

Novel Approach for Chemotype Hopping Based on Annotated Databases of Chemically Feasible Fragments and a Prospective Case Study: New Melanin Concentrating Hormone Antagonists

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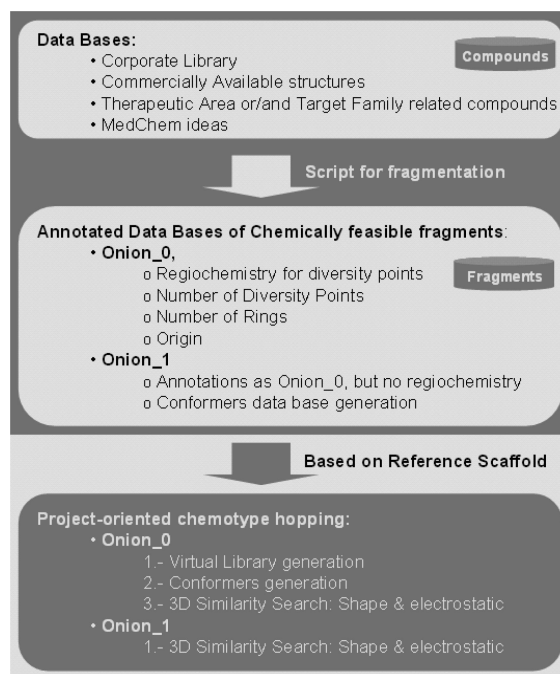
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A novel strategy for chemotype hopping, based on annotated databases of chemically feasible fragments and their oriented functionalization, is presented. A three-dimensional (3D) similarity analysis of project-oriented functionalized scaffolds provides a prioritized proposal for synthesis with the most appropriate linkers and optimal regiochemistry on R-groups. This strategy maximizes the potential of proprietary and commercially available compounds. A retrospective and prospective case study, on melanin concentrating hormone (MCH) antagonists, showing the impact on the drug discovery process of this new strategy by maintaining primary activity and improving key ADME/Tox property while enhancing intellectual property (IP) position is demonstrated.

Introduction

A primary goal of drug discovery is to reach the clinical phase with a candidate molecule having viable pharmacokinetic parameters, a low toxicity profile, and a solid intellectual property position. A failure in any one of the multifarious requirements of a candidate drug may thwart or terminate this process; therefore, it is preferable to pursue multiple chemotypes, so bioisosteres to the main chemical series are often sought. This is known as scaffold hopping. In recent years, the term scaffold has been used extensively in the context of describing the central core component of a molecule.¹ According to Schneider, scaffold hopping is defined as “identification of iso-functional molecular structures with significantly different backbones”,² therefore keeping the key interactions between scaffold and receptor while changing its chemical structure. The assumption in this process is that the key interactions with the receptor are preserved, maintaining binding affinity while modifying drug-like properties and improving IP position. In this work the scaffold hopping is focused on the central skeleton replacement while maintaining the key pharmacophoric features from a well-defined substitution pattern of R-groups transferred to the new scaffold(s). Only a few methods^{3,4} address the central skeleton as a fragment that can be replaced while keeping the R-group substituents. Published 3D scaffold hopping methods outperform bidimensional (2D) methods,^{5,6} and there is one reported method successfully linking 3D molecular properties of the scaffold with geometrical information and synthetic feasibility.⁴ Ideally, screening methods that demonstrate successful scaffold hopping should find not only a maximal number of chemotypes but also a diverse set.⁷

Scheme 1. Flow Chart of the Proposed Strategy with Two Main Phases: 1, Generation of Annotated DBs of Chemically Feasible Fragments; 2, Chemotype Hopping Based on DBs Previously Generated



To define a systematic approach ready to look for alternative chemotypes, a general strategy was implemented as shown in Scheme 1. The process is as follows: (a) build annotated database (DB)^a of chemically feasible fragments describing the number of diversity points, regiochemistry, number of rings, and origin; (b) generate a virtual library according to the substitution pattern for the reference compound (only the atoms closest to the main chemotype borne by the reference compound

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^a Abbreviations: MCH, melanin-concentrating hormone; VL, virtual library; ET, electrostatics Tanimoto; TS, Tanimoto shape; EF, enrichment factors; R, recall; TA, therapeutic area; DB, databases.

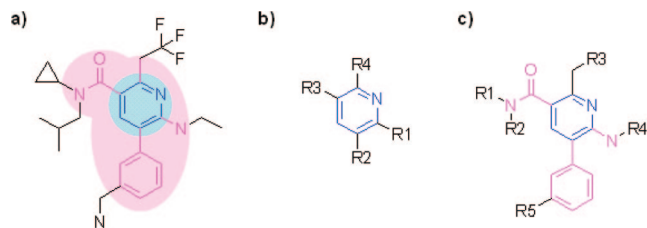


Figure 1. Illustration of the fragmentation script applied to compound **a** provides as result from "Onion0" the closest fragmentation around each ring system, e.g., driving to fragment **b**, pyridine (color-coded in blue), with its corresponding growing vectors. In this case, pyridine, more detailed information is provided through "Onion1" fragmentation **c**, color-coded in pink, including some additional functionalities. Then, from compound **a**, phenyl and cyclopropyl are also considered as ring systems, and the same fragmentation exercises, Onion0 and Onion1, are performed around them.

are considered to construct the virtual library); (c) conformer generation of the constructed virtual library; (d) alignment of conformers to the reference structure and then prioritization based on shape and electrostatic similarity in 3D, therefore avoiding bidimensional chemical structure.

In addition to a detailed description of the new strategy for chemotype hopping, a retrospective and prospective case study is reported in this paper to validate and illustrate the impact of this approach on the drug discovery process.

Method

Database Preparation. All fragments included in these databases were extracted from compounds already synthesized and so, by definition, chemically feasible. Compounds are extracted from corporate databases, external supplier databases, therapeutic area (TA) databases (in this case, central nervous system, CNS), target families related ligands databases, and a database based on MedChem experience. Before doing any fragmentation, rare elements and salts are removed. Structures are standardized, through tautomer generation and their canonization. Duplicates are eliminated by using a customized Pipeline Pilot⁸ protocol. Fragment abstraction is performed at different levels from original compound databases, by using a program coded in the scientific vector language (SVL) of the software system MOE.⁹ The SVL script utilized in this study was developed in collaboration with the Chemical Computing Group (CCG) and is publically available. In general, two fragmentation levels are utilized, Onion0 and Onion1, so each database is in duplicate with fragments from each of those two levels. Onion0 fragmentation level provides structures from the closest fragmentation around each ring system contained within compounds, plausible central scaffolds, driving to "naked" chemotypes decorated only with their corresponding growing vectors or anchor points. Onion1 fragmentation delivers a more elaborate structure with not only the information for the atom at a distance of one atom from each ring system but also information about the functionality of that atom. If the atom belongs to a functional group such as an amide or ester, for example, or is part of an aromatic ring, its whole functionality is conserved as shown in Figure 1. Sometimes functionalities close to the central core play a key driving force in ligand–receptor interactions together with main chemotype. Therefore, having these two fragmentation levels, Onion0 and Onion1, provides an additional value to our fragment database in comparison with those derived from existing approaches for fragment generation.¹⁰

All fragments included in the databases have at least one ring and are annotated with the most relevant information such as regiochemistry, the position for anchor points from where chemotypes can be functionalized, the number of diversity points, the number of fused rings, molecular weight, source, phase (preclinical, phase I, II, or III), and some other in-silico estimated properties

such as ClogP, molecular weight, and polar surface area (PSA) as calculated by ACD software¹¹ (Table 1).

Johnson & Johnson (J&J) Corporate Database. Using an updated version of the previously reported J&J database,¹⁷ currently more than 1.5 million compounds, the above-described program was utilized to obtain Onion0 and Onion1 fragment databases. Generation of each of those two databases took ~15 h in a Linux workstation (as CPU, Dual Core AMD Opteron 2.3 GHz and 8GB RAM). Onion0 fragmentation, utilized in the case study reported below, drove to a database with 42,499 unique fragments. Data mining is required to archive only those fragments useful for chemotype hopping; therefore, the following criteria were applied: (i) fragments bearing at least one ring, (ii) molecular weight between 60 and 300, and (iii) number of diversity points from 1 to 4. Thus, the Onion0 J&J corporate database contains around 12,585 unique fragments fitting these criteria. An identical procedure has been applied to our database of compounds accessible from external suppliers, ready to be acquired; in this case, we have around 39,912 unique fragments for Onion0 meeting the criteria described above. Finally, to define therapeutic area DB, in-house information from J&J together with data from external databases, such as Integrity by Prous Science,¹⁸ was utilized to build up CNS oriented fragments DB, where Onion0 CNS DB has 4,686 unique annotated fragments and there are around 10,872 Onion1 fragments. Once the fragment databases for each of these, at least four, databases (corporate, external suppliers, therapeutic area, or target family oriented and MedChem) are ready to be used, then, project-oriented chemotype hopping may start.

