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MCH-R1 antagonists: what is keeping most research programs away from the clinic?

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Despite the high number of drug-discovery programs dedicated to finding small-molecule MCH-R1 antagonists for the treatment of obesity and/or mood disorders, a very limited number of these have progressed into the clinic. Beyond the common challenges in drug design related to ADME and safety profiles, cardiovascular risk involving hERG binding and the potential for subsequent drug-induced QTc prolongation has been a major hurdle for a significant number of MCH-R1 research programs. Many of these programs have evolved, and effectively designed MCH antagonists having decreased hERG-binding affinity have emerged. Currently, however, only a selected few candidates have progressed to clinical development. Drug-design strategies, *in vivo* efficacy, ADME, and cardiovascular safety profiles for a selection of MCH-R1 antagonist research programs are discussed ahead.

Melanin Concentrating Hormone (MCH) is a cyclic nonadecapeptide expressed in the lateral hypothalamus and the natural ligand for the seven-transmembrane G-protein-coupled receptors known as MCH-R1 and MCH-R2 [1–3]. From these two receptor types, MCH-R1 has received most of the attention probably because of the fact that MCH-R1 is expressed in rodents, which has allowed for suitable animal models to probe its neurobiological functions. MCH-R2 is expressed in humans but not in rodents, and its biological function remains unclear to date. Many published studies indicate that MCH-R1 is involved in biological processes related to mammalian feeding behavior and energy expenditure [4,5]. In addition, it has been suggested that MCH-R1 plays a key role in anxiety and mood disorders since MCH-R1 antagonists have been found to have anxiolytic and antidepressant effects in various animal models [6–8]. A recent study suggests the possibility that MCH-R1 is involved in modulating cardiovascular activity in addition to regulating energy homeostasis and that MCH-R1 may be crucial for the coordination of normal responses to weight loss [9]. Proof of efficacy for MCH-R1-based therapies still awaits clinical validation; however, all of these findings have made MCH-R1 a very attractive target since an orally active MCH-R1 antagonist could find useful applications in two disease areas in high need for novel and effective therapies: obesity and depression/anxiety disorders.

Melanin Concentrating Hormone Receptor 1 (MCH-R1) has received significant attention as a potential target for novel anti-obesity therapies [10]. Small-molecule MCH-R1 antagonists have been heavily pursued by many laboratories trying to find an effective anti-obesity agent [11]. By November 2004, two MCH-R1 antagonists (AMG-076, Amgen; GSK-856464, GlaxoSmithKline) had already entered Phase I clinical trials. However, no changes in status have been reported for either MCH-R1 program to date. Interestingly, only one additional anti-obesity program (NGD-4715, Neurogen) [12,13] has been reported to enter Phase I clinical trials, despite all the drug-discovery research activity reported within this area in the past several years [14,15].

Ahead, we will review recent advances in a representative number of MCH-R1 research programs within the pharmaceutical industry. Examples will mainly focus on research programs having small-molecule MCH-R1 antagonists that effectively promote weight loss in animal models. Then, we will examine the key challenges that seem to be keeping these programs from advancing into the clinic. Corresponding drug-design strategies and their

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impact on the *in vivo* efficacy, ADME, and safety profiles of compounds will be discussed.

Circumventing cardiovascular risk: from 4-phenyl benzamides to 6-phenyl-thieno[3,2-*d*]pyrimidin-4(1H)-ones

Many experts suggest that cardiovascular risks associated with many of the reported MCH antagonists may be the major hurdle for compound progression into clinical stages [11,15]. Despite the attractive *in vitro* profile and *in vivo* results, further development of many MCH-R1 antagonists has been compromised by significant hERG channel binding *in vitro*. These hERG blockers can induce QT interval prolongation that is frequently associated with potentially lethal arrhythmias known as torsades de pointes (TdP) [16], which has led to the removal of several drugs from the market [17,18].

