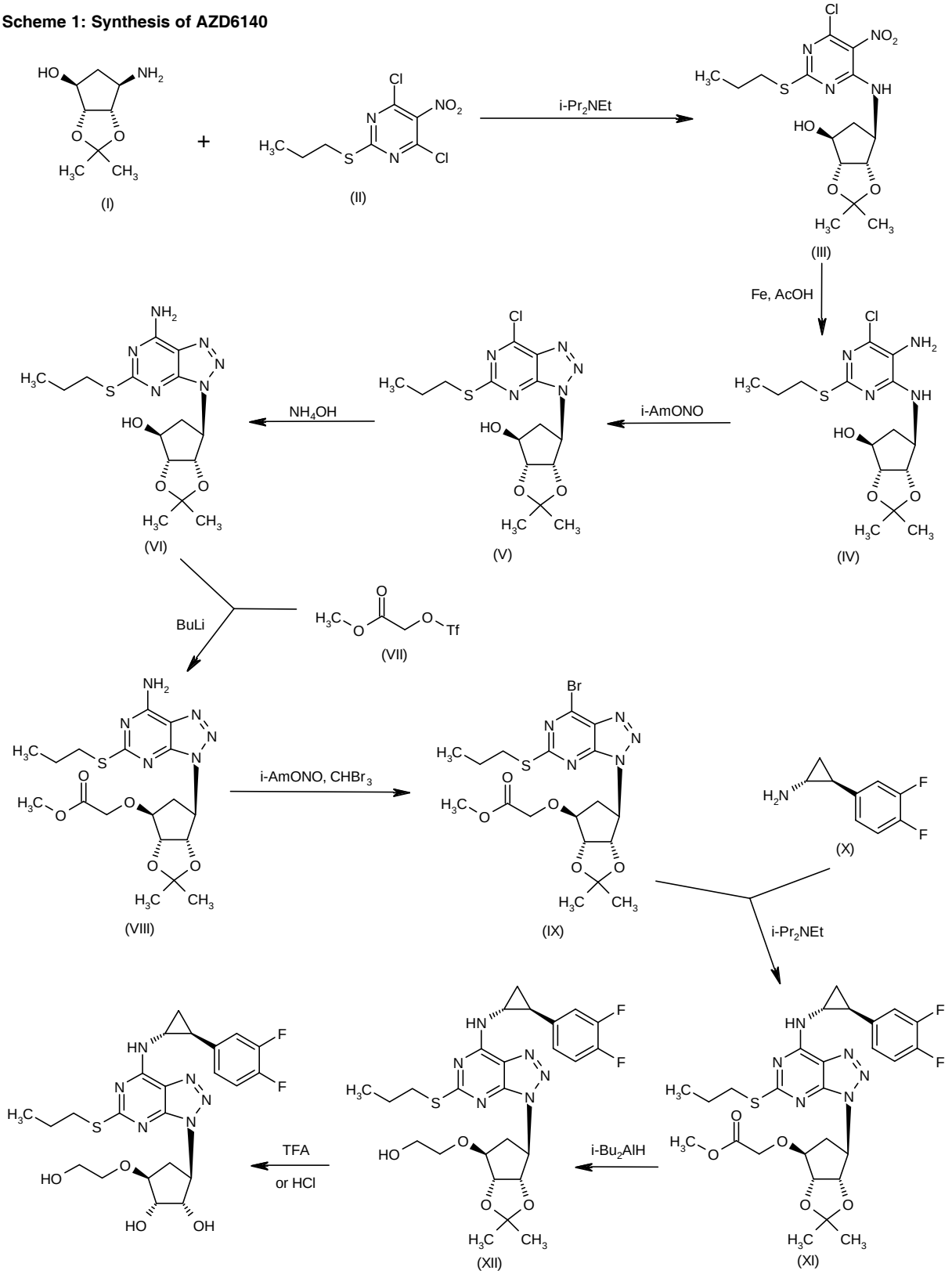