Fragments DBs in Project-Oriented Chemotype Hopping. Different strategies are applied for Onion0 and Onion1 fragment DBs, respectively, in this proposed approach for chemotype hopping. Regarding Onion0, the first step is defining which fragments from this database are used in each case; then, only those scaffolds meeting certain criteria are selected, for example, a certain number of rings and number of diversity points. This decision is guided by the reference structure. The next step is the identification of the closest key minimal substitution pattern around the reference compound at one atom distance from the central core. Then, this substitution pattern is utilized together with other potentially interesting linkers or substitutions to build up a virtual library (VL) using the annotated anchor points, their regiochemistry, from previously selected scaffolds; this is illustrated below in the case study. Regarding Onion1, all anchor points are capped as methyl and the corresponding capped Onion1 fragment DB is further utilized without any additional manipulation in any drug discovery project where it is required (Table 2); thus, no virtual library is built.

Once the focused virtual library from the Onion0 fragment DB is built and Onion1 DB is properly capped, the corresponding conformers for each of these two set of compounds are generated. Software developed by OpenEye,¹⁹ Omega,²⁰ is utilized to explore the conformational space around each functionalized chemotype within an energetic window of 25 kcal/mol, where conformers with root of mean squared deviation (rmsd) >0.4 Å are stored until a maximum number of 500.²¹ This is the most time-consuming step; a library with 58,565 structures takes ~19 h using the workstation described above. Fragments from Onion1 fragmentation are not further functionalized, just capped; therefore, once their corresponding conformer database is constructed, they can be utilized against any reference compound for any project without any additional manipulation.

Similarity Analyses. Once all conformers, from Onion0 project-oriented functionalized fragments and from Onion1 capped fragments, have been generated, we have to align them with the corresponding reference compound before doing any further analysis. In this case we utilize the ROCS (rapid overlay of chemical structures) package,²² by Open Eye, to perform the alignment because this is a fast and accurate²³ method for superimposing molecules. Shape similarity can be determined, in part, by comparing the shapes of those molecules. This effectively reduces to calculating the overlap volume between two molecules and has been

Table 1. Representative Set of Compounds from Database Obtained after Applying Fragmentation Script at Two Levels, Onion0 and Onion1, for CNS Reported Compounds

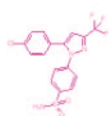
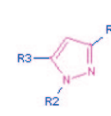
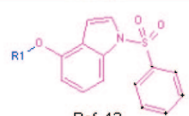
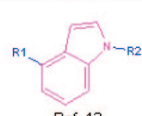
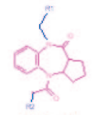
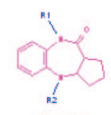
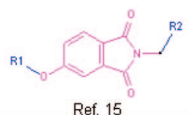
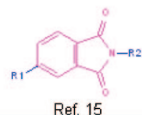
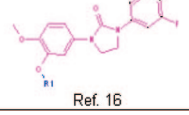
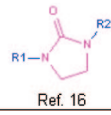
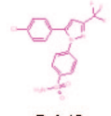
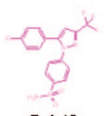
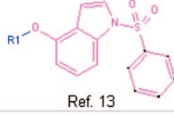
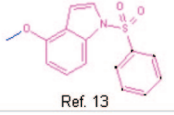
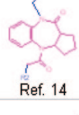
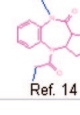
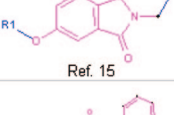
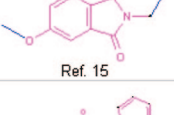
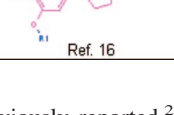
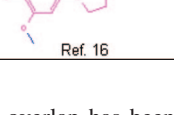
Onion_1 Fragments DB ^a	Onion_0 Fragments DB ^b	N_Diversity Points ^c	N_Rings ^c	Origin ^c	MW ^c	ClogP ^c	PSA ^c
 Ref. 12	 Ref. 12	3	1	CNS	68.08	0.32	17.82
 Ref. 13	 Ref. 13	2	2	CNS	117.15	2.14	4.93
 Ref. 14	 Ref. 14	2	3	CNS	202.25	1.73	23.55
 Ref. 15	 Ref. 15	2	2	CNS	147.13	1.15	37.38
 Ref. 16	 Ref. 16	2	1	CNS	86.09	-1.23	23.55

Table 2. Representative Set of Onion1 Fragments, for CNS Reported Compounds, Capped

Onion_1 Fragments DB	Capped Onion_1 Fragments DB	Origin ^a
 Ref. 12	 Ref. 12	CNS
 Ref. 13	 Ref. 13	CNS
 Ref. 14	 Ref. 14	CNS
 Ref. 15	 Ref. 15	CNS
 Ref. 16	 Ref. 16	CNS

previously reported.²² Once the overlap has been optimized, the shape similarity may be computed by Tanimoto equation. However, ROCS does not contain an accurate notion of charge distribution and therefore is not a complete solution to the search for molecular similarity. The electrostatic fields of molecules can be calculated and the similarity between fields expressed as the electrostatic Tanimoto. Electrostatic Tanimoto (ET) scores are calculated using the EON program,²⁴ by Open Eye. Molecules are superimposed

using ROCS, providing shape similarities versus reference compound, and electrostatic potentials calculated using OpenEye's ZAP Poisson–Boltzmann solver implemented in EON. In this case the ET is calculated using an external dielectric of 80, thus accounting for dampening of electrostatic field by aqueous solvent, and may better represent the field experienced upon binding a protein.²⁵ A normalized shape Tanimoto of unity indicates that the molecules are identical, and the Tanimoto tends to zero as molecules become less similar; the electrostatic Tanimoto ranges from -0.3 to $+1$, indicating dissimilar and similar electrostatic fields.¹⁹ From each original fragment library top-ranking compounds, in terms of shape and electrostatics, may be selected.

Biological Target Utilized in the Described Case Study and Reported Known Ligands for the Target. We were interested in melanin-concentrating hormone (MCH) as a therapeutic target in one of our projects at J&J. This was an outstanding opportunity to validate this novel strategy for chemotype hopping from two points of view: (a) retrospective validation, because there are several published patents and papers describing different MCH-R1 antagonists (Table 1), and (b) prospective validation, which is the impact of this new approach in a real scenario of a drug discovery project, looking for a new chemotype in an active project. Thus, this was our case study to check the value of this novel strategy. 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.^{26–28} Biological function for MCH-R2 remains unclear to date,²⁹ but many published studies indicate that MCH-R1 is involved in biological processes related to mammalian feeding behavior and energy expenditure.^{30,31} In addition, it has been suggested that MCH-R1 plays a key role in anxiety and mood disorders because MCH-R1 antagonists have been found to have anxiolytic and antidepressant effects in various animal models.^{32,33} MCH-R1 is a very attractive target because 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.²⁹ Despite the large number of drug discovery programs dedicated to finding small-molecule MCH-R1 antagonists for the treatment of obesity and/or mood

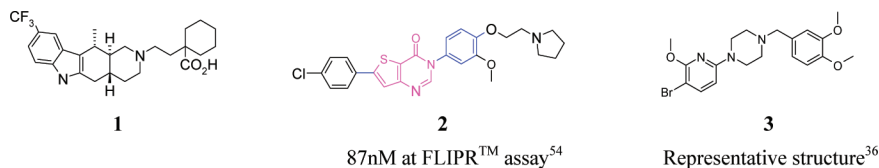


Figure 2. Melanin-concentrating hormone receptor 1, MCH-R1, antagonists in the clinic. Compound **2** is our reference structure where in magenta is the central scaffold and in blue its closest substitution pattern which is key to build the VL from Onion0.