A significant number of the reported MCH-R1 antagonists and classic hERG-binding agents have two structural elements in common: a positively charged group and at least one distal aromatic/hydrophobic region. Therefore, it is not surprising that a significant number of potent MCH-R1 antagonists are also potent hERG binders. These two common structural elements have been linked via a diverse pool of functionalities that include alkyl chains, aromatic groups, and heterocyclic systems. Given the apparent flexibility around the linking unit, competitors within this field have predominantly achieved proprietary MCH-R1 antagonists by designing novel linking units while retaining the positively charged group (alkyl amines are the most commonly used) and the distal aromatic/hydrophobic region (compare structures **4**, **5**, **6**, and **9** below in Figure 2). In terms of MCH-R1 binding, it has been widely suggested that the positively charged group putatively interacts deep in the receptor with the conserved Asp123 (helix 3) [19,20]. With regard to binding in the hERG channel, this positively charged group may participate in a cation–pi interaction with the Tyr-652 residue of the ion channel, while lipophilic linker units and the distal aromatic/hydrophobic moieties may interact with corresponding hydrophobic residues such as Phe-656 [21–23].

Examples of successful designs of MCH-R1 antagonists with improved selectivity over hERG have been described in recent literature and will be discussed ahead (see Figure 2). Improved hERG selectivity has been achieved by a variety of structural modifications to the positively charged group, the aromatic/hydrophobic regions, and linker units. However, in many cases, the structural changes responsible for lower hERG-binding activity have led to compounds that are either unsuitable for clinical development or devoid of *in vivo* activity.

Neurocrine reported that compound **4** served as a potent functional MCH-R1 antagonist but exhibited low metabolic stability (determined by Human Liver Microsomes assay) and had low oral exposure in rat [24,25]. In addition, **4** showed strong hERG binding (170 nM). Compound **5** emerged as a promising lead from a series achieved by inversion of the aminopyrrolidine unit of **4** [25]. Compound **5** proved to be a potent MCH-R1 antagonist while displaying lower hERG binding (2.6 μM), higher metabolic stability in HLM, and higher oral exposure in rats compared with **4**. Unfortunately **5**, as well as many other analogs within this new series, displayed an undesirable profile related to potent inhibition of Cytochrome P450 2D6 (CYP2D6) and poor brain penetration (up to four times lower than compound **4**). These results led Neurocrine to halt the development of this series of MCH-R1 antagonists [26].

Procter & Gamble Pharmaceuticals reported a series of MCH-R1 antagonists (**7** and **8**) that were designed by replacing the 4-phenyl-*N*-methyl benzamide moiety of compound **6** with a 4-phenethylpiperazin-2-one unit [19]. Compounds within this class promoted moderate body weight reduction in mouse diet-induced obesity studies. The lead compound **7** within this series was estimated to have moderate bioavailability (40%) following oral dosing in male Sprague–Dawley rats. Peak plasma levels were observed at 0.5 h with an estimated half-life of approximately 4 h. Further development of this class of compounds as MCH-R1 antagonists was compromised by hERG-binding activity leading to an observed dose-dependent increase in QT interval in anesthetized dogs at serum concentrations comparable to those obtained at efficacious doses [19]. MCH-R1 antagonists with improved selectivity over hERG were achieved by incorporating polar functionality proximal to the benzylic tertiary amine moiety of the (*S*)-aminomethyl tetrahydronaphthalene ketopiperazine scaffold. The *N*-acetyl piperazine derivative **8** was found to have decreased hERG activity while maintaining high MCH-R1 antagonist activity [27]. However, these structural changes resulted in compounds devoid of *in vivo* activity possibly because of poor CNS penetration. Nevertheless, a direct correlation between hERG binding and QTc prolongation was established for this series of compounds.

Researchers from GlaxoSmithKline have found that the 4-phenyl-*N*-methyl benzamide moiety of compound **9** (structural unit commonly found in many other reported MCH-R1 antagonists) can be effectively replaced with a conformationally constrained amide isostere such as the 6-phenyl-thieno[3,2-*d*]pyrimidin-4(1H)-one [28]. The clinical candidate GW803430 (**10**) emerged from these efforts [29]. This compound proved to be a potent MCH-R1 antagonist while being selective (>100) over a battery of targets in a CEREP screen. In addition, it displayed good pharmacokinetic properties (bioavailability = 31%, $t_{1/2}$ = 11 h) and brain penetration (6:1 brain:plasma concentration) in mice. During a 12-day treatment, QD oral administration of this compound promoted a sustained dose-dependent weight loss relative to vehicle controls.