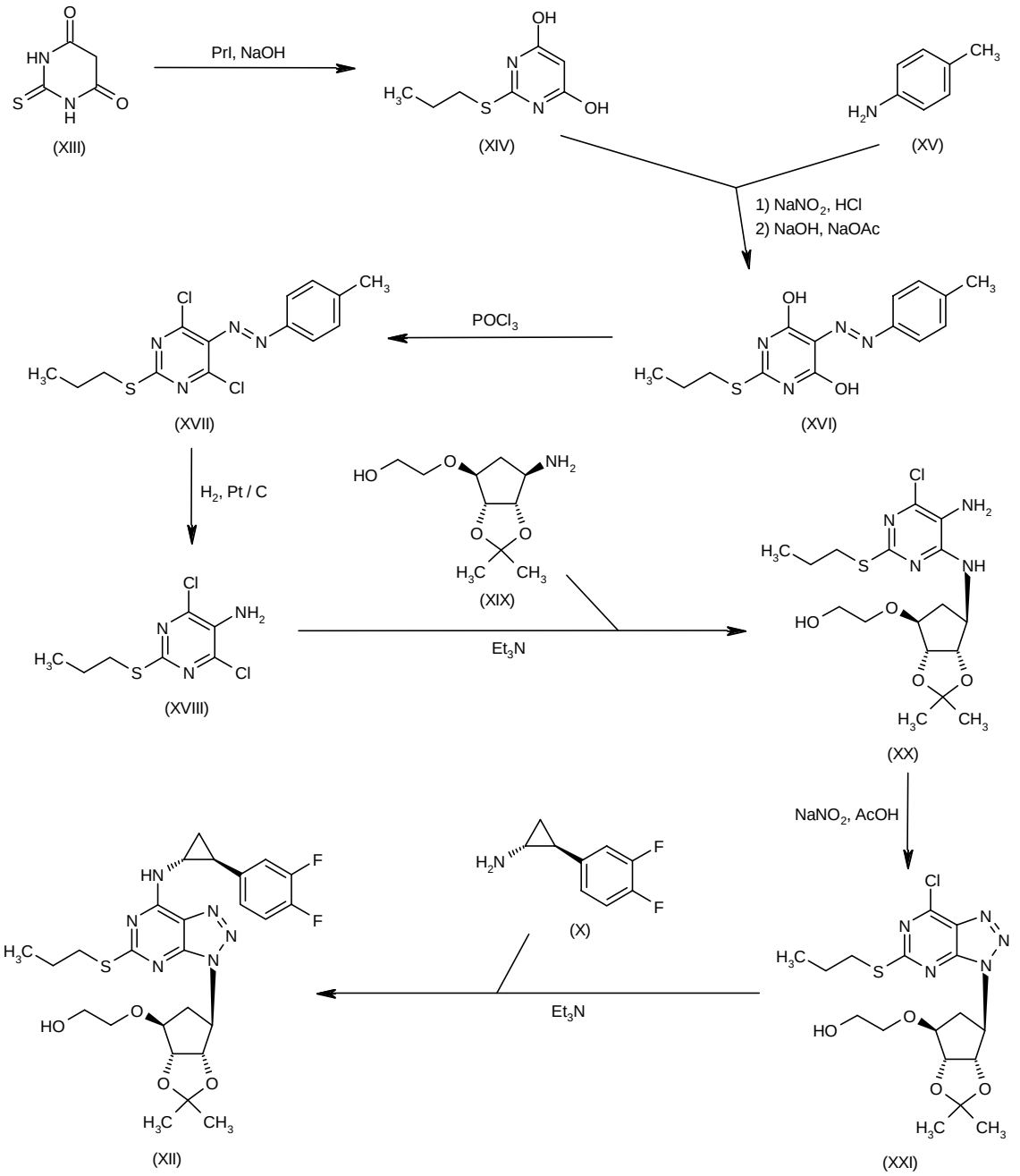
Scheme 1: Synthesis of AZD6140



