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5-HT_{2C} Receptor Agonists for the Treatment of Obesity. Biological and Chemical Adventures

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Abstract: Obesity is a major risk factor in the development of conditions such as hypertension, hyperglycemia, dyslipidemia, coronary artery disease and cancer. There is increasing evidence suggesting an important role for the 5-HT_{2C} receptor in appetite control. Collaboration between *F. Hoffmann-La Roche Ltd* and *Vernalis Research Ltd* has allowed rapid construction of a solid structure–activity relationship around a pyrroloindole core. A one-pot Sonogashira reaction followed by nucleophilic double cyclisation allows an elegant and expedient route to this central motif. Introduction of a (*2S*)-aminopropyl group in place of the aminoethyl endogenous ligand side-chain enhanced the affinity at the 5-HT_{2C} receptor and reduced affinity towards monoamine oxidase enzymes (MAO). Sulfamidate reagents were found to be very effective for the introduction of the 2-aminopropyl moiety in a stereoselective manner. The substitution at position 5 (indole numbering) was found to be crucial for both affinity and selectivity. Pyrroloindoles bearing an alkoxyether in this position exhibit promising pharmacokinetic parameters in rodent and significant reduction of food intake, after *per os* application.

Keywords: Obesity · Pyrroloindole · 5-HT_{2C} Receptor agonist · Sulfamidate

1. Introduction

The healthcare burden that the obesity epidemic now poses is highly significant [1]. In 1997, the World Health Organisation (WHO) officially declared human obesity to be one of the most significant health problems facing mankind. This declaration followed the massive expansion in the prevalence of obesity in almost all societies. In the United States of America (USA), for example, the prevalence of obesity trebled during the past 25 years [2].

Obesity is a major risk factor in the development of conditions such as hypertension, hyperglycemia, dyslipidemia, coronary artery disease, and cancer (Fig. 1) [3][4].

The two main causes for the global rise in prevalence of obesity are increasingly sedentary lifestyles and high-fat, energy rich diets.

1.1. *Scale of the Problem*

The WHO has standardised its classification using the Body Mass Index (BMI; weight [kg]/(height [m]^2) as an indicator of obesity. A person is now considered overweight with a BMI >25 and considered obese with a BMI >30. For example, using this measure, 55% of adults in the USA are overweight or obese.

The total cost in the USA for all obesity-related health problems exceeds $200 billion. More alarmingly, each year 300,000 people die prematurely in the USA from obesity-related complications.

Obviously, there is a tremendous need for efficient therapies. Conservative estimates for the obesity drug market in the USA are *ca.* $5 billion by the year 2005 [5].

1.2. *Existing Treatments*

Broadly speaking, drugs are classified by their principal mechanism of action on the energy balance. When energy intake (food intake) exceeds expenditure, a state of positive balance exists and *vice versa*. In a state of negative energy balance, weight loss ensues. Anti-obesity drugs are designed with the goal to induce a state of negative energy balance until the required weight loss is reached. Anti-obesity drugs effectively fall into four categories:

– Appetite suppressants: inhibit energy intake which act on the central nervous system (CNS) to reduce the feeling of hunger.
– Inhibitors of fat absorption: reduce energy intake and act peripherally.
– Enhancers of energy expenditure: increase thermogenesis/energy expenditure independently of physical activity and act peripherally.
– Stimulation of fat mobilisation: reduce fat mass and triglyceride synthesis, inde-

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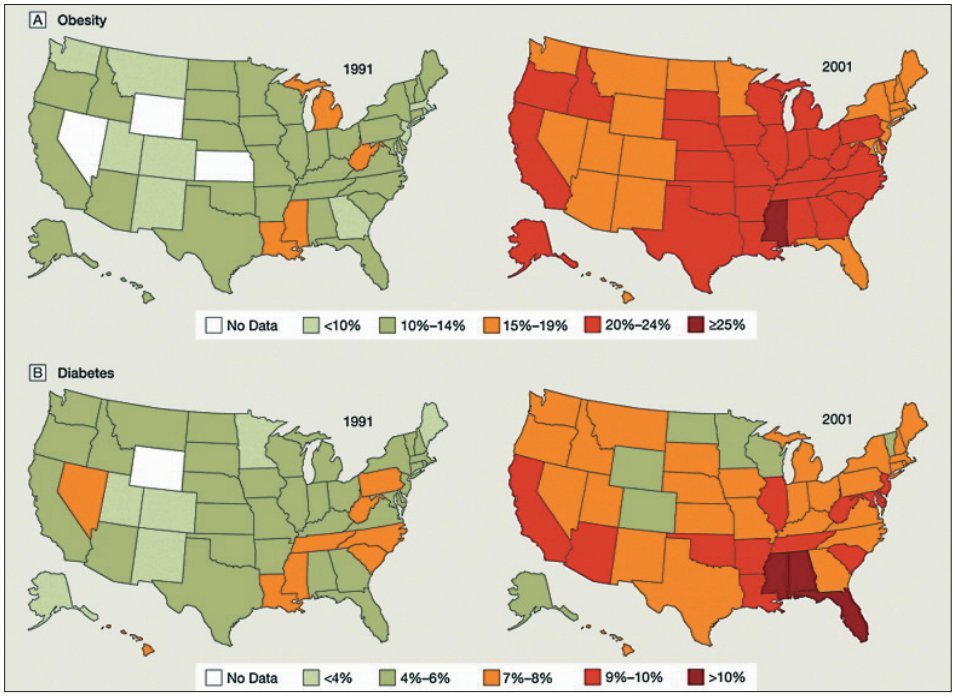


Fig. 1. Prevalence of obesity and diabetes among US adults. Copyright: A.H. Mokdad, E.S. Ford, B.A. Bowman, W.H. Dietz, F. Vinicor, V.S. Bales, J.S. Marks, *J. Am. Med. Asso.* **2003**, *289*, 76.