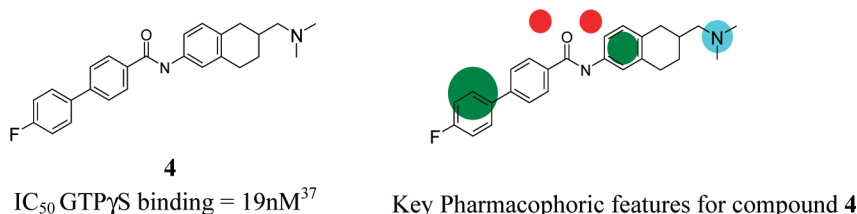


Figure 3. Takeda compound and its key pharmacophoric features as a bidimensional representation (2D): in green, aromatic as chemical feature; in red, hydrogen bond acceptor (in this case, projection points are represented); in blue, titratable nitrogen at physiological pH.

disorders (more than 15 pharmaceutical companies have been actively looking for MCH-R1 antagonists), a very limited number have progressed into the clinic; in fact, only three compounds have entered phase I clinical trials: AMG-076 **1**,³⁴ Amgen; GW803430 **2**,³⁵ GlaxoSmithKline; and NGD-4715 **3**,³⁶ Neurogen (Figure 2). The first report of oral activity by MCH-R1 antagonist came from Takeda, T226296 **4**,³⁷ and this biphenyl amide served as a template in the design of a number of series of MCH-R1 antagonists, constrained analogues, from other companies; a well-defined set of key pharmacophoric features (Figure 3) is kept constant among all of them (**5–19**)^{38–52} (Figure 4). Beyond the common challenges in drug design related to ADME and safety profiles, cardiovascular risk involving the human ether-a-go-go related gene (hERG) binding activity and drug-induced QTc prolongation has been the major hurdle for a significant number of MCH-R1 research programs^{29,36} due to this frequently being associated with potential lethal arrhythmias known as torsades de pointes (TdP), which has led to the removal of several drugs from the market.⁵³

Finding optimal small-molecule MCH-R1 antagonists is a real challenge due to (a) target attractiveness, two potential therapeutic applications; (b) cardiovascular risk associated with many reported MCH antagonists; and (c) several pharmaceutical companies³⁶ focused on the same aim; in fact, from 2000, there were more than 55 published patents before ours. Therefore, this was an optimal case to utilize and validate this novel strategy for chemotype hopping: looking for novel chemical series circumventing the cardiovascular issue, keeping primary activity, and providing strong IP position.

Results and Discussion

Retrospective Analysis. Once the new strategy has been defined and its corresponding infrastructure, fragment databases, set up, the approach was validated. Taking advantage of the considerable number of diverse chemotypes reported as MCH-R1 antagonists, 15 different central cores (Figure 4), scaffold hopping was performed. In this case, the central core from the well-known MCH-R1 antagonist in the clinic, **2**, together with its closest substitution pattern (magenta- and blue-colored, respectively) is utilized as reference structure (Figure 5). According to the flowchart implemented with this new strategy (Scheme 1), the first step for project-oriented chemotype hopping is applied: those chemotypes that might fit better with reference substructure, that is, fragments with one or two fused rings and two diversity points, were selected from the Onion0 database. Then, these fragments together with those 15 chemotypes from reported MCH-R1 antagonists, in magenta at Figure 4, were utilized to build up virtual libraries bearing as decoration those

linkers and key substitutions illustrated in the reference substructure, methyl and phenyl, because this may have an impact on the electrostatics of the main chemotype of the reference structure. In addition to these two key R-groups (blue-colored in reference structure **20**), *N*-methyl, *S*-methyl, and methoxy were considered as potential alternatives to methyl; therefore, eight potential virtual libraries were constructed. Considering all scaffolds from the Onion0 fragment DB meeting the previously reported criteria and the additional 15, the corresponding virtual libraries (VL) were generated: (a) VL_A, keeping phenyl at position R₁ and four different options at R₂: methyl, methoxy, thiomethyl, and methylamino; and (b) VL_B, in which those four different options will be borne, in this case, at R₁ and phenyl at position R₂ (Figure 6). Selection of R-groups to build this virtual library was mainly based on the closest substitution pattern around central cores from reported reference compounds (Figures 2, 3 and 4); however, any R-group may be included in this analysis. The most critical stage of this approach is defining the closest substitution pattern for reference scaffold as only one reference structure has to be utilized and many options may be feasible.

These libraries are constructed using MOE software,⁹ and their generation is very fast, just a few seconds. Then, to remove any compound with unwanted chemistry (e.g., any nitrogen–oxygen bond) a Pipeline Pilot⁸ protocol was built and run, obtaining the final, project-based, virtual library from annotated fragments. In total, this final VL contains 58,565 functionalized chemically feasible fragments: 10,811 unique chemotypes. The corresponding conformer database was constructed for this VL, using Omega, and all conformers were aligned with the minimized reference substructure, **20**, using ROCS; the latest process took just 20 min. Then, once overlap was optimized, 3D similarity analysis based on electrostatic fields was computed by Tanimoto equation implemented in EON, as described above. This final step is not time-consuming either, only 55 min for the whole library.

3D similarity values, shape and electrostatics, were computed for the whole virtual library (Figure 7A); therefore, we were able to assess the performance of this analysis using the reported known MCH-R1 antagonists as hits, **5–19**. For this assessment two different points of view were considered: (a) matching not just the chemotype (colored in magenta) but also the substitution pattern (colored in blue), therefore using as the total number of potential samples the whole virtual library, 58,565 compounds; and (b) identifying the chemotype, independent of its substitution