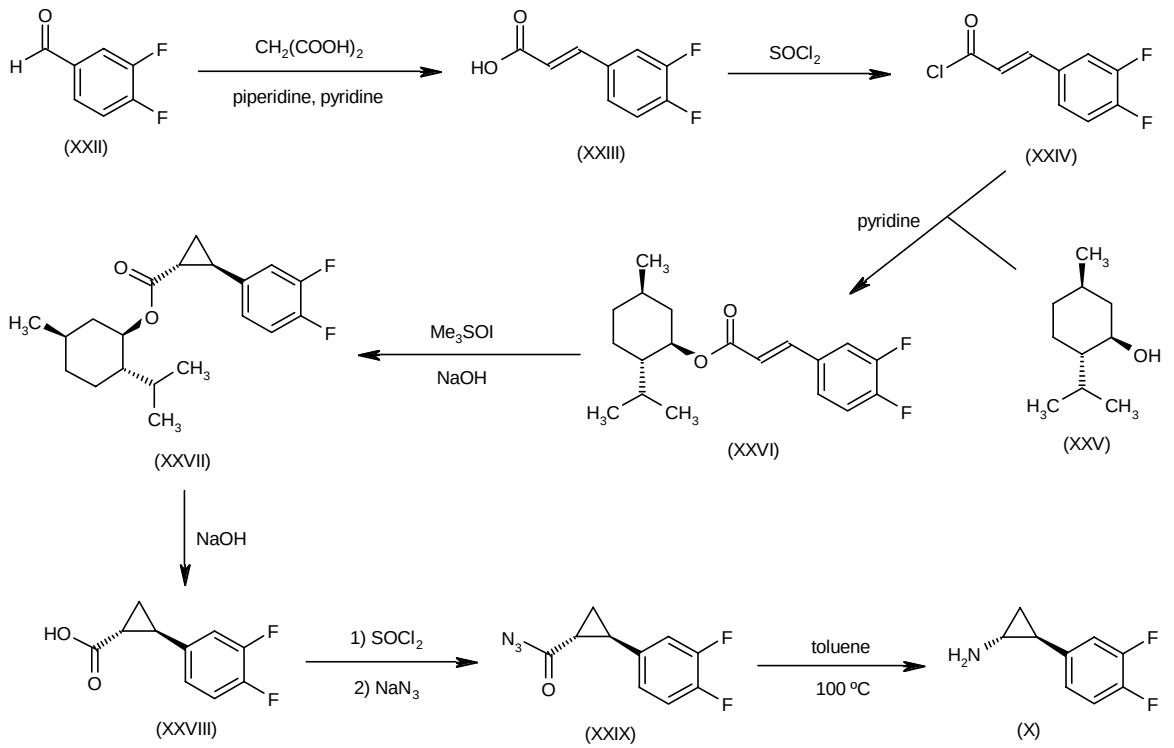
Scheme 2: Synthesis of AZD6140



acetic acid. Then, substitution of chloride (XXI) with 2-(3,4-difluorophenyl)cyclopropylamine (X) in the presence of triethylamine in acetonitrile affords the acetonide (XII), which is finally hydrolyzed to the title compound as in the above method (3). Scheme 2.

The cyclopropylamine building block (X) is obtained as follows. Knoevenagel condensation of 3,4-difluorobenzaldehyde (XXII) with malonic acid in the presence of piperidine in hot pyridine produces 3,4-difluorocinnamic acid (XXIII). After conversion of (XXIII) to the corresponding acid chloride (XXIV) by means of $SOCl_2$, condensation with L-menthol (XXV) provides the menthyl difluorocinnamate (XXVI). Cyclopropanation of (XXVI) employing dimethylsulfoxonium methylide (generated

Scheme 3: Synthesis of Intermediate (X)



from trimethylsulfoxonium iodide and NaOH in DMSO) gives the cyclopropanecarboxylate ester (XXVII), which is hydrolyzed to the carboxylic acid (XXVIII) by means of NaOH in aqueous ethanol. Subsequent chlorination of acid (XXVIII) followed by treatment with aqueous NaN_3 in the presence of Na_2CO_3 and Bu_4NBr yields the acyl azide (XXIX), which is converted to the target amine (X) by Curtius rearrangement in hot toluene (3). Scheme 3.