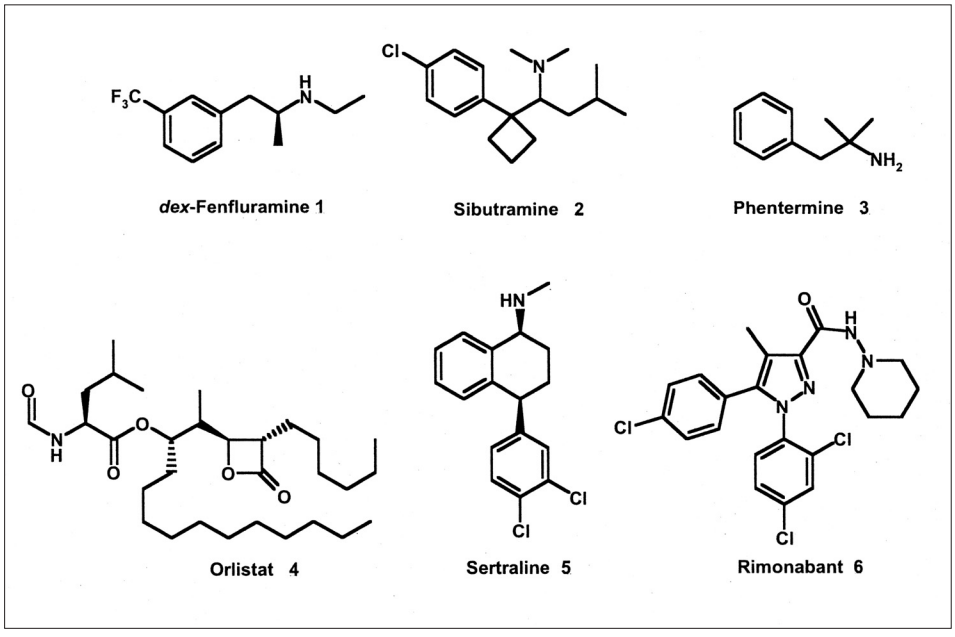


Fig. 2.

pendently of changes in food intake and exercise regimes and act peripherally.

After the withdrawal of *dex*-fenfluramine **1** (Serotonin Re-uptake Inhibitor/5-HT releaser, Servier) in 1999, only three drugs are currently approved for the treatment of obesity: Sibutramine (**2**, Serotonin-Noradrenaline-Dopamine Re-uptake Inhibitor -SNRI-, Abbott), Phentermine (**3**, Noradrenergic, generic, USA-market only), and Orlistat (**4**, Lipase inhibitor, Roche) exemplifying how difficult it is to tackle this pandemic (Fig. 2).

Additional drugs have entered clinical trials and may reach the market in the next two years. Phase III clinical trials are ongoing to evaluate the potential of Sertraline (**5**, Selective Serotonin Re-uptake inhibitor -SSRI-, Pfizer) as anorectic. This drug is already widely marketed for depression, obsessive compulsive disorder (OCD) and anxiety (Zoloft®). Axokine® (Recombinant human Ciliary Neurotrophic Factor -CNTF-, Regeneron) and Rimonabant (**6**, CB-1 receptor inverse agonist, Sanofi-Synthelabo), specifically designed to treat obesity, are currently also in Phase III clinical trials [2].

A specific aspect in the medication of obesity is the discrepancy between patient expectation of up to 30% body weight loss in the first year, possibly without dieting, and current therapy performance of typically 5% body weight loss over the same period of time, with specific diet (compared to a placebo group under the same diet).

This huge difference in expectation is hampering patient compliance. Therefore even minor side effects can become critical.

The limited efficacy might be due to redundancies and compensatory effects in the mechanism regulating energy intake. Combination therapies, such as co-administration of a lipase inhibitor and an appetite suppressant might be the key to achieve high efficacy by synergistic or simply additive effect.

1.3. *Obesity and 5-HT$_{2C}$ Receptor Agonists*

5-Hydroxytryptamine (Serotonin, 5-HT, **7**) is a major neurotransmitter in the mammalian CNS, mediating a diverse range of actions. Of the 14 mammalian serotonin receptor subtypes, all but one (5-HT$_3$) belong to the super-family of G-protein-coupled receptors (GPCRs) [6]. The 5-HT$_2$ receptor family consists of 3 subtypes (2A, 2B, and 2C), which have been grouped together on the basis of primary structure, secondary messenger system and pharmacological profile [3]. Increasing evidence suggest an important role for Serotonin (5-HT) and the 5-HT$_{2C}$ receptor in appetite control, besides other clinical indications including anxiety, depression, OCD, migraine, sleep, epilepsy and schizophrenia [7–9].

The non-selective 5-HT$_{2C}$ receptor agonist mCPP (**8**, *m*-chlorophenylpiperazine) reduces appetite and body weight in obese patients. The anorectic action of mCPP is absent in 5-HT$_{2C}$ receptor knockout mutant mice and is antagonized by the selective 5-HT$_{2C}$ receptor antagonist SB-242084 **9** (Fig. 3) [10–12]. Similarly, the 5-HT$_2$ agonist RO0600175 **10** [13] suppresses palatable food intake in rats. Mice with a targeted disruption of the 5-HT$_{2C}$ receptor have increased food consumption and develop late-onset obesity. In view of these findings, a number of companies are currently in the process of developing 5-HT$_{2C}$ receptor agonists.

Recently, phase II clinical trials have demonstrated significant weight loss with the 5-HT$_{2C}$ receptor agonist BVT-933 (Biovitrum, structure not published).

One of the most challenging goals in the serotoninergic field is to achieve a high degree of selectivity towards the different receptors, in terms of affinity and function.