Following GW803430 (**10**), additional compounds within this new class of 6-phenyl-thieno[3,2-*d*]pyrimidin-4(1H)-one-based MCH-R1 antagonists have shown to have improved hERG selectivity while having desirable pharmacokinetic properties and effectively promoting weight loss *in vivo*. Compound **11** is a potent MCH-R1 antagonist having negligible hERG activity (pIC50 = 4.66 in patch clamp assay) and very high selectivity over human MCH-R2 [30]. Compound **11** displayed excellent systemic exposure, with a bioavailability of 98% and quite a good half-life ($t_{1/2}$ = 7.7 h). The clearance (39.7 mL/min/kg) was found to be higher than desirable, possibly because of *N*-demethylation of the piperazine ring. Compound **11** proved to be both highly efficacious in a 26-day mouse diet-induced obesity study and to effectively penetrate the brain with a brain/serum ratio of 31.

Compound **12** is an analog of **11** that was obtained by replacing the quinoline ring system with a benzo[*b*]thiophene unit [31].

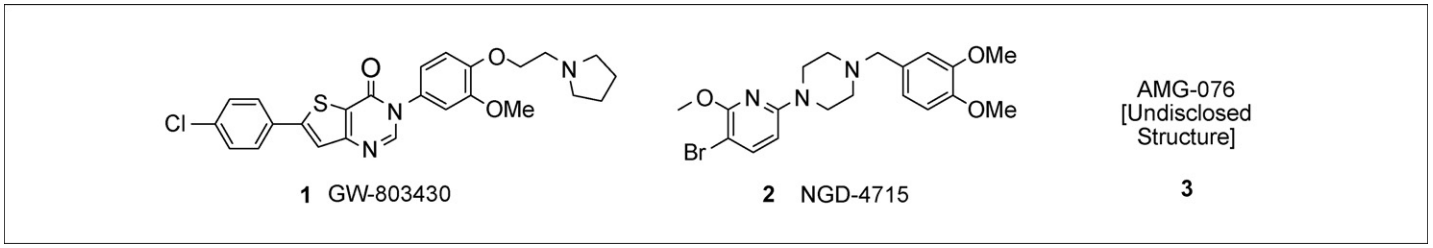

FIGURE 1

MCH-R1 antagonists that have progressed to Phase I clinical trials.

Similar to **11**, compound **12** exhibited good bioavailability (66%/mouse), a half-life of 9.1 h, and moderate-to-high clearance (39 mL/min/kg). During a 21-day mouse diet-induced obesity study, oral administration of compound **12** at 1, 3, and 10 mg/kg once daily caused a dose-dependent weight loss of −1.1, −3.2, and −11.8%, respectively. In the same study, rimonabant, a CB1 receptor inverse agonist currently approved for treatment of obesity in the EU, caused −8.4% weight loss.

Compound **14** (see Figure 3) is an analog of **12** and was obtained by replacing the quinoline ring system for a *N*,*N*,1-trimethyl-1*H*-

