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Parallel Solid-Phase Synthesis of Zatebradine Analogues as Potential I_f Channel Blockers

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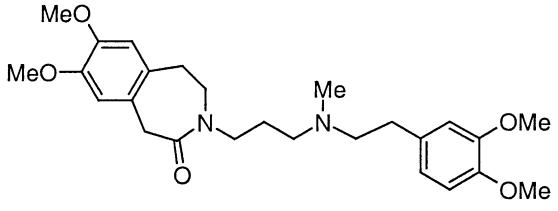
Abstract—The first solid-phase synthesis of zatebradine **1** and its analogues is reported. This has resulted in the preparation of compounds with increased ability to reduce the spontaneous beating of isolated guinea-pig atria in a concentration-dependent manner. One example, **8g**, showed a maximum reduction of beating of 80% at 3 μM compared to a reduction of 40% at 3 μM with zatebradine **1**.

Channel-mediated currents, consisting of small background currents such as I_{K1}, I_B and I_f and large voltage-gated currents such as I_{ca} and $I_{K,}$ play an important role in the generation of spontaneous diastolic depolarisation and action potential of cardiac pacemaking cells.[1,2] They can contribute to changes in spontaneous pacemaker activity, affecting slow diastolic depolarisation and hence threshold potential for action potential generation and resting potential of pacemaker cells. Selective reduction in heart rate with no important changes in contractility and wall tension, may have several advantages in the treatment of ischaemic heart diseases.[3] A slower heart rate would increase the diastolic perfusion time, thus increasing coronary perfusion and contractile function, and reduce the oxygen requirements of the myocardium.[3]

Zatebradine **1** is a representative compound of the therapeutic class of sino-atrial node modulators which has been shown to inhibit the hyperpolarisation-activated current I_f.[3–5] Selective blockade of the I_f current causes a slowing down of the spontaneous rate of firing of the pacemaker cells without resulting in abolition of pacemaker activity.[6]



Zatebradine **1**

The synthesis of zatebradine analogues **8** and **9** is outlined below (Scheme 1).

Amines **3a–g** were attached to REM resin[7] by Michael addition to give the resin-bound secondary amines **4a–g**. Attempted alkylation of **4a–g** with *N*-chloro- or *N*-bromopropylbenzazepinone under a variety of conditions did not afford the desired products after cleavage from the resin. Optimum conditions for alkylation were found to be using *N*-iodopropylbenzazepinone **5** in dimethylformamide DMF at 50 °C in the presence of diisopropylethylamine (DIPEA).[8] The resultant tertiary amine **6** was quaternised with activated alkyl halides and the resin-bound quaternary salt **7** subsequently treated with DIPEA to liberate the dehydrozatebradine analogues **8**. Products were purified by solid-phase extraction (silica cartridges with dichloromethane–2% ammonia saturated methanol as eluent). Subsequent cleavage from the resin followed by hydrogenation afforded the zatebradine analogues **9**.[4]