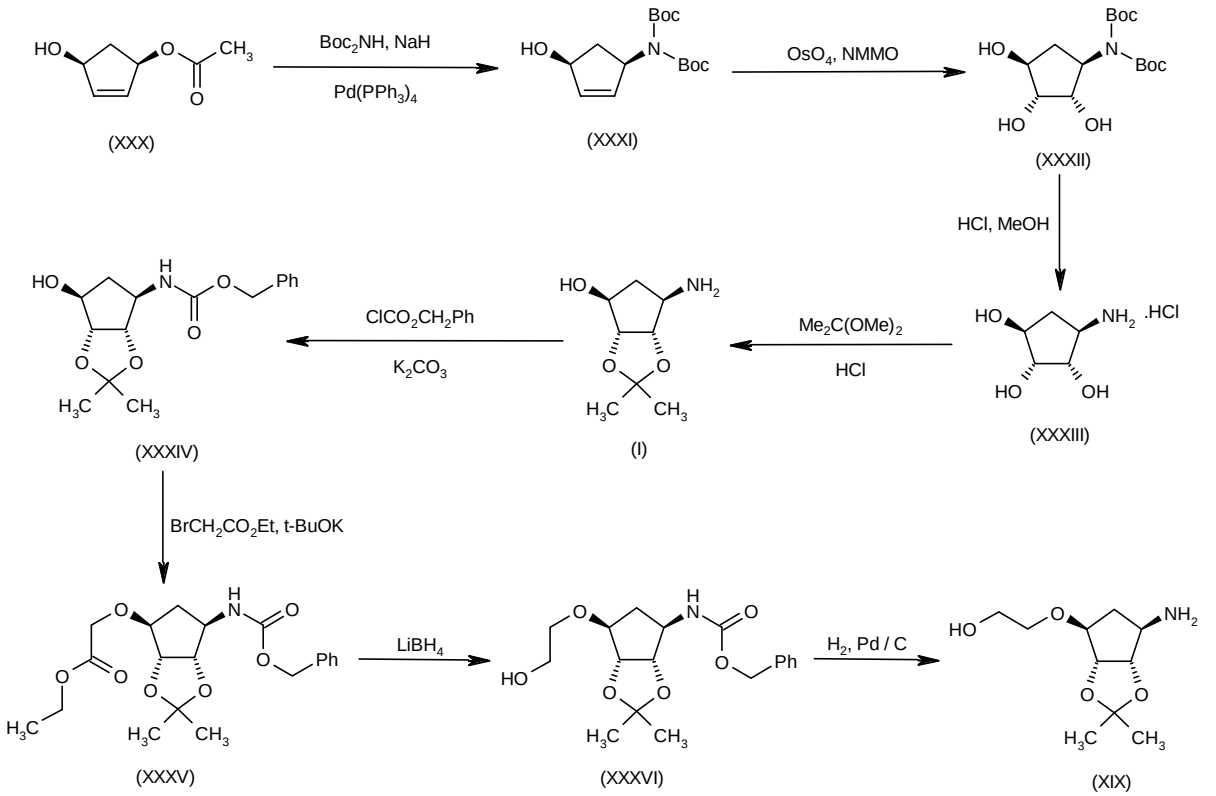
The preparation of the cyclopentylamino intermediates (I) and (XIX) is shown in Scheme 4. Reaction of (1*S*,4*R*)-4-acetoxy-2-cyclopentenol (XXX) with di-*tert*-butyl iminodicarboxylate in the presence of NaH and $Pd(PPh_3)_4$ produces the di-Boc-protected aminocyclopentenol (XXXI), which undergoes dihydroxylation to triol (XXXII) by means of *N*-methylmorpholine *N*-oxide and a catalytic amount of osmium tetroxide. After acidic deprotection of the di-Boc derivative (XXXII), the resulting amino triol (XXXIII) is converted to the key acetonide (I) upon heating with 2,2-dimethoxypropane and catalytic HCl in acetone (1, 2). The *O*-hydroxyethyl derivative (XIX) is prepared by protection of aminoalcohol (I) as the benzyl carbamate (XXXIV), followed by *O*-alkylation with ethyl bromoacetate and potassium *tert*-butoxide to give (XXXV). Subsequent reduction of ester (XXXV) with $LiBH_4$ in THF furnishes the corresponding hydroxyethyl derivative (XXXVI), from which the *N*-(benzyloxycarbonyl) group is removed by catalytic hydrogenation over Pd/C (3). Scheme 4.

Background

Oral antiplatelet agents have become the mainstay of pharmacotherapy for the prevention of atherosclerosis progression and acute thromboembolic events such as myocardial infarction (MI) and ischemic stroke (4). Aspirin and thienopyridines (*e.g.*, clopidogrel and ticlopidine) reduce the risk of these events when used as daily therapy. The risk reduction is even greater when aspirin and a thienopyridine are taken in combination (5, 6) due to the complementary mechanisms of action of the drugs: aspirin blocks the action of cyclooxygenase to decrease thromboxane A_2 (TxA_2) production, and the thienopyridines bind to the platelet purinergic receptor $P2Y_{12}$, a well-established target for the inhibition of ADP-mediated platelet aggregation (7).