In 1997, the widely prescribed appetite suppressant *dex*-fenfluramine (**1**) was withdrawn from the market due to treatment-related cardiac valve alterations and pulmo-

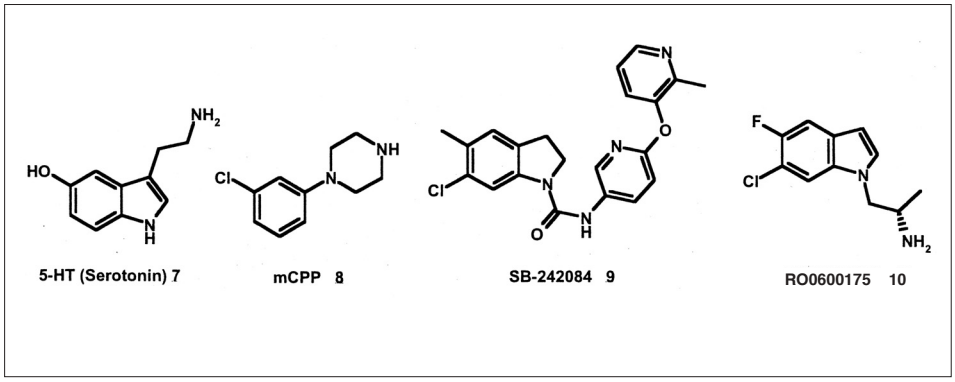


Fig. 3.

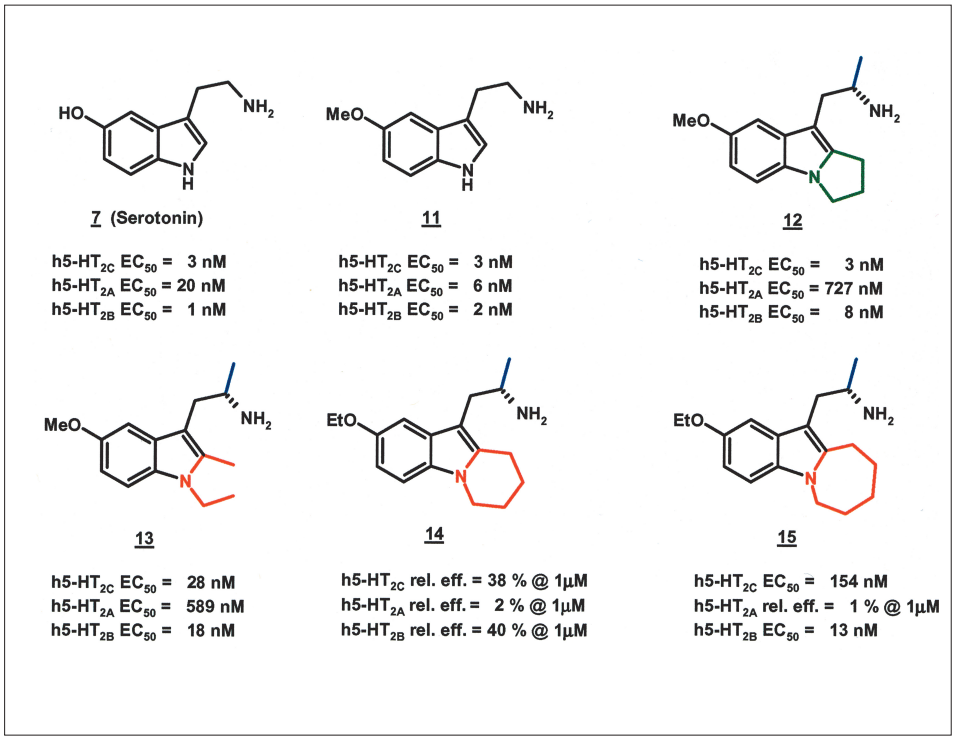


Fig. 4.

nary hypertension. A recent publication indicates a possible role of 5-HT_{2B} receptor [14] in this alteration. 5-HT_{2A} agonism may mediate the effects of hallucinogens such as LSD-25. Therefore, high 5-HT_{2C} receptor subtype selectivity is of prime importance.

Overall, the selective 5-HT_{2C} receptor agonist approach should lead to a better safety profile than for the known 5-HT releasing and 5-HT reuptake inhibitors, such as *dex*-fenfluramine (**1**).

2. Early SAR and Chemistry

2.1. *Biased Screening and Discovery of Pyrroloindole*

Agents with high affinity for 5-HT_{2C} receptors typically possess high affinity for 5-HT_{2A} receptors and rarely display >10-fold selectivity [15]. While Serotonin (**7**), the endogenous ligand of the 5-HT receptors, shows some functional selectivity for the 5-HT_{2B} receptor (Fig. 4) and the O-methyl-serotonin (**11**) exhibits no significant selectivity, a biased screening has highlighted the interesting properties of the pyrroloindole core (*i.e.* **12**), particularly with regard to the 5-HT_{2A} receptor selectivity.

Pyrrole-ring opening (**13**) reduces potency around one log-unit while the piperidine-homologue **14** lost potency almost completely. Interestingly, the larger 7-membered homologue **15** regained some potency, however only modestly (Fig. 4).

The α-methyl group was incorporated into the amino side chain in order to suppress metabolic side chain deamination by monoamine oxidases (MAO). The slight increase of lipophilicity also allows for better CNS permeation [13]. However, this modification did not increase potency and selectivity significantly.

2.2. *First Synthetic Route*

The initial synthesis started from 5-methoxy indole (**16**) and involved construction of the third ring by radical cyclisation [16]: Vilsmeier-Hack condensation with phosphorus oxychloride in N,N-dimethylformamide at 40 °C introduced the aldehyde in the 3-position of the indole. N-alkylation using 3-chloro-1-bromopropane and potassium hydroxide in dimethyl sulfoxide at room temperature followed by Finkelstein activation with sodium iodide in refluxing acetonitrile provided the desired iodo intermediate **18**. Tributyltin hydride-mediated 5-*exo-trig* radical cyclisation in toluene at reflux led to the desired tricyclic pyrroloindole **19** core in poor yield (13%), along with reduced material [16]. The side-chain was introduced by reaction of the aldehyde with nitroethane in the presence of ammonium acetate at 100 °C, which provided the nitroalkene **20**. Reduction with lithium aluminium hydride in refluxing tetrahydrofuran afforded the desired racemic product (***rac*-12**) in moderate yield [17]. Optical resolution by chiral HPLC was feasible only on small scale due to poor separation (Scheme 1).