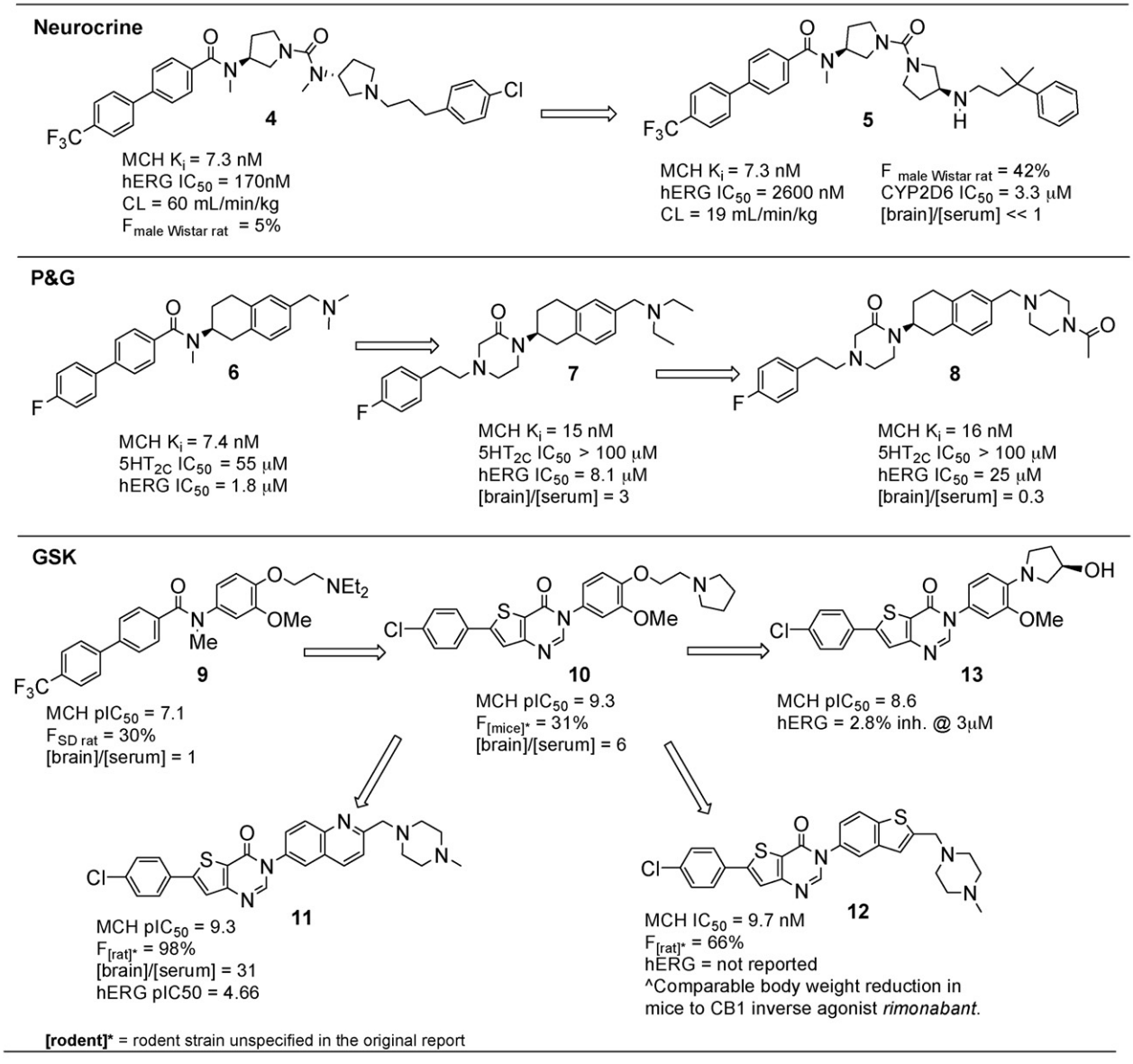

FIGURE 2

MCH-R1 antagonists research programs: balancing cardiovascular risks and overall ADME profile.

benzo[*d*]imidazol-2-amine unit [32]. Like the previous two examples within this class, this compound exhibited good pharmacokinetic properties in mouse (bioavailability > 90%, $t_{1/2}$ = 6 h) with good brain penetration (brain:plasma ratio = 2.6) and caused a sustained dose-dependent change in body weight (0.3, 1, 3, and 10 mg/kg once daily in diet-induced obese AKR/J mice led to body weight reductions of 1.6, 2.1, 5.1, and 10%, respectively.)

A recent patent publication from GlaxoSmithKline describes compound **13** (Figure 1) as potent MCH-R1 antagonist having negligible hERG activity [33]. Interestingly, this compound incorporates a (*R*)-3-pyrrolidinol unit instead of the basic alkyl amine functionality characteristic of all the MCH-R1 antagonists discussed so far in this review. In this case, the hypothesis is that the hydroxy group engages in a hydrogen-bond interaction with Asp123 leading to MCH-R1 antagonism as effectively as in the cases where salt bridges are formed with alkyl amines. Additional reports by Tavares *et al.* support this hypothesis [30,31]. The MCH-R1/hERG selectivity displayed by compound **13** may be easily explained by the limited ability for a hydroxy group to engage in strong cation–pi interactions when compared with a charged alkyl amine group [21]. However, there have been no reports indicating that this new class of compounds had advanced into the clinic, which suggests for the possibility that additional technical challenges may have been encountered by researchers at GlaxoSmithKline.