Nevertheless, the management of atherosclerotic disease remains less than ideal, despite the availability of safe and effective antiplatelet drugs. Even with daily treatment, many patients continue to experience acute thrombotic events (8). There have also been reports of resistance to aspirin and clopidogrel, as well as substantial interpatient variability in response (9-11). Moreover, the thienopyridines have a number of drawbacks specific to the class. First, they are prodrugs requiring hepatic conversion to the bioactive metabolite, which may limit their effectiveness when used with competing drugs. Second,

Scheme 4: Synthesis of Intermediates (I) and (XIX)



thienopyridines bind irreversibly to the $P2Y_{12}$ receptor, which can permanently inactivate the platelet, raising concerns in patients who require immediate surgery. Third, these drugs produce only a modest mean platelet inhibition (30-40% or less), leading to moderate ADP-induced aggregation and the risk of recurrent ischemia following percutaneous coronary intervention (PCI), as well as stent thrombosis (12, 13). The inhibition of ADP-induced platelet aggregation *ex vivo* is only modest as well. Fourth, clopidogrel and ticlopidine are associated with a number of important adverse events (AEs), including thrombotic thrombocytopenic purpura and neutropenia (14). For these reasons, new treatment options are necessary.

The oral, reversible $P2Y_{12}$ receptor antagonist AZD6140 is currently in clinical development for reducing the risk of thromboembolic events in patients with atherosclerosis. The first in a new class of compounds, the cyclopentyltriazolopyrimidines, AZD6140 binds to the platelet $P2Y_{12}$ receptor to inhibit the ischemic effects of ADP. However, the drug differs from the thienopyridines in its reversible binding mechanism, nearly complete inhibition of the platelet aggregation response to ADP *ex vivo* and the ability to produce a less variable response in patients (15). Based on these characteristics, AZD6140 has the potential to overcome the limitations of available antiplatelet therapies.

Preclinical Pharmacology

Unlike the thienopyridines, AZD6140 is not a prodrug and it therefore does not require metabolic activation (16). Its sole known active metabolite (AR-C126910) reaches serum levels about 30% those of the parent molecule. This metabolite is also a potent inhibitor of the $P2Y_{12}$ receptor and may contribute to the antiplatelet action of AZD6140 (15). *In vitro* studies demonstrated that both molecules have no significant affinity for other P2 receptors, even at concentrations above 3 μM (17). These studies also showed that AZD6140 is a potent inhibitor of ADP-induced platelet function, giving pIC_{50} values of 7.9 and 7.2 in the washed platelet and diluted whole blood impedance aggregometry assays, respectively.

The ability of AZD6140 to modulate the platelet response was investigated in multiple animal models. The drug was absorbed quickly and rapidly inhibited platelet reactivity, suppressed platelet aggregation over 24 h and attenuated platelet adhesion on isolated fibrinogen under arterial shear conditions in diabetic rats (18). AZD6140 also reduced thrombus formation in a murine laser injury

model to levels similar to those seen in $P2Y_{12}$ knockout mice (19). Administration of AZD6140 to $P2Y_{12}^{-/-}$ mice produced no further thrombus inhibition, demonstrating selective suppression of the $P2Y_{12}$ receptor. Finally, in a canine model of arterial thrombosis comparing AZD6140, clopidogrel and the gpIIb/IIIa inhibitor orbofiban, van Giezen and Humphries demonstrated that at 90% inhibition of the thrombotic response clopidogrel induced a 120% increase in bleeding (17). In contrast, the rate of increase with AZD6140 was only 40%. Similar results were reported using both rat and dog models of combined thrombosis and hemostasis (20).

Platelet $P2Y_{12}$ receptors are found on vascular smooth muscle cells (VSMC), where they mediate vasoconstriction following stimulation by ADP. Wihlborg and colleagues showed that clopidogrel is unable to block VSMC contraction, perhaps because the drug's highly unstable active metabolite does not circulate systemically (21). In contrast, AZD6140 blocked ADP-induced VSMC constriction mediated by $P2Y_{12}$ receptors in denuded mouse aortic rings, even following pretreatment with clopidogrel (22). Untreated and clopidogrel-pretreated control groups showed maximal contraction values of 59% and 64%, respectively. After exposure to AZD6140, the contraction was reduced significantly to 33% ($p = 0.15$) and 32% ($p = 0.002$), respectively. This finding suggests that AZD6140 may modulate ADP-induced vasoreactivity, although the clinical relevance of this activity remains to be established.