Joint efforts at *F. Hoffmann-La Roche Ltd* and *Vernalis Research Ltd* have allowed the construction of a solid structure–activity relationship around the pyrroloindole core.

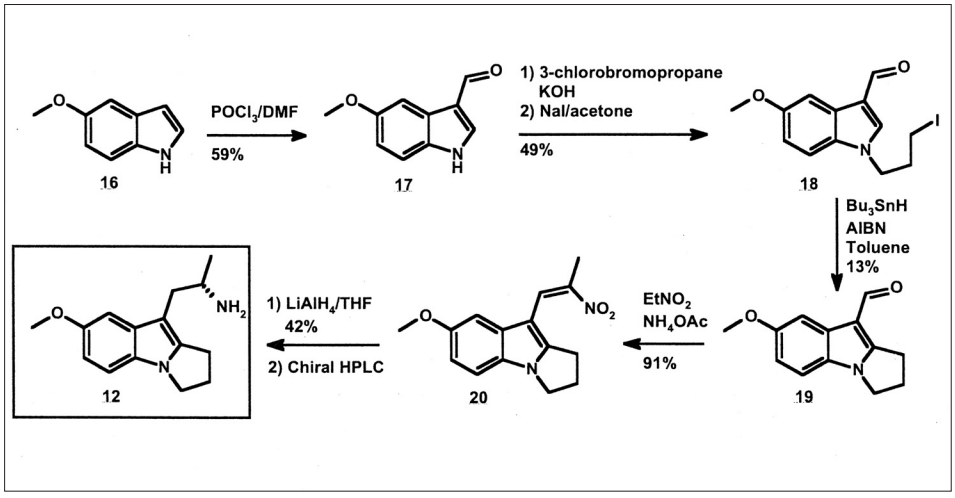
The double bond of the indole ring was shown to be mandatory for the affinity to the 5-HT_{2C} receptor. Substitution of the amino group was not tolerated; however mono or di-N-methylation might be envisioned in a pro-drug approach. The optimal absolute configuration was found to be (*S*). The (*R*)-antipode was one log unit less potent. Further modifications of the 2-aminopropyl side chain, with the aim to tune the selectivity or the basicity were not successful. Equally, the SAR around the benzene ring was found to be quite narrow, with the exception of the 5-position, where large variations were allowed (Fig. 5, see also Section 5.)

3. Chemistry

3.1. *Pyrroloindole Construction*

Further exploration focused on the 5-position. For that purpose a new, efficient, flexible, and preferably chiral synthetic approach was deemed mandatory. The issues of the initial approach (*i.e.* low yield and tedious chiral HPLC enantiomer separation) were overcome by a novel and expedient approach that gave rapid access to key intermediates and target compounds in a stereochemically defined form.

Starting from 4-bromoaniline (**21**) the amine was protected as the methylcarbamate and selectively *ortho*-iodinated using N-iodosuccinimide (NIS), leading to **22**. So-



Scheme 1.

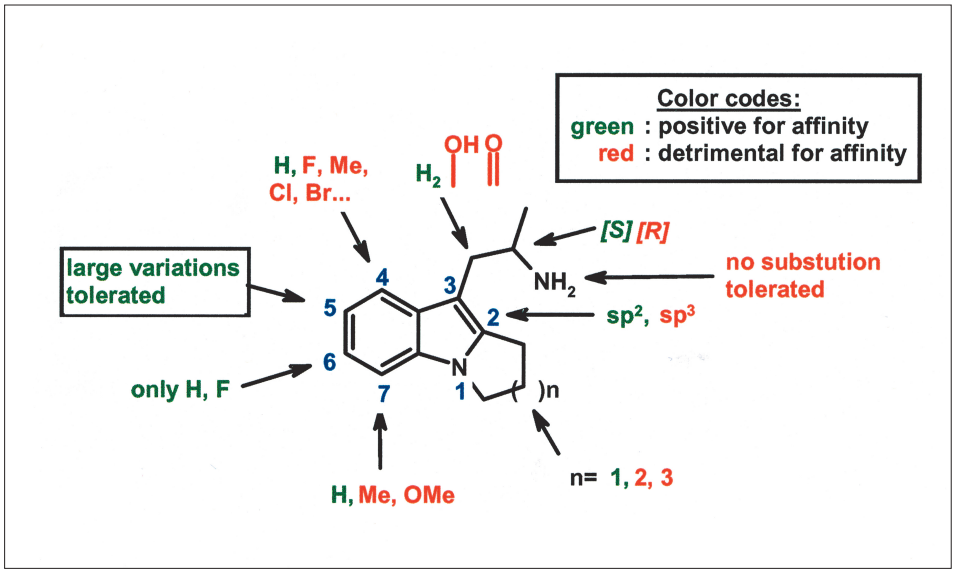
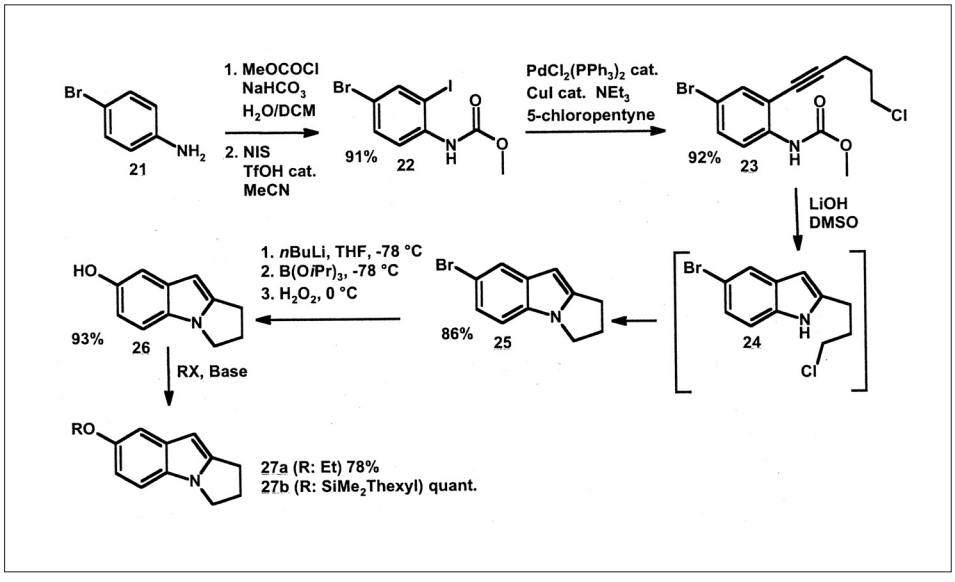