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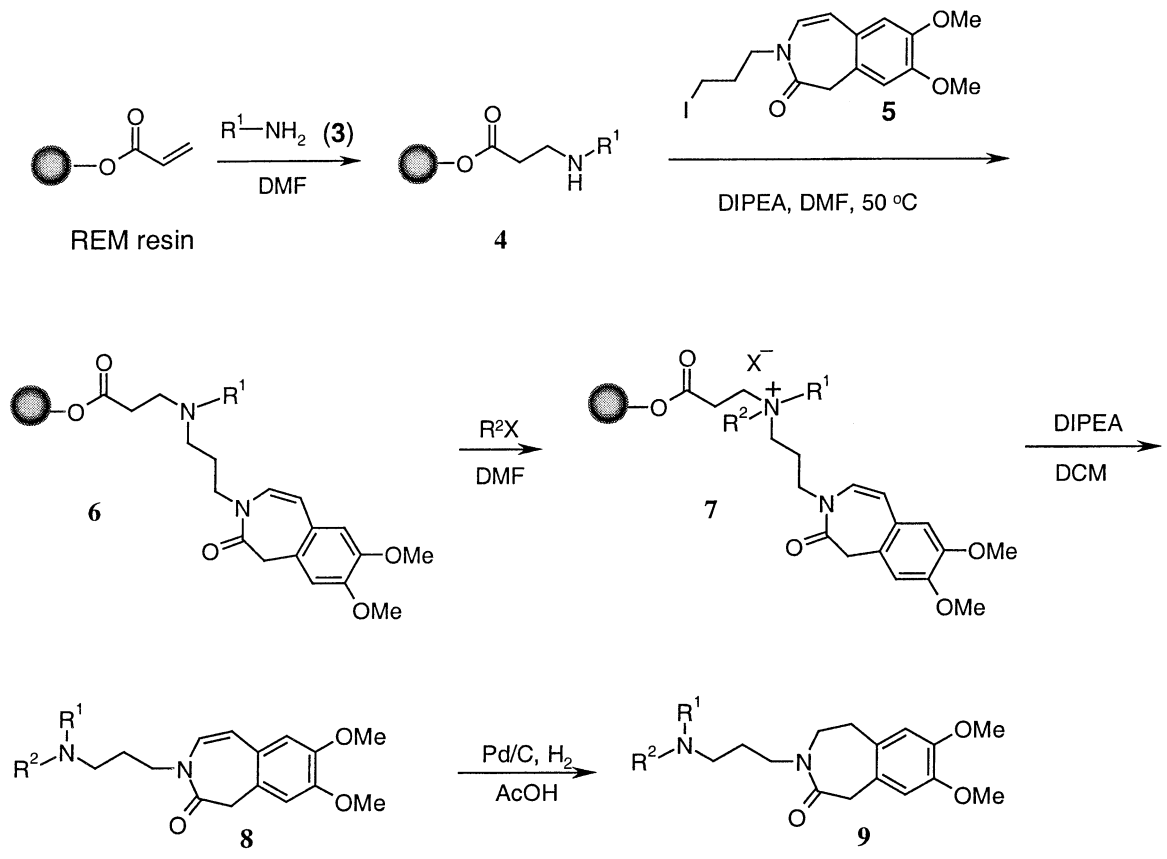


Scheme 1.

Preliminary biological data suggested that the dehydrozatebradine analogues **8** also inhibited the I_f current to a similar degree as zatebradine itself. It was, therefore, decided to prepare a library of 21 compounds comprising of seven different amines at R^1 and three different alkyl halides at R^2 (Table 1).

The effects of dehydrozatebradine analogues **8a**–**o** on the rate of beating were studied in isolated guinea-pig atria. The potency and efficacy data are summarised and compared to zatebradine in Table 2. Eight compounds (**8b**, **e**, **g**, **h**, **j**, **k**, **l** and **n**) showed a stronger inhibition, four compounds (**8a**, **c**, **f** and **m**) were similar, whilst three (**8d**, **i** and **o**) were less effective than zatebradine at 3 μM. There is no conclusive structure–activity relationship which can be drawn from the data, as the experimental method does not differentiate between the blockade of the I_f channel and blockade of the L-type calcium channel. Compounds that block both channels will show a stronger inhibition than compounds that act at one single channel. To differentiate between the two mechanisms, vascular preparations that lack the I_f channel but retain the L-type calcium channel will be needed

A solid-phase synthesis of zatebradine and its analogues has been developed allowing the rapid synthesis of a 21-compound library. This has resulted in the discovery of a series of compounds with increased ability to reduce the spontaneous beating of isolated guinea-pig atria. Further studies are needed to study the putative actions on calcium channels.