Pharmacokinetics and Metabolism

The pharmacokinetic and pharmacodynamic parameters of AZD6140 were investigated in 13 healthy volunteers who received ascending single doses ranging from 30 to 400 mg daily (16). Multiple blood samples of AZD6140 and its active metabolite were collected over a 36-h period and assayed to determine ADP-stimulated platelet aggregation. The drug was rapidly absorbed and showed linear, dose-dependent pharmacokinetics that were best fit by a two-compartment open model. The inhibition of platelet aggregation was dose- and time-dependent, with the highest levels of inhibition recorded for the once-daily doses of 300 and 400 mg. The effect was maintained over a period of 24 h.

A subsequent parallel-group study in healthy volunteers compared ascending once- or twice-daily doses of AZD6140 with clopidogrel or placebo (23). Group A received increasing doses of 50, 100 and 200 mg once daily (n=7) or twice daily (n=7); in group B, AZD6140 was administered at doses of 200, 300, 400 and 600 mg once daily (n=7) or twice daily (n=7). Group C patients received a 300-mg loading dose of clopidogrel, followed by a 75-mg maintenance regimen (n=14), or placebo (n=2). Each dose was followed by a 5-day washout period and the total treatment period was 14-20 days. Plasma levels of AZD6140 peaked at 1.5-3.0 h after dosing, reaching steady-state levels after 2-3 days. The mean elimination half-life ranged from 6 to 13 h across the various dosing groups. Daily doses at or above 100 mg twice daily and 300 mg once daily provided superior mean platelet inhibition with less variability compared to clopidogrel, with the dose of 300 mg twice daily producing maximum inhibition of 97-100% throughout the dosing interval. In both studies, the compound was well tolerated, and no serious or dose-related AEs were reported. In general, the incidence of side effects was comparable to clopidogrel.

Clinical Studies

In the multinational phase IIa DISPERSE (Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 Versus Clopidogrel in NSTEMI) trial, 200 patients with stable atherosclerotic disease were randomized to receive different doses of AZD6140 (50, 100 or 200 mg twice daily or 400 mg once daily) or clopidogrel (75 mg once daily) plus aspirin (75-100 mg once daily) for 28 days (24). At doses at or above 100 mg twice daily, AZD6140 exhibited more rapid, consistent and greater inhibition of platelet aggregation compared to clopidogrel (90% *vs.* 60%) (Table I). The drug was well tolerated overall. All bleeding events were minor to moderate in severity, except for 1 major hemorrhagic event that occurred in a patient receiving a once-daily dose of 400 mg AZD6140. There also was a dose-dependent increase in dyspnea in AZD6140 patients (10% in the groups receiving 50 and 100 mg twice daily, 16% in the group receiving 200 mg twice daily and 20% in the group receiving 400 mg once daily). None of these cases was serious or associated with heart failure or bronchospasm. An increase in the rate of discontinuations due to AEs was dose-related as well, increasing from 2.5% to 8.6% from 50 mg twice daily to 400 mg once daily AZD6140 compared to 2.7% with clopidogrel. In summary, the DISPERSE trial demonstrated that AZD6140 was well tolerated and provided a rapid onset of action beginning on day 1 and greater and more consistent platelet suppression throughout treatment compared with clopidogrel in patients with atherosclerosis.

A second phase IIb trial (DISPERSE2) randomized 990 patients from 14 countries with non-ST segment elevation acute coronary syndromes (NSTE-ACS) to receive AZD6140 (90 or 180 mg twice daily) or clopidogrel (300-mg loading dose plus 75 mg once daily) for 12 weeks (25). Half of the AZD6140 cohort received a 270-mg loading dose, and all patients took 75-100 mg of aspirin a day. The primary trial investigated the safety and tolerability of AZD6140 (Table II). Compared with clopidogrel, the adjudicated total bleeding rates (based on age, gender, weight and prior clopidogrel use) for doses of AZD6140 of 90 and 180 mg twice daily were similar: 6.2%, 8% and 7.8%, respectively, for AZD6140 90 and 180 mg and clopidogrel. However, a *post hoc* analysis found slightly more dose-related minor bleeding events in the AZD6140 groups (26). The drug was generally well tolerated, with similar rates of discontinuation (6%, 7% and 6%, respectively, for AZD6140 90 and 180 mg and clopidogrel).