Fig. 5.



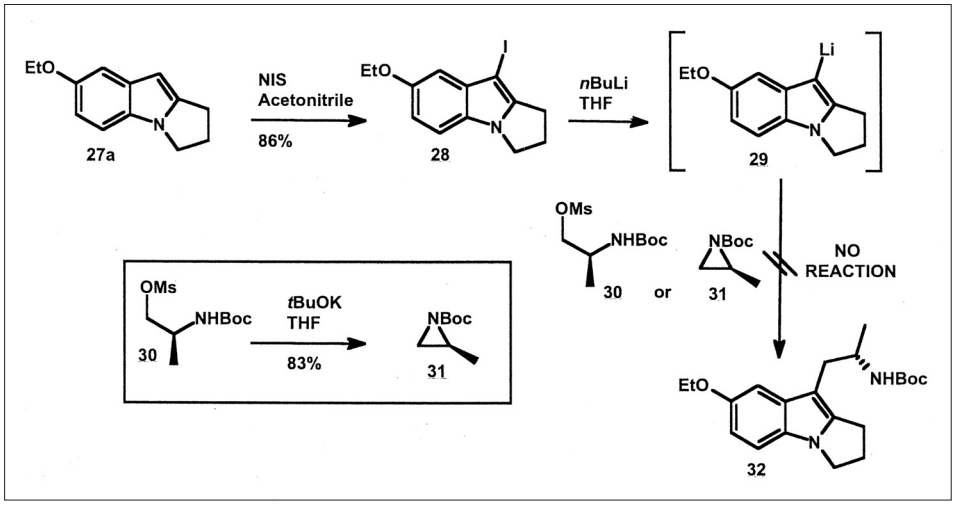
Scheme 2.

nogashira reaction of this material with 5-chloro-1-pentyne allowed smooth and efficient incorporation of the 5-carbon unit (Scheme 2). Treatment of acetylene **23** with lithium hydroxide in wet DMSO at 80 °C led to deprotection of the carbamate, formation of the indole ring and a second annelation to install the pyrroloindole central motif **25** [18]. As a further simplification the Sonogashira and annelation reactions were combined in a one-pot procedure with equally good yields. The bromotricyclic compound **25** was converted to the phenol **26** by metallation with n-BuLi, reaction with triisopropylborate and oxidation with hydrogen peroxide. For preparative purposes a defined alkyl side chain could be introduced at this stage by simple alkylation to furnish *e.g.* **27a**. For late stage derivatisation the phenol **26** was protected as the thexyldimethylsilyl ether **27b**.

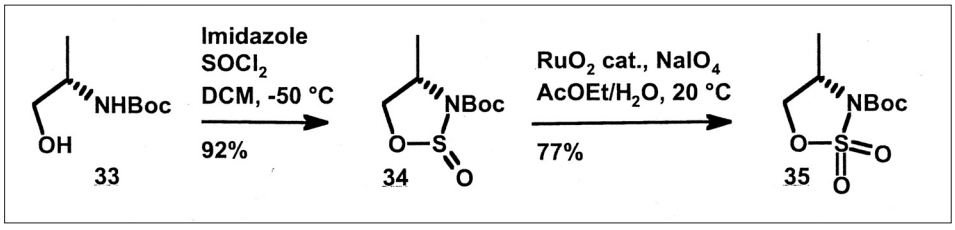
3.2. *(S)-Aminopropyl Side Chain Incorporation*

The stereocontrolled incorporation of the aminopropyl side chain was envisioned by reaction of an indole or the 3-lithio analogue **29** with an electrophilic chiral aminopropyl synthon. For this purpose, the pyrroloindole **27a** was iodinated in good yield using NIS and subsequently metallated at low temperature (–78 °C). Quenching of the lithio-indole **29** with water confirmed the completion of the metal-halogen exchange. However, attempts to trap the organolithium with the methanesulfonic acid 2-*tert*-butoxycarbonylamino-propyl ester **30** met with no success (Scheme 3). Under strongly basic conditions, cyclisation to the N-Boc protected methylaziridine **31** took place [19]. No ring opening of aziridine **31** with lithio pyrroloindole **29** to **32** occurred even after addition of copper or zinc salts. As a consequence more reactive aminopropyl synthons which were devoid of an acidic proton were designed.