Table 1. Library building blocks

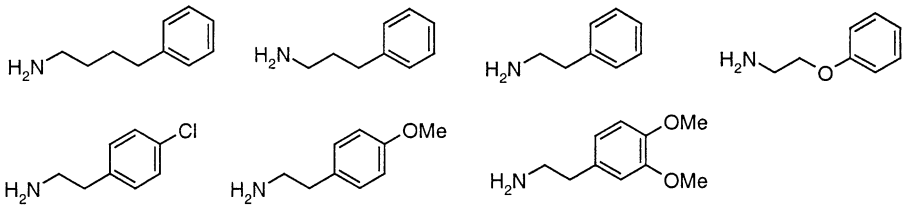
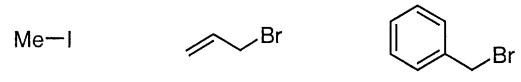
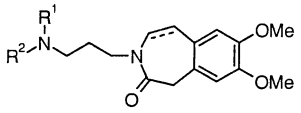
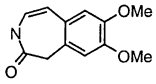
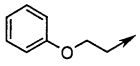
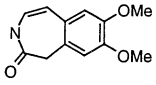
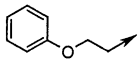
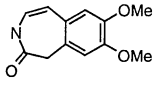
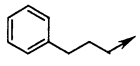
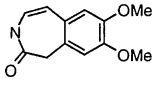
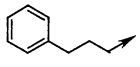
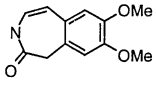
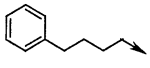
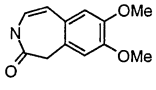
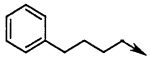
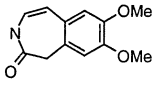
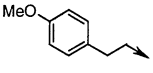
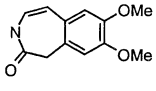
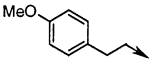
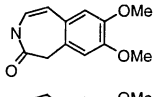
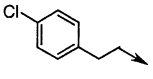
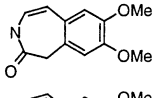
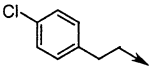
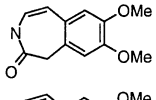
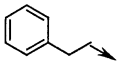
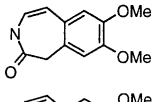
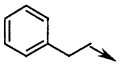
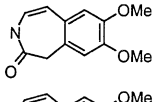
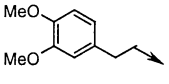
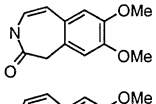
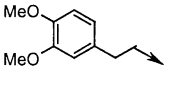
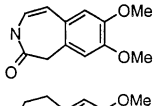
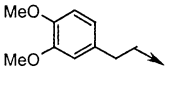
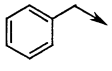
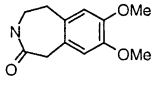
R^1-NH_2 (**3**)	
R^2-X	

Table 2. Effects of amines on beating rate



		R^1	R^2	Beating rate[9]	
				% inhibition at 3 μM	Max. inhibition
8a				42±11	100±0
8b				53±0	80±6
8c				44±27	100±0
8d				31±1	60±2
8e				54±3	91±9
8f				43±11	84±16
8g				80±2	81±2
8h				60±1	69±4
8i				31±1	60±2
8j				60±2	68±7
8k				53±6	71±1
8l				60±12	81±2
8m				34±12	69±13
8n				59±17	77±8
8o				25±1	59±4
1				40±10	68±1

Mean±SEM; $n=2$.

Acknowledgements

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References and Notes

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7. Brown, A.; Rees, D. C.; Rankovic, Z.; Morphy, J. R. *J. Am. Chem. Soc.* **1997**, *119*, 3288.
8. *N*-Chloropropylbenzazepinone was prepared according to the procedure outlined in ref 4. It was converted to *N*-iodopropylbenzazepinone by heating with sodium iodide (5 mol equiv) in acetone under reflux for 12 h.
9. Male Dunkin–Hartley guinea pigs (Harlan) of 250–300 g were used throughout. Guinea pigs were killed by cervical dislocation, the thorax opened and the right atria removed. Atria were suspended on tissue holders in 30 mL organ baths containing Krebs solution, maintained at 37 °C and gassed with 95% O_2 and 5% CO_2. The composition of Krebs was (mM) NaCl (118), KCl (5.3), $MgSO_4 \cdot 7H_2O$ (0.85), KH_2PO_4 (1.2), $NaHCO_3$ (2.5), glucose (11.7) and $CaCl_2$ (2.5). Atria were left for approximately 1 h to equilibriate. Resting force was set between 1 and 2 g and was readjusted during the equilibrium period, which lasted 60–70 min. This was followed by the constriction of a cumulative concentration–response curve (CCRC). Every 10 min, concentrations were increased with half-log unit intervals. At the end of the CCRC, the drugs were washed out and after 30 min the viability of the preparation was tested with 0.1 μm (±)-isoprenaline. All preparations responded to (±)-isoprenaline with an increase in spontaneous beating rate. Force was measured by Grass Force Displacement Transducers (FT03) and recorded on a two-channel Gould recorder with transducer and ECG/Biotach amplifiers. Experiments were carried out in duplicate.