Compounds within this new class have shown to be potent MCH-R1 antagonists with improved hERG selectivity while having desirable pharmacokinetic properties and effectively promoting weight loss *in vivo*. However, the relationship between hERG *in vitro* activity and the observed QTc interval prolongation in animal models has not yet been reported for this class of MCH-R1 antagonists. Nevertheless, the results obtained from GW803430 (**10**) have encouraged other companies to pursue MCH-R1 antagonists based on 6-phenyl-thieno[3,2-*d*]pyrimidin-4(1H)-one scaffolds, or to find additional isosteric replacements for the 4-phenyl-*N*-methyl benzamide functionality. This trend is exemplified by recently reported MCH-R1 antagonists by Procter & Gamble [34], Pharmacopeia [35], AstraZeneca [36–38], Neurocrine [39], and Cerep [40,41] (compounds **14**–**19**, Figure 3).

Diverse scaffolds; diverse challenges

The MCH-R1 antagonists discussed so far shared many similarities in terms of the nature and relative location of the key pharmacophores believed to be responsible for biological activity. For most of these programs, the drug-design strategies depart from a lead scaffold containing a 4-phenyl benzamide unit or a suitable isosteric replacement, such as the 6-phenyl-thieno[3,2-*d*]pyrimidin-4(1H)-one unit. Ahead, we will discuss the MCH-R1 programs from Abbott, Schering, and Taisho that, along with Neurogen (see compound **2**, Figure 1), focus on MCH-R1 antagonists that are structurally different from those discussed in the previous section and among themselves (Figure 4).

Abbott has explored a variety of analogs in the aminopiperidine scaffold, as exemplified by compounds **20** and **21**. Compound **20** was an initial attempt to optimize a potent *N*-cinnamyl substituted HTS lead via replacement with a benzodioxolane group [42]. Compound **20** proved to be potent at MCH-R1 (2 nM) and showed good improvement in pharmacokinetic parameters (AUC plasma: 6.35 μg h/mL, AUC brain: 4.17 μg h/g) and *in vivo* in a 28-day mouse diet-induced obesity model (30% body weight reduction @ 30 mg/kg, po, bid). However, compound **20** suffered from affinity to the hERG channel (2.5 μM) and proved cardiotoxic in dogs. Later, Abbott reported a series of studies focused to finding MCH-R1 antagonists with lower cardiotoxicity, higher plasma and brain exposure, and improved overall pharmacokinetic profiles compared with **20** [43–45]. Despite all the research efforts, MCH-R1 antagonists having the desired properties for clinical evaluation did not emerge.

The early cardiovascular effects seen in the Abbott program led to a complete evaluation of all of the lead scaffolds, using an internally developed inactin-anesthetized rat cardiovascular (CV) assay to triage scaffolds upstream in the drug design and screening process [46]. The results of the screening process suggested that the chromone moiety found in compound **21a** helped to mitigate the potential cardiovascular risks seen with the scaffolds screened. As a result, optimization of the scaffold produced the 7-fluorochromone-2-carboxamide **21b** in an attempt to reduce the apparent cardiovascular risks going forward [47]. Compound **21b** proved to be a potent MCH-R1 antagonist (MCH-R1 ~ 3 nM; AUC plasma:

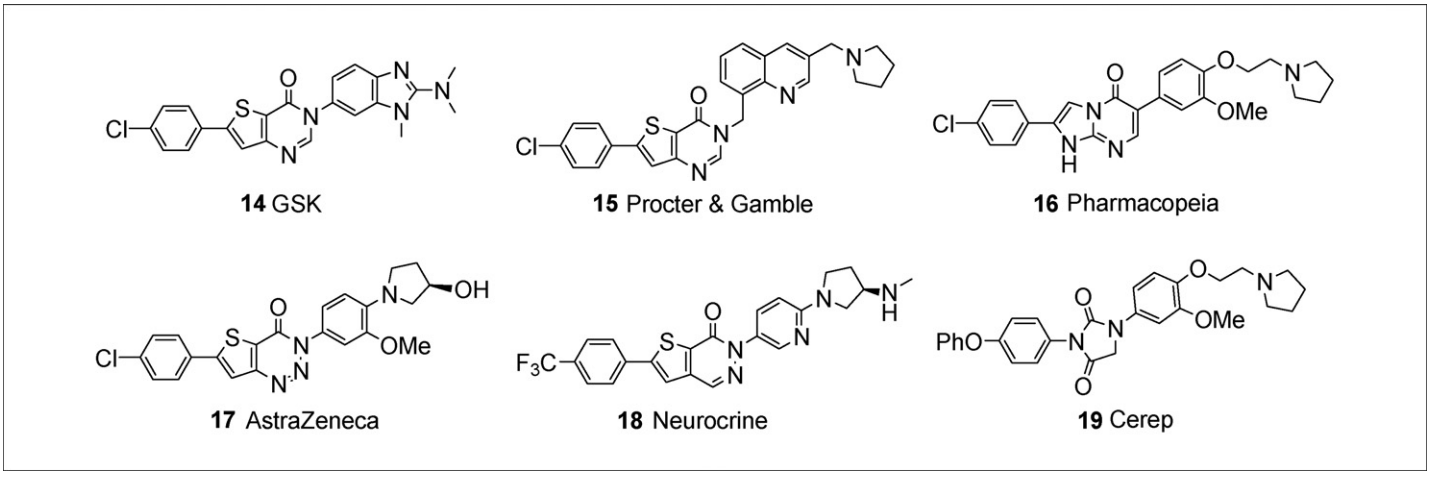

FIGURE 3

The influence of GW803430 (**10**): MCH-R1 antagonists based on 6-phenyl-thieno[3,2-*d*]pyrimidin-4(1H)-one scaffolds or isosteric replacements.