Table I: Key outcomes of a phase IIa trial of AZD6140 (DISPERSE) (data from Refs. 15 and 24).

Indication	Study design	Treatments*	n	% Mean peak inhibition of ADP-induced platelet aggregation (final extent)		Median difference (%) between AZD6140 and clopidogrel for % inhibition of ADP-induced platelet aggregation (final extent)	
				Day 1	Day 28**	Day 14+	Day 28+
Stable atherosclerosis	Randomized Double-blind Double-dummy Multicenter	AZD6140, 50 mg b.i.d.	41	65++	71	7	13
		AZD6140, 100 mg b.i.d.	39	85++	88	23	25
		AZD6140, 200 mg b.i.d.	37	90++	93	25	30
		AZD6140, 400 mg o.d.	46	96**	95	29	31
	Active-controlled	Clopidogrel, 75 mg o.d.	37	< 20	60	n/a	n/a

*All patients received aspirin 75-100 mg once daily maintained at a stable dose for a given patient. **Data from Ref. 24. +n values for AZD6140 groups vary from 68 to 81 as calculation combines n values from AZD6140 and clopidogrel groups. ++Estimated from Figure 2 in Ref 15. n/a: not applicable.

Table II: Key outcomes from the phase IIb DISPERSE2 trial of AZD6140 (data from Ref. 25 poster).

Indication	Design	Treatment*	n	Adjudicated major and minor bleeding rate (%)		MI (%)	Stroke (%)	Recurrent ischemia (%)	Death (%)
				Week 4	Overall				
NSTE-ACS	Randomized Double-blind Parallel-group Multicenter	AZD6140, 90 mg b.i.d.	334	9.5	10.2	2.7	0.6	3.8	2.1
		AZD6140, 180 mg b.i.d.	323	7.7	10.2	2.1	0.0	2.7	1.8
		Clopidogrel, 75 mg o.d.	327	8.0	9.2	4.3	0.3	2.8	1.2

NSTE-ACS: Non-ST segment elevation acute coronary syndrome; MI: myocardial infarction. *All patients also received aspirin up to 325 mg for the first dose, then 75-100 mg once daily, maintained at a stable dose for each patient, and heparin/low-molecular-weight heparin (LMWH) and/or gpIIb/IIIa inhibitors. Half the patients in each AZD6140 group received a 270-mg loading dose of AZD6140. The clopidogrel patients received a loading dose of 300 mg clopidogrel followed by a 75-mg maintenance dose for 12 weeks.

Dyspnea was also more common in patients receiving AZD6140 compared to clopidogrel-treated subjects (10.5% and 15.8%, respectively, in the 90- and 180-mg AZD6140 groups *vs.* 6.4% on clopidogrel).

DISPERSE2 also assessed clinical outcomes, including the incidence of MI, a composite endpoint of all-cause death, cardiovascular death, stroke, severe recurrent ischemia and recurrent ischemia, and *ex vivo* platelet inhibition (27). AZD6140, especially the 180-mg dose, was associated with a decrease in MI: 3.6%, 2.5% and 4.6%, respectively, for AZD6140 90 and 180 mg and clopidogrel. The group treated with the higher dose of AZD6140 also had a lower incidence of the composite event endpoint relative to the lower dose of AZD6140 and clopidogrel, which was largely due to the reduced rate of MI. As the number of clinical events was low during the trial, the incidence of individual events did not differ between the groups. Finally, DISPERSE2 compared plasma concentrations of inflammatory markers (C-reactive protein, CD40 ligand, myeloperoxidase and interleukin-6) for the three treatment groups at baseline, discharge and at week 4 (28). There was little change from baseline and no apparent differences between the AZD6140 and clopidogrel cohorts, suggesting that the clinical benefit of $P2Y_{12}$ inhibition involves antithrombotic rather than antiinflammatory mechanisms.

Several substudies of DISPERSE2 examined the effects of AZD6140 on the suppression of platelet aggregation in treatment-naïve patients with ACS and those who previously received clopidogrel (29, 30). In those subjects who had not taken clopidogrel prior to enrollment, AZD6140 showed more rapid, consistent and superior inhibition of platelet aggregation (63% and 70%, respectively, at doses of 90 and 180 mg *vs.* 28% for clopidogrel). Moreover, patients currently taking clopidogrel experienced rapid and additional suppression of platelet aggregation following the introduction of AZD6140 therapy. Of note is the finding that clopidogrel pretreatment did not affect either the time course or values of AZD6140 plasma concentrations.