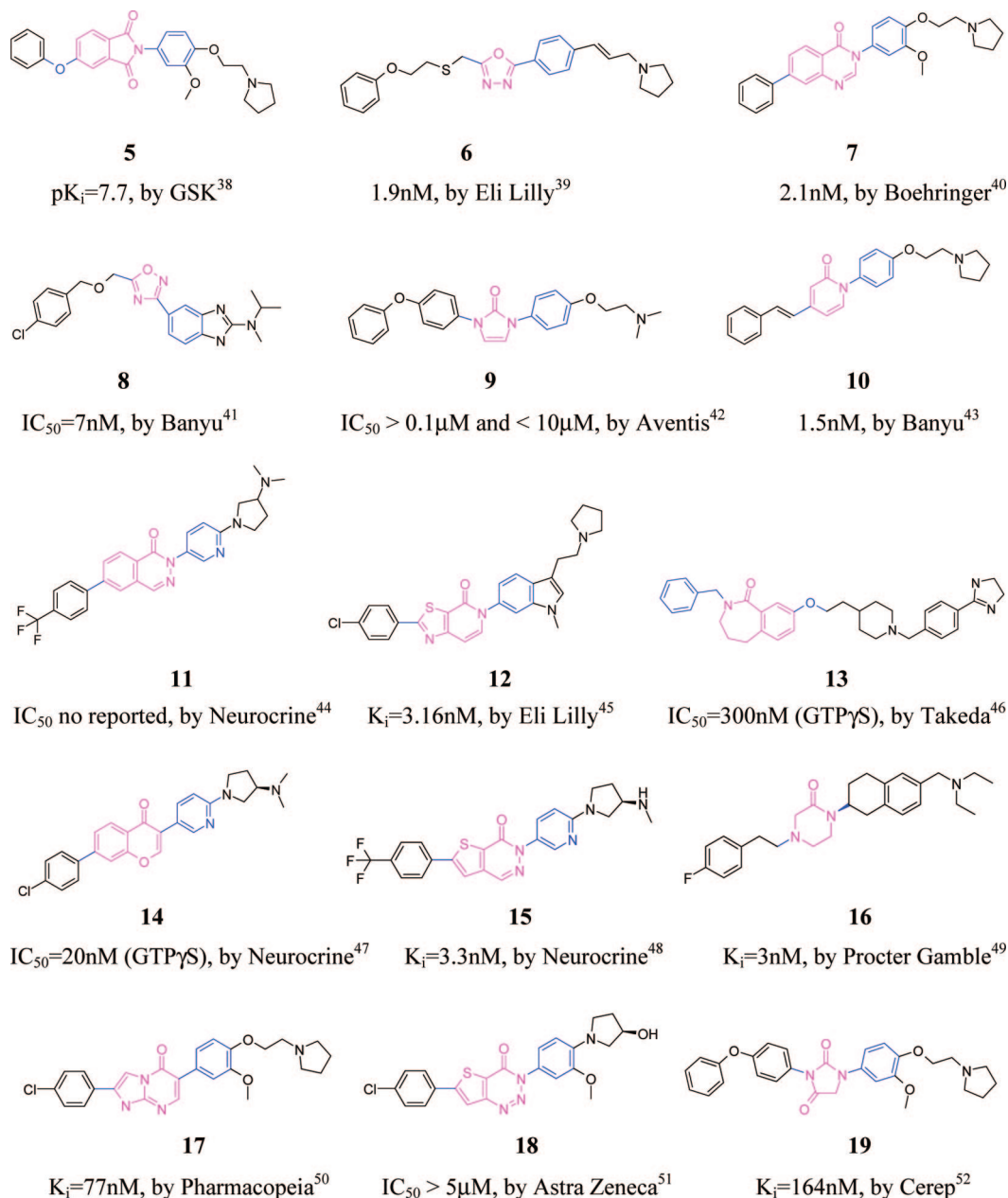


Figure 4. Patented MCH-R1 antagonists bearing different chemotypes (in magenta) but keeping the same pharmacophoric features as compound in clinical phases, **2**, which is a constrained analogue of Takeda's structure, **4**.^{35b} The optimal substitution pattern we will look for during our scaffold hopping approach, in addition to the chemotype, is in blue.

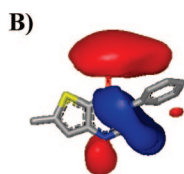
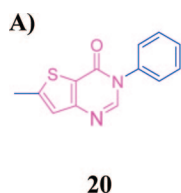


Figure 5. (A) Key substructure **20**, from reference compound **2**, utilized as template for 3D similarity analysis; (B) electrostatic map, obtained with EON, for the reference substructure **20** utilized for chemotype hopping.

pattern; in this case, the total number of samples to consider in the statistical analysis is 10,811 unique chemotypes.

Analyzing similarity values, according to their ranking position based on shape and electrostatics similarity values, we identified at which levels from the whole library those 15 known hits were placed. Thus, corresponding enrichment factors (EF)

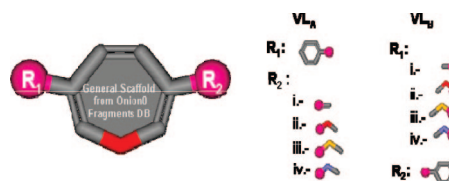


Figure 6. Virtual library generated from those scaffolds from Onion0 as sum of VL_A and VL_B. For R-groups, attachment points are defined by pink balls.

were estimated at different percentages of total number of analyzed samples. These metrics (EF) were utilized not just to assess the value of the approach, retrospectively in this case, but also, together with its corresponding recall (*R*), to define the optimal percentage of the library to be analyzed in a prospective analysis in order to have higher probability to find hits with a reduced number of false positives. In general, queries

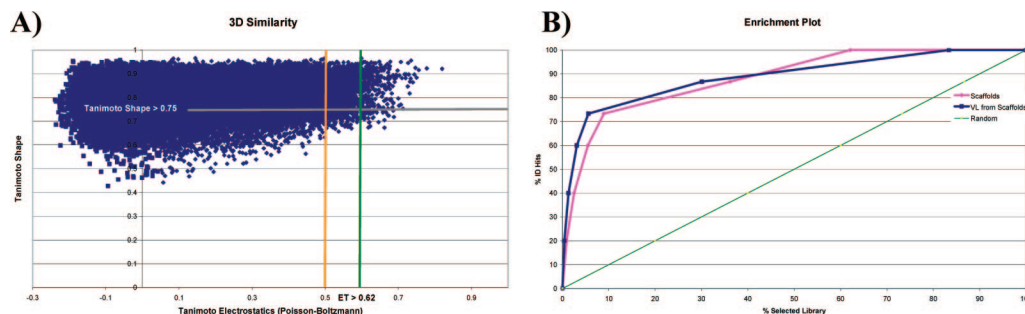


Figure 7. (A) 3D similarity scores: Tanimoto shape and electrostatics values after comparison of the whole virtual library versus reference substructure **20**. (B) Boost plots of the percent hits identified versus percentage of the 3D similarity: score-ordered list selected considering both hit definitions.

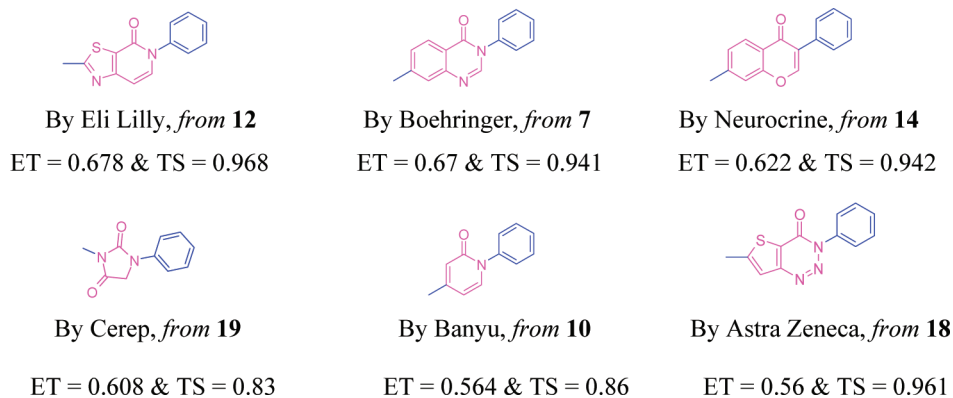


Figure 8. Six hits, chemotypes (in magenta), with proposed optimal substitution pattern (in blue).

with high EF, equivalent to high precision (P), and low recall (R) are likely to be overtrained and therefore poor in prediction, whereas a higher recall and lower precision query may be more appropriate in a virtual screening context;⁵⁵ therefore, combinations of these two parameters, EF and R , were considered to get the optimal balance and, thus, prediction. Formulas for the EF and R are usually expressed as follows (eqs 1 and 2 respectively):^{55,56}

$$EF = (L \times V_A) / (V \times L_A) \quad (1)$$

$$R = V_A / L_A \quad (2)$$

Here L and L_A mean the total number of compounds in a library and the number of experimentally verified bioactive compounds in the library, respectively. V and V_A mean the number of compounds predicted as active and the number of known bioactive compounds contained in V , respectively. An enrichment factor of 1 is equally good as random selection. Recall indicates how many of those known active molecules are selected from the whole set of evaluated structures; a recall value of 0.5 means 50% of hits are identified.

The blue line represented in Figure 7B reports those results (enrichment factor) obtained after considering as hits those compounds from the virtual library that fit chemotypes and substitution pattern (and their regiochemistry) as they are described in Figure 4, magenta and blue substructures (case a, reported above). In this scenario, the highest EF is obtained after analyzing 0.4% of the whole library (234 compounds), where 3 hits, of 15, were found: EF = 50.1 but R = 0.2; this EF is similar to the best value obtained in a previously reported scaffold hopping where a broad set of different virtual screening methods, 2D and 3D, were evaluated: EF = 50.0, after analyzing 2% of the DB.⁶ In this case, the threshold value for electrostatic

Tanimoto (ET) is >0.62 and for Tanimoto shape (TS) >0.75. However, considering as hits those compounds just fitting the main chemotype (magenta-colored substructures in Figure 4; case b, reported above), the results are slightly worse (magenta line in Figure 7B). Thus, using identical criteria as above for ET and TS, 0.62 and 0.75, the top 0.9% ranking of all scaffolds is analyzed: 93 chemotypes of 10,811. For this setup the EF is 23.2; 3 hits were identified, so its corresponding recall is 0.2.

To identify optimal balance, and therefore prediction, between enrichment factor and recall, different combinations for those 3D similarity values reported in Figure 7A have been evaluated as thresholds. In those cases where the threshold value for ET is >0.56 and TS >0.75, the top 1.3% of the whole library (777 compounds; EF = 30.1 and R = 0.4) or the top 2.5% of the whole set of chemotypes (275 scaffolds; EF = 15.7 and R = 0.4), a more balanced situation between EF and R values is obtained. The most important point to highlight from these results, together with this improvement in the balance between EF and R , is the structural diversity provided by those six hits identified in both scenarios: among them and with reference substructure **20**. It is noteworthy that each of these six hits has been patented by a different pharmaceutical company (Figure 8): four hits contain two fused rings, two of those hits contain two fused six-member rings; therefore, they are different from the reference substructure. In addition, there was one hit where the chemotype was just one ring, an aromatic six-member ring, and, finally, one hit with an aliphatic five-member ring as scaffold. This diversity degree within the top-ranked hits, where hit means identifying a different chemotype (no analogue), provides a very important additional value to those metrics (EF and R) utilized for the assessment of this approach.