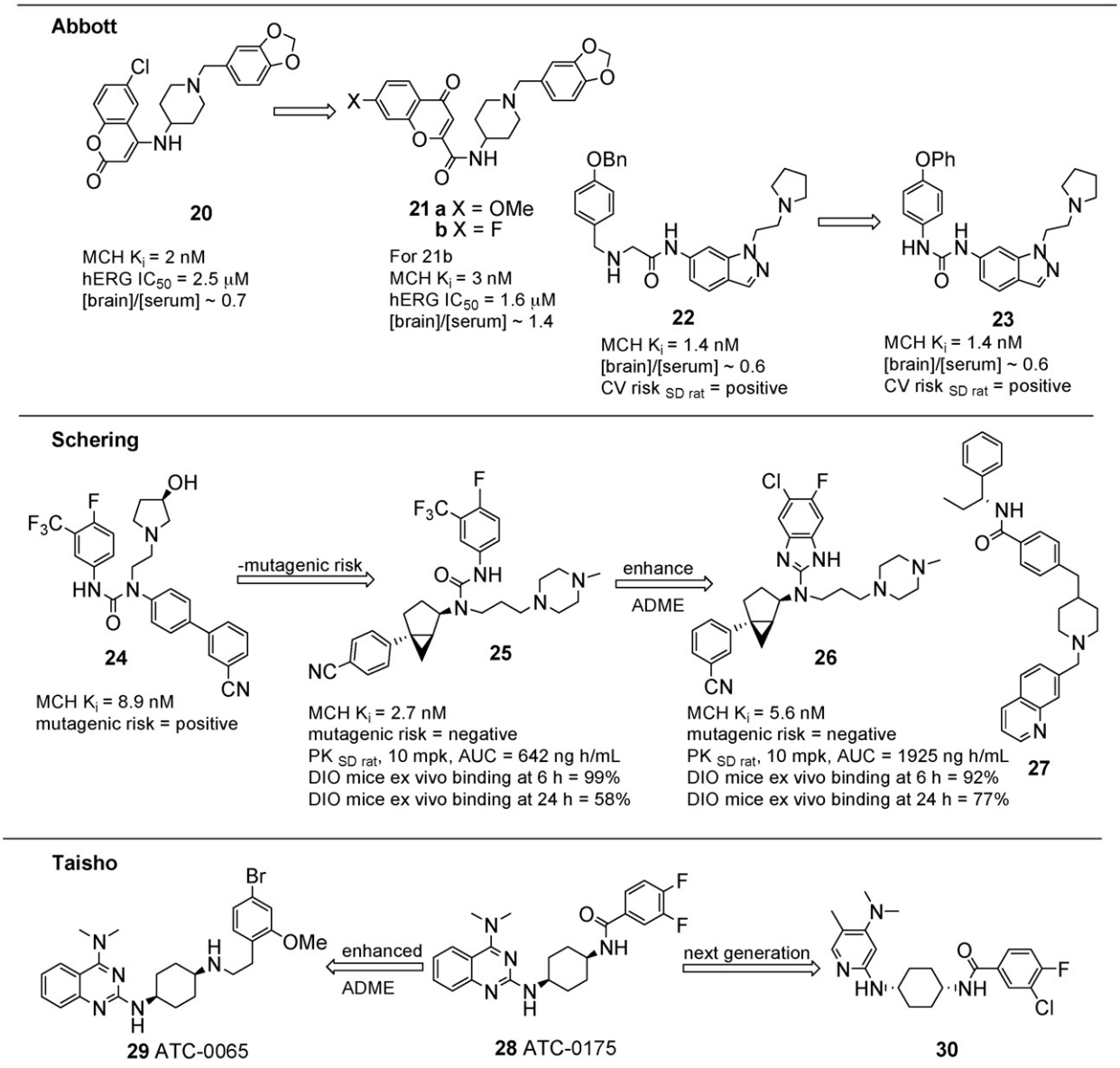

FIGURE 4

MCH-R1 antagonists research programs: balancing cardiovascular risks, mutagenic risk, and overall ADME profile.

9262 ng h/mL, AUC brain: 12 658 ng h/g; 28-day mouse diet-induced obesity model: body weight reduction ~7% @ 10 mg/kg, po, bid); however, **21b** also proved to be a potent binder to hERG (1.6 μM) and caused QT prolongation in dogs at unacceptable therapeutic doses. Attempts to modify the class by replacing the benzodioxalane with an aryl carboxamide group did not impact the cardiovascular profile [48].

Abbott has also reported on the use of the indazole scaffold **22**, which was a modification of the poorly CNS-penetrant indole analog resulting from HTS [49]. Compound **22** has excellent potency at MCH-R1 (1.4 nM) and good exposure and efficacy (AUC plasma: 2.12 μg h/mL, AUC brain: 1.33 μg h/g; 14-day mouse diet-induced obesity model: body weight reduction ~8% @ 10 mg/kg, po, bid; 15% @ 30 mg/kg, po, bid). Subsequent replacement of the amide bond with a urea linkage led to compound **23** with improved exposure levels in plasma and the brain [50]. Unfortunately, these classes were found to have cardiovascular effects based on the rat CV model [46]. Abbott has also published several patents covering an indazole series of MCH antagonists for weight loss and eating disorders [51,52]. Abbott announced the discontinuation of their metabolic disease focus area in 2007.

Schering has maintained an active interest in the MCH-R1 receptor and has published aggressively in the field recently. The main emphasis has been to find replacements for the potentially mutagenic diphenyl aniline moiety imbedded in the early lead compound **24** [53]. Although this scaffold proved potent and efficacious as an MCH-R1-mediated weight loss agent (MCH-R1 = 8.9 nM, 16.9% body weight reduction @ 3 mg/mg, 13.2% body weight reduction @ 10 mg/kg) with no apparent change in