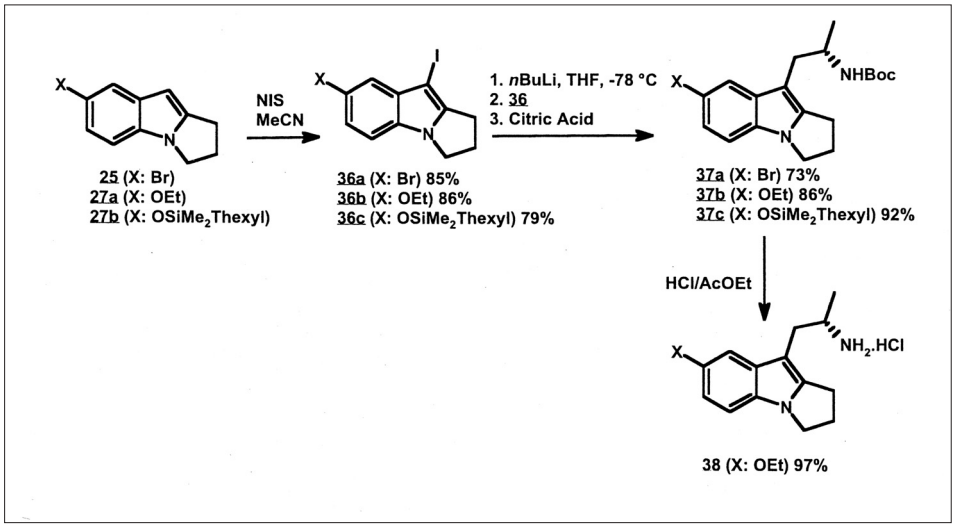
Based on the synthetic equivalence of epoxides and cyclic sulfates suggested by Sharpless [20][21], we envisioned the cyclic sulfamidate **35** as an aziridine equivalent with enhanced reactivity (Scheme 4). The synthesis of **35** started from the readily available chiral (*S*)-alaninol which was N-Boc-protected (**33**), cyclized to the 2-oxo-[1,2,3]oxathiazolidine **34** with thionylchloride and oxidised with $NaIO_4$ in the presence of catalytic amounts of RuO_2 to give the stable crystalline alkylating agent **35** [22]. Although described for the sulfate analogs and for the prolinol derived sulfamidate, the direct synthesis of the cyclic sulfamidate from (*S*)-prolinol using sulfuryl chloride did not work, presumably due to high reactivity of the N-Boc sulfamidate, which does not tolerate the presence of a nucleophilic base such as imidazole or pyridine [23][24].



Scheme 3.



Scheme 4.



Scheme 5.

This powerful alkylating agent **35** was reacted with the lithio-indole derived from **36**, in good yields and with complete retention of configuration (Scheme 5). The scope and limitations of this useful class of reagents are now under investigation. This method has been applied successfully to the synthesis of several 5-substituted pyrroloindoles (*i.e.* 5-bromo **37a**, 5-ethoxy **37b**, 5-silyloxy **37c**), including applications on a large scale (over 50 g).

Simple reaction of the N-Boc protected amines with hydrogen chloride in ethyl acetate led to precipitation of unprotected amine as the hydrochloride salt. Differential deprotection of the silyl-protected phenol function in **37c** with NH_4F in methanol allowed for late variation of the alkoxy substituent.

4. *In vitro* Results

4.1. *Affinity, Potency and Selectivity*

The compounds were screened for functional activity at recombinant 5-HT_{2C} receptors expressed in CHO cells using a fluorimetric imaging plate reader (FLIPR). The maximum fluorescent signal (annotated as rel. eff. in Fig. 4 and the Table) obtained at 1 μM was measured and compared with the response produced by 10 μM 5-HT (defined as 100%).

For compounds showing potency above 50% (compared with 5-HT) from this functional assay, a full concentration-response curve using the same techniques was generated (annotated as EC_{50} in Fig. 4). In parallel, these compounds were compared in radioligand binding displacement assay at recombinant human 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors expressed in CHO cells (annotated as Ki h5-HT_{2A}, Ki h5-HT_{2B}, and Ki h5-HT_{2C}, respectively; Table). For the 5-HT_{2A} receptor [^{125}I]-DOI (*rac*-2,5-dimethoxy-4-iodoamphetamine) was used as the radioligand whereas [^{3}H]-5-HT (*cf.* compound **4**) was used at the 5-HT_{2B} and 5-HT_{2C} receptor subtypes [25]. Some results are shown in the Table.

The presence of a heteroatom attached to the phenyl ring is mandatory. Increasing chain length (entry 3 *versus* 5) enhances selectivity towards the 5-HT_{2B} receptor subtype. Steric hindrance on the α-carbon is detrimental for affinity (entry 8); only cyclopropyl is tolerated (entry 7). Decoration on the β-carbon is allowed (entry 9). However, despite various substituents on the β- and γ-position, no significant improvements were found (*e.g.* entry 12). Linear hydroxyethoxy (entry 10), and methoxypropoxy were found to be the most interesting variations in terms of potency, affinity and selectivity towards 2A and 2B receptor subtypes (>70-fold).

4.2. *Metabolic Stability*

In vitro intrinsic clearance in human hepatocyte preparations has been determined for the most promising compounds. From these values the hepatic *in vivo* clearance was extrapolated (Table, annotated as Cl h-hepat) through direct scaling, this last value being more representative of the *in vivo* situation.

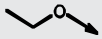
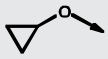
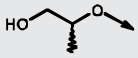
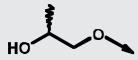
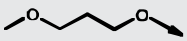
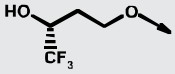
Phenol derivatives were generally observed as the main metabolites, presumably through oxidation of the α-carbon followed by dealkylation. Increasing sp^2 character of this carbon (entry 7) or local polarity (entries 10–11) significantly increased metabolic stability (Table).

5. Modelling

5.1. *Ligand Pharmacophore*

One very important concept of medicinal chemistry is the idea of pharmacophores. A pharmacophore is defined as the minimum functionality a molecule has to contain in order to show activity at a certain receptor. A pharmacophore is normally represented as a set of features (such as positive charge, negative charge, hydropho-

Table.