The lowest limit considered to get a good balance between enrichment factor and recall is defined by ET similarity values

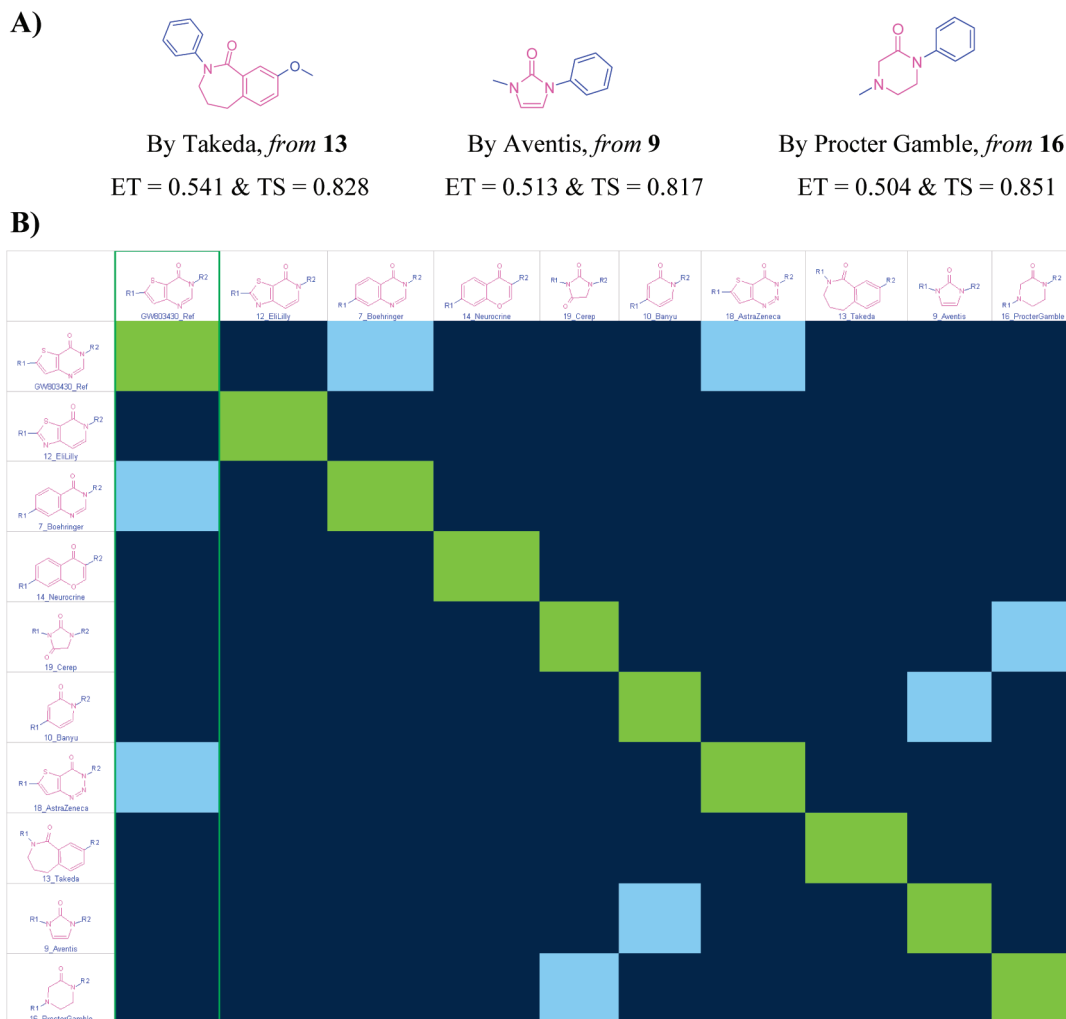


Figure 9. (A) Three additional hits, chemotypes (in magenta), with proposed optimal substitution pattern (in blue). (B) Heat map computing 2D structural similarity, where dark blue means Tanimoto fingerprint (TF) value of <0.3 , light blue for $TF < 0.5$, and green for $TF \geq 0.5$.

>0.50 and $TS >0.75$. In the similarity space defined by these two values the enrichment factor is >10 , and recall has a good value, too, 0.6 . Looking at those compounds placed at this area, the chemical diversity of those three compounds identified hits must be highlighted (Figure 9A): One hit is based on a scaffold built by two fused rings, a seven-member ring and a phenyl, an additional hit is a six-member aliphatic ring, and, finally, we have a five-member ring, a cyclic urea, as the main chemotype for the last hit. The heat map shown in Figure 9B, based on 2D similarity Tanimoto values, quantifies 2D structural similarity among the chemotypes (in magenta) from these nine identified hits and reference substructure **20**, confirming, objectively, the degree of 2D structural diversity among those scaffolds borne by the identified hits. A detailed analysis around the reference chemotype **20**, the box defined by a bright green line, shows that only two of those nine identified chemotypes have a 2D similarity $>30\%$, always lower than 42% (Figure 9B). Two-dimensional structural similarity for these chemotypes (in magenta) together with their proper substitution pattern (in blue) was generated as well to analyze the 2D similarity degree among them; results indicate that only three structures have 2D similarity values $>30\%$, always lower than 50% (this plot is available as Supporting Information, Figure S1). This comparison highlights the poorer sensitivity of the 2D similarity; most of the compounds are collapsed in a range between 0 and 0.3 , thus stressing the use of these 3D approaches to perform a proper prioritization among potential bioisosteric replacements, as was

described in previous papers.^{5,6} Two-dimensional structural similarity analyses are based on circular molecular fingerprints using ECFP_6 descriptors,⁵⁷ implemented in Pipeline Pilot,⁸ that define molecular structure using radial atom neighborhoods.

Retrospective analysis, to validate this new strategy for chemotype hopping, provided us three important keys: the first two assess (a) a clear metric, very good enrichment factors (in a scenario where no analogue is possible), and (b) an additional qualitative added value, confirmed by the heat map, a good degree of structural diversity in top-ranked identified chemotypes; the third key to be applied in a prospective analysis is (c) identification of optimal thresholds, for similarity values (ET and TS), to achieve good balance between enrichment factor (EF) and recall (R) and, thus, prediction.

Prospective Analysis. Finding a small molecule, from novel chemical series, that is a MCH-R1 antagonist circumventing the cardiovascular issue, keeping its primary activity, and providing strong IP position is a real challenge. However, the positive results obtained from this retrospective analysis encourage us to proceed and try to identify new scaffolds by using this new strategy for chemotype hopping. Therefore, the aim for this prospective analysis, applied to an active project, was replacing reference substructure **20** that comes from a compound in clinical phases, **2**, by a new chemotype meeting those criteria described above. Thus, taking advantage of the setup and analysis done in the retrospective analysis, we do not need any additional virtual library from Onion0 and, on the other hand,