lean mass [54], it was decided that the mutagenic risks for use in chronic treatment would dictate replacement of the aniline moiety with a potentially safer scaffold. As a result, concurrent strategies lead to the discovery of the [n.1.0] bicyclic alkane series represented by **25**. Although Schering has recently reported various novel scaffolds having significant MCH-R1 activity [55], the majority of efforts appeared to concentrate on the optimization of the scaffold **25**, as this compound appeared a promising lead (MCH-R1 ~ 2.7 nM, $t_{1/2}$(iv) = 4 h, AUC_{oral} = 2140 ng h/mL, food intake reduction (mouse): 77% @ 2 h, 76% @ 6 h, 78% @ 24 h). A variety of efforts included modifications on the bicyclic ring (4.1.0 < 3.1.0) and the replacement of the aryl rings with heteroaryl ring systems [56]. Pharmacokinetic data suggested that the urea linkage may have been a potential issue, as a result, a series of SAR studies led to the identification of potent MCH-R1 antagonists by using the benzimidazole as a bioisotere for the urea in **25** [57]. This SAR understanding was subsequently incorporated into the lead [3.1.0] bicycloalkane series to provide compounds such as **26** [58]. Schering has recently disclosed additional SAR and brain penetration data on the bicyclo [3.1.0] hexyl urea scaffold, suggesting that this class may be most advanced currently [59]. However, no cardiovascular data have been disclosed in any of the publications reviewed above.

In addition, Schering has published work on the 4-substituted piperidine scaffold **27**, which had emerged from an HTS screen of 600 compounds [60], and on a tetrahydroisoquinoline scaffold [61], both of which provided submicromolar antagonists at MCH-R1. No *in vivo* efficacy data were given. Finally, it appeared that no patent applications published in the 2005–2006 timeframe from Schering on MCH-R1 antagonists.

Taisho has recently reported a number of 4-(dimethylamino) quinazoline analogs that have potent MCH-R1 antagonist activity. From this class of compounds, ATC-0175 (**28**) emerged from a series of SAR studies directed to optimize MCH-R1 antagonist activity of early non-selective leads from HTS using Arena's CART platform [62]. ATC-0175 (**28**) proved to be a highly selective MCH antagonist (MCH-R1 = 3.4 nM, Y5 = 2700 nM, α2a = 260 nM, α2a/MCH = 76) that was progressed to *in vivo* studies [63]. In the 4-day mouse diet-induced obesity model, ATC-0175 reduced body weight significantly without changes in lean mass [64]. More recently, Taisho has reported further modifications in order to improve pharmacokinetic parameters of compounds in the series, resulting in the cyclohexylaminoquinazoline scaffold, of which ATC-0065 (**29**) proved to have the best profile overall (MCH-R1 = 16 nM, $t_{1/2}$ human liver microsomes = 73 min, $t_{1/2}$ rat liver microsomes = 30 - min) [65]. Although there have been no reports of cardiovascular effects for these classes of antagonists, Taisho has recently reported on the *in vivo* effects of several leads in models of anxiety and depression [66]. In addition, Taisho has recently filed several applications covering simplified versions of the quinazoline scaffold, such as the substituted pyridine **30**, which may represent the next generation of emerging antagonists within this family [67–69].

Conclusions

Despite the large number of drug-discovery programs dedicated to finding small-molecule MCH-R1 antagonists for the treatment of obesity and/or mood disorders, a very limited number of these have progressed into the clinic. Beyond the common challenges in drug design related to ADME and safety profiles, cardiovascular risk involving hERG-binding activity and drug-induced QTc prolongation has been a major hurdle for a significant number of MCH-R1 research programs. Early leads MCH-R1 antagonists containing a 4-phenyl benzamide functionality (in particular those based on Takeda's early lead T-226296 [70]) have had the tendency to display significant hERG-binding activity. Many of these programs have evolved, and now more selective MCH-R1 antagonists are emerging in order to address the potential for cardiac risk. A few novel and promising MCH-R1 antagonists have progressed from these efforts; however, in the majority of the cases, the design elements addressing the hERG issue have led to compounds that are either devoid of *in vivo* activity or unsuitable for clinical development on the basis of their overall ADME and safety profiles. Cardiovascular risk associated to hERG-binding activity has not yet been reported for research programs by Taisho and Neurogen that have structurally unique MCH antagonists not derived from biaryl-containing early leads. Neurogen's MCH-R1 program is the only one reported to advance into Phase I clinical trials in the past two years from among all other existing pre-clinical programs. Despite the significant challenges encountered by many research programs, pharmaceutical companies continue to pursue this very attractive target since an orally active MCH-R1 antagonist could find multiple applications as an effective treatment for obesity and/or depression–anxiety disorders.

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