An unexpected finding of both DISPERSE trials was the high frequency of dyspnea in patients receiving AZD6140. Reviewing the safety literature for antiplatelet therapies, Serebruany and colleagues reported that dyspnea is a rare complication of currently available drugs, most likely a consequence of an underlying condition (*e.g.*, heart failure or coronary artery disease) rather than the treatment itself (31). They offered two possible explanations for the DISPERSE results: 1) the reversible binding mechanism of AZD6140 may damage the platelets, leading to the development of mild asymptomatic thrombotic thrombocytopenic purpura, fluid retention and dysp-

nea; and 2) AZD6140 is an ATP analogue and adenosine is a well-documented bronchial irritant that can cause bronchoconstriction, respiratory distress and dyspnea.

There are several problems with these hypotheses (32). First, thrombocytopenia has not been observed in any of the cases of dyspnea observed to date, so it is unlikely that thrombotic thrombocytopenic purpura is a possible mechanism. Moreover, reversible blockade of the $P2Y_{12}$ receptor would be far less likely to cause platelet damage than would the covalent binding of the thienopyridine active metabolite to the receptor; in fact, the latter process has a much greater potential to cause structural damage. Second, AZD6140 is not a true ATP analogue, as the compound lacks the triphosphate moiety. Moreover, adenosine is not one of its measured metabolites, and those metabolites do not possess any adenosine-like properties. Additional research will be necessary to clarify the nature of the relationship between AZD6140 and dyspnea.

It is important to emphasize that the dyspnea AEs observed with AZD6140 were not considered serious. Most cases did not prompt further diagnostic evaluation and, as noted previously, were not believed to be related to either heart failure or bronchospasm (15). Only 1 patient discontinued therapy. Additional studies are now investigating the frequency and etiology of this complication.

Conclusions

AZD6140 is an oral, selective, reversible $P2Y_{12}$ receptor antagonist that does not require metabolic conversion to produce its platelet antiaggregant effects. Its pharmacokinetic profile is characterized by rapid absorption and approximately dose-proportional increases in plasma concentrations. AZD6140 is a more potent and consistent inhibitor of ADP-induced platelet aggregation than clopidogrel, regardless of prior antiplatelet drug exposure and the baseline degree of platelet inhibition. The early and consistent antiplatelet effect could prove advantageous prior to PCI, when superior and predictable platelet suppression could improve clinical outcomes. Also, reversible $P2Y_{12}$ binding may benefit cardiovascular and other surgery patients at risk for excessive bleeding from current irreversible antiplatelet drugs (33).

Overall, the combined rates of major and minor bleeding events were comparable for AZD6140 and clopidogrel, despite the greater platelet inhibition produced by the former agent, and were not affected by such demographic characteristics as age, gender, weight or clopidogrel pretreatment. Important clinical outcomes such as stroke, recurrent ischemia or cardiovascular deaths were low and similar in clopidogrel and AZD6140 patients with NSTE-ACS, although the rate of MI was half that of clopidogrel in the group treated with AZD6140 180 mg twice daily (2.1% *vs.* 4.3%). Further work in larger trials will document the potential therapeutic benefits of AZD6140. One such study, a phase III trial called PLATO (PLATelet Inhibition and Patient Outcomes) will compare AZD6140 (90 mg twice daily) and clopidogrel (both with adjuvant aspirin therapy) for the prevention of vascular death, MI and stroke in patients with unstable angina, non-ST or ST segment elevation acute coronary syndrome (34). Among other objectives, PLATO will provide strong evidence to evaluate whether platelet function holds the key to the development of post-MI thrombotic events.

Several outstanding issues remain to be resolved. Despite its limited clinical impact, the association between AZD6140 and dyspnea requires further exploration. More research will also be necessary to establish whether the reversibility of antiplatelet effect or the mediation of vasoconstriction in VSMC confers a therapeutic advantage. If these matters can be resolved favorably and the drug's efficacy demonstrated, AZD6140 may offer clinicians a superior approach to the treatment of atherothrombotic diseases.

Source

AstraZeneca (GB).

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