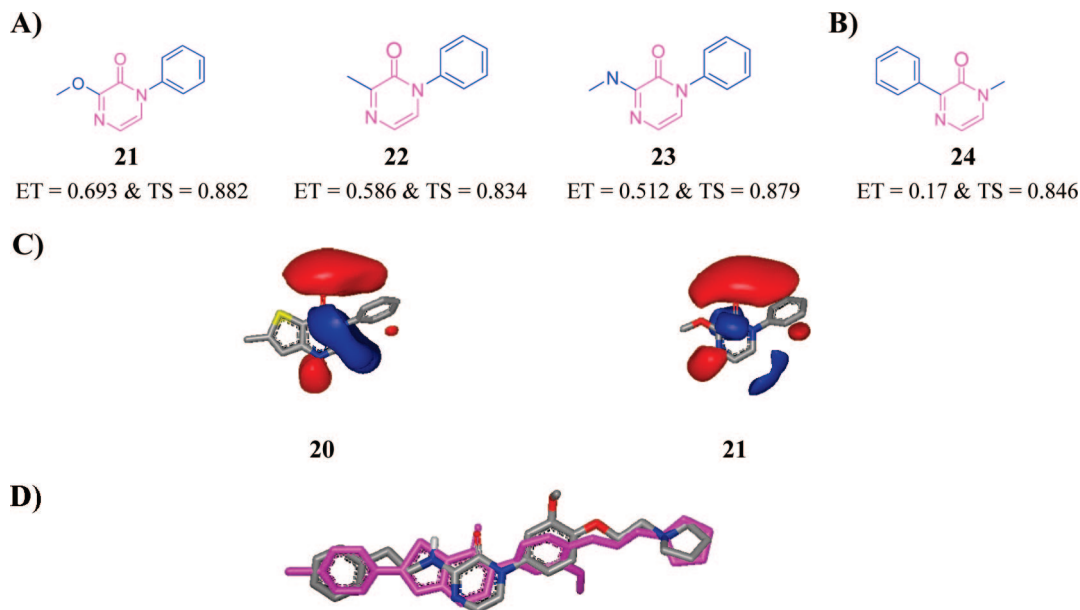
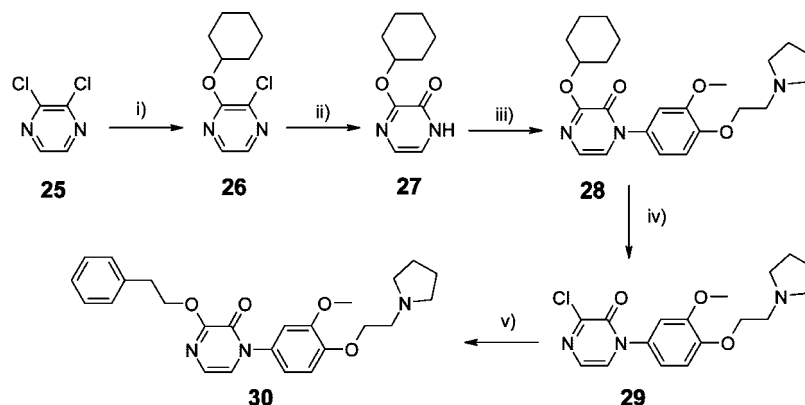


Figure 10. (A) Plausible alternative chemotype, pyrazinone, as central core from these top-ranked structures based on their 3D similarity values vs reference substructure **20**. (B) Impact of linker regiochemistry on electrostatics (ET), comparison between **24** and **22**. (C) Graphical comparison, based on electrostatic maps, between **20** and **21**. (D) 3D alignment of compound **2**, in magenta, with **37**, which bears structure **23**: Omega and ROCS were utilized to perform this alignment.

Scheme 2^a



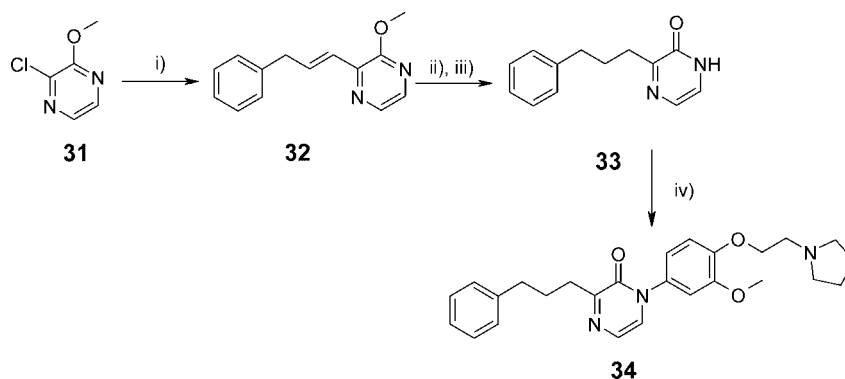
^a (i) NaH (60%), cyclohexanol, 1,2-dimethoxyethane, reflux, 30 min; (ii) NaOH (50%), DMSO, reflux, 1.5 h; (iii) 1-[2-(4-bromo-2-methoxyphenoxy)ethyl]pyrrolidine, CuI, *N,N'*-dimethylethylenediamine, potassium phosphate, dioxane:DMF 5:1, μ W 180 °C, 15 min; (iv) POCl₃, 1,2-dichloroethane, μ W, 150 °C, 30 min; (v) NaH (60%), phenethyl alcohol, 1,2-dimethoxyethane, μ W, 80 °C, 10 min.

the Onion1 conformer database is always ready to be launched. In this case, we were focused on Onion0 and performed a detailed analysis for those top-ranking hits from the virtual library previously described, 58,565 compounds.

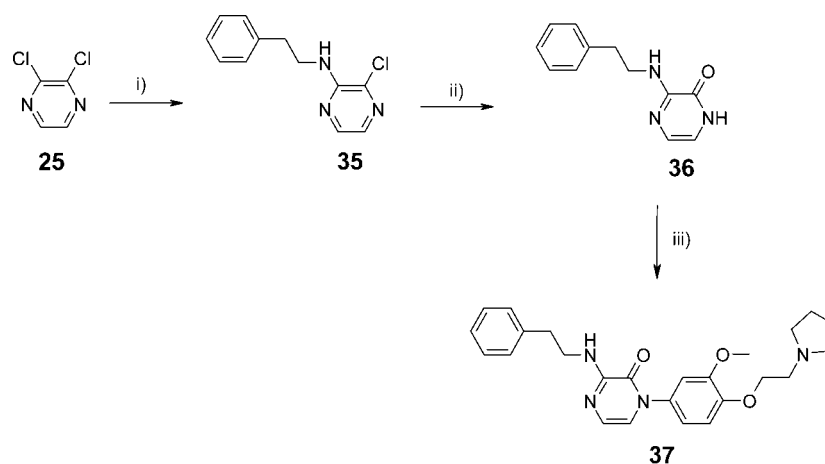
Considering the information obtained in the previous analysis, we were initially focused on those top-ranking compounds with scores for electrostatic Tanimoto (ET) >0.62 and shape >0.75; therefore, we looked at the area (Figure 7A) with highest values for 3D similarity to reference substructure **20**, where we obtained the highest enrichment factors and a moderate recall. Among those 234 compounds, 93 unique chemotypes, there is an interesting virtual compound, **21**, built from a chemically feasible scaffold (in magenta), pyrazinone, that might provide an interesting IP position. Further analyses around this scaffold showed that there were more functionalized fragments bearing this chemotype, among those structures within the constructed virtual library, placed at those areas where there is still a good enrichment factor and the recall is clearly optimized: ET values greater than 0.56 or 0.50, where the latter is the lower limit considered to obtain a reasonably good balance—EF > 10 and

$R = 0.6$ (Figure 10). Comparing electrostatic similarity values between virtual compounds **22** and **24** highlights the impact of this approach to identify not just the most appropriate linkers around the proposed chemotype but also their optimal regiochemistry and, therefore, to address medicinal chemistry efforts.

Once pyrazinone was identified as a potential alternative scaffold to **20**, to check the hypothesis, the synthesis of three tool compounds bearing this chemotype and the optimal linkers with the appropriate regiochemistry, **21–23**, was evaluated. Regarding R-groups around chemotype, the structural information described by all MCH-R1 patented compounds, **2** and **4–19**, which fit the pharmacophoric features described in Figure 3, was taken into account; thus, this knowledge was transferred to the selected new chemotype, with these three linkers, leading to compounds meeting pharmacophoric criteria. Therefore, compounds **30**, **34**, and **37** were proposed and synthesized according to strategies depicted in Schemes 2–4. Two-dimensional differences between compound **2** and proposed compounds bearing this new chemotype are not spectacular, as Figure 10D shows, but drove us to an optimal starting point

Scheme 3^a

^a (i) *trans*-3-Phenylpropen-1-yl-boronic acid, Pd(PH₃P)₄, NaHCO₃ (1 M), dioxane, μ W, 150 °C, 0.5 h; (ii) H₂, Pd/C 10%, MeOH, RT, 4 h; (iii) HCl (6 N)/THF 2:1 μ W 140 °C, 1 h; (iv) 1-[2-(4-bromo-2-methoxyphenoxy)ethyl]pyrrolidine, CuI, *N,N'*-dimethylethylenediamine, potassium phosphate, dioxane:DMF 9:1, μ W 175 °C, 30 min.