Entry *(Conf.)*	5-substituent	Relative Efficacy h5-HT_{2C}	h5-HT_{2A} Ki (nM)	h5-HT_{2B} Ki (nM)	h5-HT_{2C} Ki (nM)	Cl h-hepat. ml/min/kg
1 *(Rac)*		68%	457	229	110	
2 *(S)*		-	-	-	>1000	-
3 *(S)*	**20** 	87%	723	170	6	20
4 *(S)*		80%	2430	231	22	-
5 *(S)*	**38** 	87%	410	830	11	18
6 *(R)*		66%	675	518	84	-
7 *(S)*		84%	407	199	26	6
8 *(S)*		89%	6114	2673	478	-
9 *(S)*		74%	2189	1510	37	-
10 *(S)*		87%	992	289	2.9	4
11 *(S)*		93%	663	111	1.4	10
12 *(S)*		87%	255	187	36	-

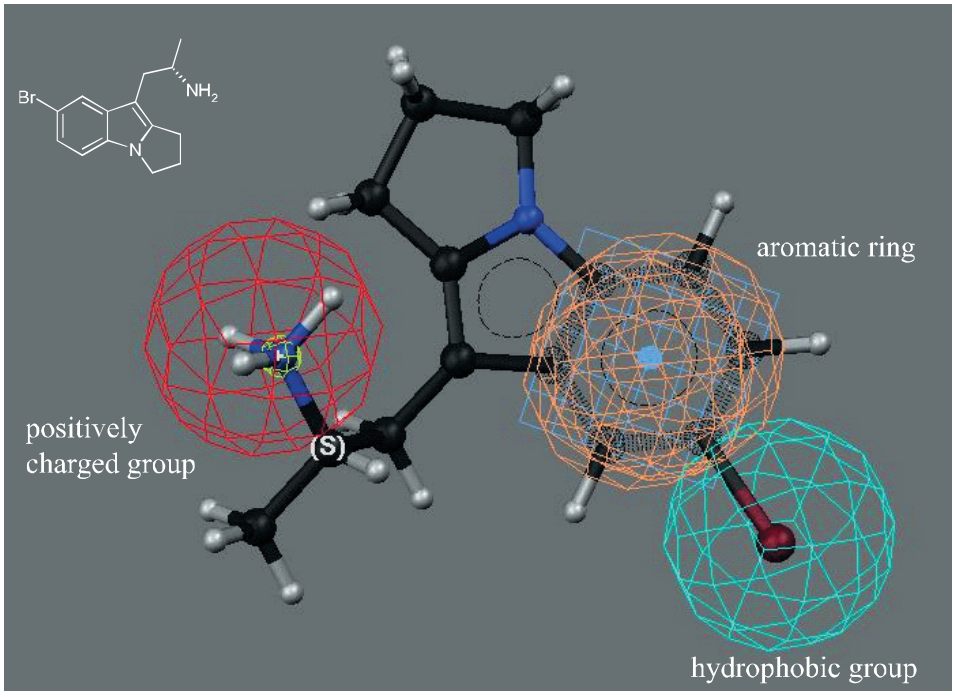


Fig. 6.

bic region, aromatic ring center, H-bond donor, H-bond acceptor) in a defined spatial arrangement. Molecules interacting with a receptor in the same way should all include these features as minimum requirement even if the molecules have completely different chemical structures. By defining such a pharmacophore, we can learn a lot about what makes a certain compound active at a receptor.

Using CATALYST [26] and ten known 5-HT_{2C} agonists, a 3-point ligand pharmacophore was defined which consisted of a protonated amine, an aromatic ring and an additional hydrophobic substituent in a defined spatial orientation (Fig. 6). This means that all 5-HT_{2C} agonists activating the receptor in the same way as the known agonists should possess at least these three features.

The alignment of the pyrroloindole core onto the pharmacophore showed that the requirement of a hydrophobic substituent is fulfilled by the substituent in position 5, which can explain the relative importance of substituents in this position for activity.

5.2. *5-HT_{2C} Receptor Model*

While the pharmacophore approach uses only ligand information to understand what functionalities are required for a compound to be active, such information can also be gained by investigating how compounds of a series interact with the receptor. In this approach, a three-dimensional structure of the binding site of the receptor is required. This is preferentially an experimentally determined X-ray structure obtained by cristallography, but alternatively homology models may be used where such information is unavailable.

Until now the only high-resolution X-ray structure of a GPCR that has been solved is the structure of bovine rhodopsin [27]. Structure information of other GPCRs may, therefore only be obtained from homology models using the X-ray structure of bovine rhodopsin as a template.

To construct this homology model, the amino acid sequence of human 5-HT_{2C} receptor was aligned with the sequence of bovine rhodopsin. The X-ray strucuture of bovine rhodopsin was then modified by changing the amino acid side chains to the respective side-chains of the 5-HT_{2C} receptor.

The pyrroloindole core was then docked into the initial 5-HT_{2C} receptor model such that the basic amine formed a salt bridge with an aspartate and the benzene ring formed π-π interactions with a phenylalanine, interactions that are conserved in most biogenic amine receptors. The energy of the receptor/ligand complex was then minimized by Amber 6.0 [28]. In the final model, substituents in position 5 of the pyrroloindole are located in a large pocket between the transmembrane domains 3, 4,