Scheme 4^a

^a (i) Phenethylamine, DBU, acetonitrile, μ W, 180 °C, 20 min; (ii) NaOH (50%), DMSO, μ W, 150 °C, 30 min; (iii) 1-[2-(4-bromo-2-methoxyphenoxy)-ethyl]pyrrolidine, CuI, *N,N'*-dimethylethylenediamine, potassium phosphate, dioxane:DMF 9:1, μ W 175 °C, 20 min.

(hit), improving key ADME/Tox property while keeping primary activity and enhancing IP position through a systematic approach.

To prepare the target compounds in a fast and efficient way, microwave irradiation was used in an extensive way.⁵⁸ For the synthesis of target compound **30** (Scheme 2), cyclohexanol was used as protecting group. This group allowed us to hydrolyze selectively the chlorine atom and obtain pyrazinone **27**. Subsequent copper coupling with the corresponding bromoarene under microwave irradiation afforded compound **28**. Cleavage of the protecting group and subsequent chlorination was achieved in one step using phosphorus oxychloride under microwave irradiation to afford compound **29**. Finally, target compound **30** was obtained by nucleophilic aromatic substitution of intermediate **29** with the sodium salt of phenethyl alcohol.

The key step for the preparation of target compound **34** was the formation of the carbon–carbon bond at position 3 of the pyrazinone (Scheme 3). This was achieved by Suzuki reaction of commercially available 2-chloro-3-methoxypyrazine **31** with *trans*-3-phenylpropen-1-ylboronic acid. Further reduction of the double bond by catalytic hydrogenation and acidic hydrolysis of the methoxy group of the intermediate obtained afforded compound **33**, which was coupled with the bromoarene under microwave irradiation conditions to afford target compound **34**.

Preparation of target compound **37** was fast and efficient using a sequence of three steps under microwave irradiation with a total reaction time of 70 min. The first step was the introduction of phenethylamine to get intermediate **35**. Then hydrolysis of

the chlorine atom and subsequent coupling with the bromoarene afforded the desired compound **37**.

Once these three compounds, **30**, **34**, and **37**, were synthesized, they were tested in a cell-based FLIPR assay⁵⁴ measuring their functional antagonism. In all cases, these newly synthesized compounds were equipotent to the reference compound **2**. In addition, due to the cardiovascular risk associated with many reported MCH antagonists, hERG activity⁵⁹ was measured as well driving to in vitro binding affinities >5 times lower than the reference compound in clinical phases, **2** (Table 3).

Through this prospective analysis, real case study, the impact that this new strategy for chemotype hopping may have in drug discovery programs has been clearly exemplified. In this particular case, looking for MCH-R1 antagonists, this new strategy for scaffold hopping drove us to (a) compounds from a new chemically feasible series, where primary functional activity in cells was kept constant and equipotent, (b) a chemotype with good IP position, in fact, a new patent was filled around it,⁶⁰ and (c) changes in the ADME profile; in this case, their affinity for hERG was reduced, >5 times lower. Thus, this case perfectly fits with scaffold hopping definition described in the Introduction: alternative chemical structure, ideally with optimal IP position, preserving the original profile as ligand and binding affinity and improving its drug-like properties.

In addition to the pyrazinone ring, among those 93 unique chemotypes from the top-ranking 234 compounds, there are chemotypes without the amide moiety, which is present in most

Purity for all assayed target compounds **34**, **34**, **37**, and **2** is >95%, as described in the Supporting Information. An ACE C-18 column, 30 × 4.6 mm i.d., 3.0 μm, from Advanced Chromatography Technologies was used with a flow rate of either 2.0 or 1.5 mL/min and a generic gradient of either 80:10:10 AcONH₄ 0.05%/CH₃CN/MeOH to 50:50 CH₃CN/MeOH in 5.2 min to 100% CH₃CN at 5.5 min and equilibrated to initial conditions at 5.8 min until 7.0 min (method 1) or 80:10:10 AcONH₄ 0.05%/CH₃CN/MeOH to 50:50 CH₃CN/MeOH in 6.5 min to 100% CH₃CN at 7.0 min and equilibrated to initial conditions at 7.5 min until 9.0 min (method 2). Flow from the column was split to a single-quadrupole mass spectrometer from Waters for mass spectra acquisition (either a Platform series II, or a ZQ or an LCT Time of Flight) configured with an electrospray ionization source (ESI) using MassLynx-Openlynx software.

2-Chloro-3-cyclohexyloxy-pyrazine (26). A solution of cyclohexanol (5.4 mL, 0.05 mol) in 1,2-dimethoxyethane (15 mL) was added dropwise to a mixture of NaH 60% (2.0 g, 0.05 mol) in 1,2-dimethoxyethane (10 mL), stirred at 0 °C. The mixture was stirred for 10 min at 0 °C. Then a solution of 2,3-dichloropyrazine (5.0 g, 0.034 mol) in 1,2-dimethoxyethane (25 mL) was added, and the resultant reaction mixture was stirred and refluxed for 30 min. Water was added. This mixture was extracted with EtOAc. The separated organic layer was dried (Na₂SO₄) and filtered, and the solvent was evaporated, affording 9.0 g of crude compound **26** (quantitative yield; used in next reaction step without further purification): MS *m/z* 213 [M + H]⁺.

3-Cyclohexyloxy-1H-pyrazin-2-one (27). A mixture of compound **26** (9.0 g, 0.034 mol) in NaOH (25 mL) and DMSO (25 mL) was heated for 90 min at 120 °C. Water was added. This mixture was extracted with EtOAc. A saturated aqueous NH₄Cl solution was added to the separated organic phase. This mixture was extracted with EtOAc. The combined organic layers were dried (Na₂SO₄) and filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂ and EtOAc). The product fractions were collected, and the solvent was evaporated. The residue was treated with diisopropyl ether, then filtered off, and dried, affording 2.4 g of compound **27** (36% two steps): ¹H NMR (500 MHz CDCl₃) δ 1.20–1.31 (m, 1 H), 1.35–1.47 (m, 2 H), 1.55–1.67 (m, 3 H), 1.79–1.87 (m, 2 H), 2.04–2.14 (m, 2 H), 5.03 (tt, *J* = 10.11, 4.05 Hz, 1 H), 6.88 (d, *J* = 4.34 Hz, 1 H), 6.95 (d, *J* = 4.33 Hz, 1 H), 13.01 (br s, 1 H); MS *m/z* 195 [M + H]⁺.

3-Cyclohexyloxy-1-[3-methoxy-4-(2-pyrrolidin-1-ylethoxy)phenyl]-1H-pyrazin-2-one (28). A mixture of compound **27** (2.3 g, 0.012 mol), 1-[2-(4-bromo-2-methoxyphenoxy)ethyl]pyrrolidine⁶¹ (4.5 g, 0.015 mol), CuI (2.3 g, 0.012 mol), *N,N'*-dimethylethylenediamine (2.55 mL, 0.024 mol), and K₃PO₄ (5.1 g, 0.024 mol) in dioxane/DMF 5:1 (35 mL) was heated for 15 min at 180 °C in a microwave oven. CH₂Cl₂ was added. The solid was filtered off through a Celite pad, and to the filtrate was added a 32% NH₃ solution. The organic layer was separated, washed with brine, dried (Na₂SO₄), and filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel. The product fractions were collected, and the solvent was evaporated, affording 4.2 g of compound **28** (85%), used in next reaction step without further purification: MS *m/z* 414 [M + H]⁺.

3-Chloro-1-[3-methoxy-4-(2-pyrrolidin-1-ylethoxy)phenyl]-1H-pyrazin-2-one (29). POCl₃ (5.2 mL, 0.0564 mol) was added to a mixture of compound **28** (4.67, 0.0112 mol) in 1,2-dichloroethane (45 mL), and the resultant reaction mixture was heated for 30 min at 150 °C in a microwave oven. The reaction was poured in an ice–water bath and then basified with a saturated aqueous Na₂CO₃ solution. This mixture was extracted with CH₂Cl₂, then dried (Na₂SO₄), and filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂/MeOH(NH₃) 95:5). The product fractions were collected, and the solvent was evaporated, affording 3 g of compound **29** (77%), used in next reaction step without further purification: MS *m/z* 350 [M + H]⁺.