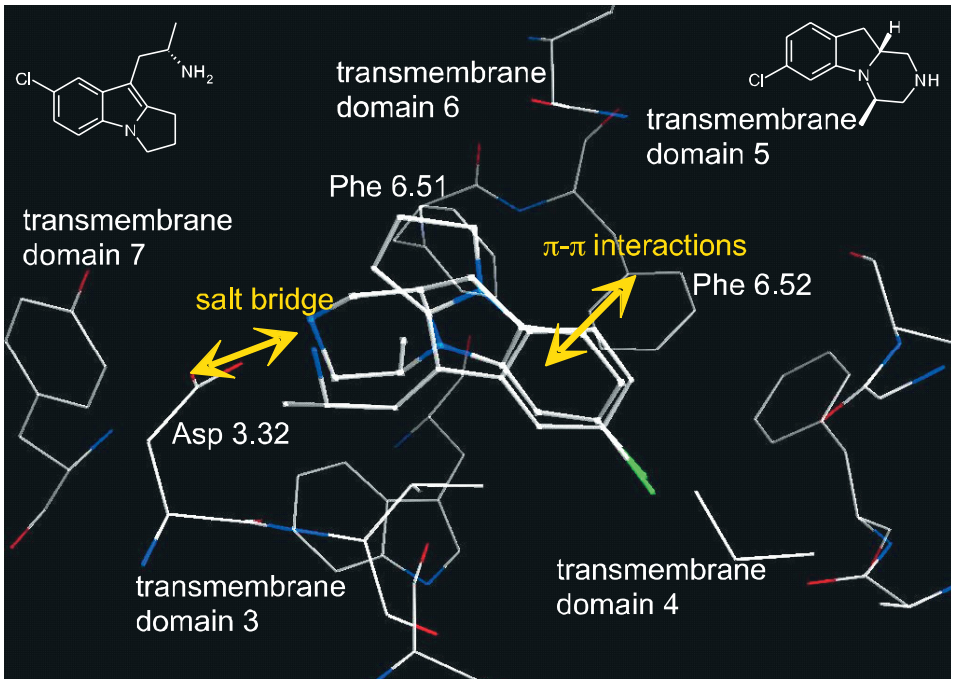


Fig. 7.

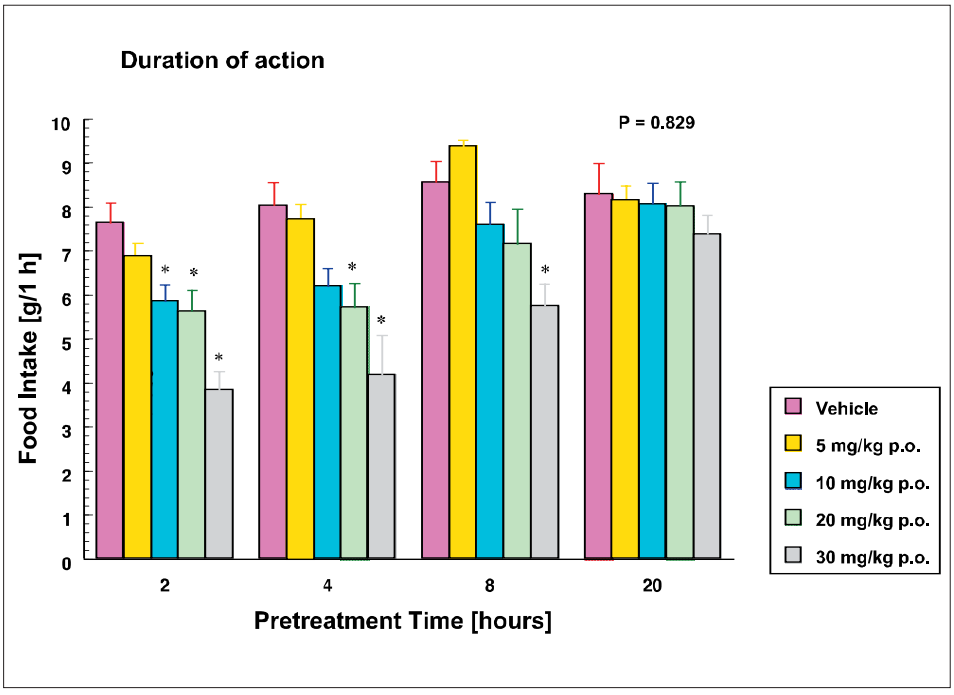


Fig. 8. Effect of **38** on food intake in Lister hooded rats under 23 h food deprivation. 7–8 rats were used per group. Either compound **38** (5, 10, 20, 30 mg/kg) or saline were administered orally at different time points (2, 4, 8 and 20 h) before the 1 h food intake session. *P <0.05 compared to vehicle-treated rats (Anova followed by Dunnett's t-test).

5, and 6. This may explain why large variations are tolerated in this position (Fig. 7). In contrast, the environment of the pyrole ring, close to the extracellular loop between TM 4 and 5 could not be modelled robustly.

Although most of the optimization was driven by SAR, ligand- and structure-based modelling approaches provided valuable information to target this GPCR.

6. *In vivo* Activity

6.1. *Animals*

Male hooded Lister rats, weighing 160–230 g at the beginning of the experiment, were used, each rat being used once. Ambient temperature was approximately 21 °C and relative humidity 55–65%. A 12 h light–dark cycle was maintained, with all tests being performed during the light phase. Access to tap water was *ad libitum*.

6.2. *Method*

Rats were kept individually and were deprived of food for 23 h. They were housed in plexiglass boxes with a grid on the floor and paper was placed below the cage floor to collect the spillage. A food dispenser filled with a preweighed amount of food was presented to them for 1h. At the end of the food intake session, rats were returned to their home cage.

6.3. *Results*

Compounds were tested for their ability to reduce food intake in food-deprived rats. Compound **38** (*cf.* Table) dose-dependently decreased food intake during the 1 h period of food access with a minimum efficacious dose (MED) of 10 mg/kg p.o., as shown in Fig. 8. The duration of action exceeded 8 h at 30 mg/kg. After a pre-treatment time of 20 h, decrease of food intake was no longer observed at any dose.

The anorexic effect was dose-dependently blocked by pre-treatment with the selective 5-HT_{2C} receptor antagonist SB-2420849, indicating a 5-HT_{2C} receptor mediated effect.

7. Conclusions

Obesity is becoming a major disease around the world. Collaboration between F. Hoffmann-La Roche Ltd and Vernalis Research Ltd has allowed the discovery and the rapid development of chiral pyrroloindoles as potent 5-HT_{2C} receptor agonists.

Several compounds were found to be very selective over other 5-HT_2 receptor subtypes (>25 fold). Effective access to the pyrroloindole motif, using a tandem Sonogashira/double cyclisation reaction was developed. For the first time, chiral sulfamidates were used for the stereospecific introduction of a (2*S*)-aminopropyl side chain. This synthetic route could be scaled up to 50 g of final product. Optimisation of pharmacokinetic parameters has allowed good *in vivo* efficacy after *per os* application in a rodent food-deprived model.

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