1-[3-Methoxy-4-(2-pyrrolidin-1-ylethoxy)phenyl]-3-phenethyloxy-1H-pyrazin-2-one (30). Phenethyl alcohol (32.5 μL, 0.27 mmol) was added to a mixture of NaH 60% (17 mg, 0.43 mmol) in 1,2-dimethoxyethane (0.5 mL), stirred at 0 °C. The mixture was stirred for 30 min at room temperature. Then a solution of compound **29** (100 mg, 0.28 mmol) in 1,2-dimethoxyethane (1.5 mL) was added, and the resultant reaction mixture was heated in a microwave oven for 10 min at 80 °C. Water was added. This mixture was extracted with CH₂Cl₂. The separated organic layer was dried (Na₂SO₄) and filtered, and the solvent was evaporated. The residue was purified by column chromatography over silica gel (CH₂Cl₂/MeOH 97.5:2.5), affording 32 mg of compound **30**: ¹H NMR (400 MHz CDCl₃) δ 1.77–1.86 (m, 4 H), 2.59–2.69 (m, 4 H), 2.97 (t, *J* = 6.43 Hz, 2 H), 3.18 (t, *J* = 7.46 Hz, 2 H), 3.86 (s, 3 H), 4.19 (t, *J* = 6.43 Hz, 2 H), 4.54 (t, *J* = 7.67 Hz, 2 H), 6.83–6.90 (m, 3 H), 6.92–6.99 (m, 2 H), 7.19–7.25 (m, 1 H), 7.27–7.36 (m, 4 H); MS *m/z* 436 [M + H]⁺.

2-Methoxy-3-(3-phenylpropenyl)pyrazine (32). A mixture of 2-chloro-3-methoxypyrazine (300 mg, 21 mmol), *trans*-3-phenylpropen-1-ylboronic acid (336 mg, 21 mmol), and Pd(Ph₃P)₄ (243 mg, 0.21 mmol) in dioxane (3 mL) and NaHCO₃ aqueous 1 M (1 mL) was stirred under microwave irradiation at 150 °C for 0.5 h. The solvent was concentrated under reduced pressure. The residue was purified by automated flash column chromatography over silica gel (eluent: CH₂Cl₂ and CH₂Cl₂/MeOH(NH₃); gradient from 100 to 97:3), affording 120 mg of desired compound **32** as a colorless oil (25%): MS *m/z* 227 [M + H]⁺.

3-(3-Phenylpropyl)-1H-pyrazin-2-one (33). To a solution of **32** (120 mg, 0.5 mmol) in MeOH (20 mL) was added Pd/C 10% (catalytic amount), and the mixture was stirred at room temperature under hydrogen atmosphere for 4 h. The reaction was filtered, and the filtrate was evaporated. The residue was dissolved in a mixture of HCl 6 N (2 mL) and THF (1 mL) and stirred under microwave irradiation at 140 °C for 1 h. The mixture was evaporated, affording 94 mg of desired compound **33** (100%): MS *m/z* 215 [M + H]⁺.

1-[3-Methoxy-4-(2-pyrrolidin-1-ylethoxy)phenyl]-3-(3-phenylpropyl)-1H-pyrazin-2-one (34). To a solution of **33** (100 mg, 0.5 mmol) in a mixture of dioxane/DMF 9:1 (2 mL) flushed with N₂ was added 1-[2-(4-bromo-2-methoxyphenoxy)ethyl]pyrrolidine (210 mg, 0.7 mmol) followed by CuI (94 mg, 0.5 mmol), *N,N'*-dimethylethylenediamine (50 μL, 0.5 mmol) and K₃PO₄ (210 mg, 0.9 mmol). The reaction mixture was stirred under microwave irradiation at 175 °C for 0.5 h. The solvent was evaporated, and the residue was purified by automated flash column chromatography over silica gel (eluent: CH₂Cl₂ and CH₂Cl₂/MeOH(NH₃); gradient from 100 to 95:5), affording 20 mg of the desired compound. The compound was precipitated with a mixture of DIPE/heptane (2:1), leading to 10 mg of desired compound **34** as a foam (5%): ¹H NMR (400 MHz, CDCl₃) δ 1.77–1.85 (m, 4 H), 2.05–2.15 (m, 2 H), 2.59–2.69 (m, 4 H), 2.75 (t, *J* = 7.46 Hz, 2 H), 2.92 (t, *J* = 7.67 Hz, 2 H), 2.97 (t, *J* = 6.43 Hz, 2 H), 3.87 (s, 3 H), 4.19 (t, *J* = 6.43 Hz, 2 H), 6.86 (dd, *J* = 8.50, 2.28 Hz, 1 H), 6.92 (d, *J* = 2.49 Hz, 1 H), 6.97 (d, *J* = 8.50 Hz, 1 H), 7.07 (d, *J* = 4.56 Hz, 1 H), 7.13–7.19 (m, 1 H), 7.20–7.31 (m, 5 H); MS *m/z* 434 [M + H]⁺.

2-Chloro-3-phenethylaminopyrazine (35). A mixture of phenethylamine (3.5 mL, 0.028 mol), 2,3-dichloropyrazine (5 g, 0.034 mol), and 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) (5 mL, 0.034 mol) in CH₃CN (60 mL) was heated in a microwave oven for 20 min at 180 °C. The solvent was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH₂Cl₂). The product fractions were collected, and the solvent was evaporated, affording 5.2 g of compound **35** (quantitative yield; used in next reaction step, without further purification): MS *m/z* 234 [M + H]⁺.

3-Phenethylamino-1H-pyrazin-2-one (36). A mixture of compound **35** (5.2 g, 0.028 mol) in NaOH (25 mL) and DMSO (25 mL) was heated in a microwave oven for 30 min at 150 °C. Water was added. This mixture was extracted with EtOAc. The organic layer was dried (Na₂SO₄) and filtered, and the solvent was evaporated. The residue was purified by column chromatography

over silica gel (eluent: CH₂Cl₂/EtOAc 4:1 and 1:1). The product fractions were collected, and the solvent was evaporated, affording 4.4 g of compound **36** (73% two steps): ¹H NMR (500 MHz CDCl₃) δ 2.95 (t, *J* = 7.08 Hz, 2 H), 3.69 (q, *J* = 6.94 Hz, 2 H), 6.10 (t, *J* = 5.49 Hz, 1 H), 6.50 (d, *J* = 4.33 Hz, 1 H), 6.96 (d, *J* = 4.33 Hz, 1 H), 7.19–7.27 (m, 3 H), 7.28–7.36 (m, 2 H), 11.73 (br s, 1 H); MS *m/z* 216 [M + H]⁺.

1-[3-Methoxy-4-(2-pyrrolidin-1-ylethoxy)phenyl]-3-phenethylamino-1H-pyrazin-2-one (37). A mixture of compound **36** (100 mg, 0.46 mmol) 1-[2-(4-bromo-2-methoxyphenoxy)ethyl]pyrrolidine (160 mg, 0.55 mmol), CuI (80 mg, 0.46 mmol), *N,N'*-dimethylethylenediamine (98 μL, 0.92 mmol), and K₃PO₄ (190 mg, 0.92 mmol) in dioxane/DMF (3.5 mL; 9:1) was heated for 20 min at 175 °C. CH₂Cl₂ was added. The whole was filtered through a Celite pad, and the filtrate was treated with an aqueous NH₄Cl solution. The organic layer was separated, dried (Na₂SO₄), and filtered, and the solvent was evaporated. The residue was purified by column chromatography (eluent: CH₂Cl₂ and CH₂Cl₂/CH₃OH 97.5:2.5, 95:5, and 90:10). The product fractions were collected, and the solvent was evaporated, affording 130 mg of compound **37** (65%): ¹H NMR (400 MHz CDCl₃) δ 1.78–1.89 (m, 4 H), 2.69 (br s, 4 H), 2.98 (t, *J* = 7.05 Hz, 2 H), 3.00 (t, *J* = 6.22 Hz, 2 H), 3.71 (q, *J* = 7.05 Hz, 2 H), 3.86 (s, 3 H), 4.21 (t, *J* = 6.43 Hz, 2 H), 6.33 (t, *J* = 5.81 Hz, 1 H), 6.55 (d, *J* = 4.77 Hz, 1 H), 6.87–6.93 (m, 3 H), 6.97 (d, *J* = 8.29 Hz, 1 H), 7.18–7.35 (m, 5 H); MS *m/z* 435 [M + H]⁺.

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Supporting Information Available: Purity and retention times for reported synthetic intermediates **26–29**, **32**, **33**, **35**, and **36** as well as HPLC traces for assayed target compounds **30**, **34**, **37**, and **2**; an additional figure, S1, is also included. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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