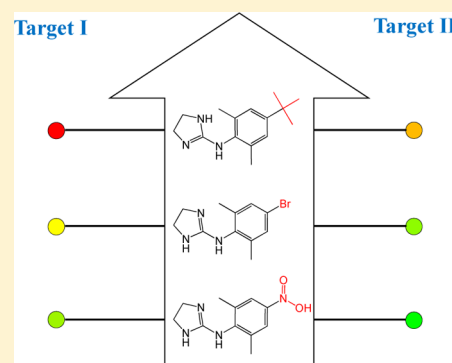


SAR Transfer across Different Targets

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ABSTRACT: Despite obvious relevance for the practice of medicinal chemistry, SAR transfer events have thus far only been little investigated in a systematic manner. Two types of SAR transfer can principally be distinguished. In *target-based* SAR (*T_SAR*) transfer, a series of corresponding analogs with different core structures display comparable potency progression against a given target. In addition, in *series-based* SAR (*S_SAR*) transfer, a given analog series shows comparable potency progression against two or more targets. Only a few studies have previously investigated *T_SAR* transfer. In these studies, *T_SAR* transfer series were frequently found for targets belonging to different families. By contrast, *S_SAR* transfer has thus far not been explored. It is currently unknown to what extent these *S_SAR* transfer events might occur in available compound data. We have devised an approach to detect *S_SAR* transfer and systematically searched public domain compound data for *S_SAR* transfer events. In total, 63 *S_SAR* transfer series involving two targets and 26 series involving three targets were identified. Series involving four targets were not found. The majority of *S_SAR* transfer series were identified for different subfamilies of G protein coupled receptors, but transfer series were also found for other target families. However, *S_SAR* transfer across different families was not observed. On average, *S_SAR* transfer series consisted of five to six analogs. The series were structurally diverse and represented SARs with varying degrees of continuity or discontinuity but displayed closely corresponding potency progression across related targets. All series and the corresponding source data sets are made freely available.



INTRODUCTION

In medicinal chemistry, transfer of SAR information can be rationalized in at least two ways. First, SAR transfer can involve different compound series with activity against a given target. In this case, an SAR transfer event is facilitated if series with different core structures share pairs of corresponding analogs that display comparable potency progression against the target, as illustrated in Figure 1a. We term this type of transfer event *target-based* SAR (*T_SAR*) transfer. The attractiveness of *T_SAR* transfer for the practice of medicinal chemistry is evident. If a compound series with promising SAR characteristics is synthetically difficult to evolve or associated with ADME/Tox liabilities, one would like to replace the common scaffold with another one that can be further developed by making prospective use of the already obtained SAR information. The underlying assumption is that both core structures and corresponding analogs have conserved binding modes and form very similar interactions within the target's binding site. Another type of SAR transfer can also be considered that involves an individual series and different targets. In this case, a single compound series should display comparable potency progression against two or more targets, as illustrated in Figure 1b. Thus, one would like to transfer a given series from one target to another, without significant loss of SAR information. Accordingly, we term this type of SAR transfer event *series-based* SAR (*S_SAR*) transfer. It should be pointed out that target specificity/selectivity of active compounds and *S_SAR* transfer are essentially mutually

exclusive concepts. In addition to *T_SAR* transfer, *S_SAR* transfer is also relevant for medicinal chemistry and chemical biology, for example, for the chemical exploration of a target family or selectivity studies of closely related targets. The underlying assumption is that two targets interact very similarly with given compounds. It follows that these targets should have similar binding sites, and we would thus expect that *S_SAR* transfer might mostly be confined to related targets. Although SAR transfer represents an intuitive concept that is attractive for medicinal chemistry, surprisingly little efforts have thus far been made to analyze SAR transfer events in a systematic manner. Only a few studies have computationally (and in different ways) analyzed *T_SAR* transfer events^{1–3} but not *S_SAR* transfer. Different from *T_SAR* transfer, the systematic study of *S_SAR* transfer is distantly related to comparative QSAR where activity of a series of analogs is compared for two closely related targets such as enzyme or receptor isoforms. Comparative QSAR has a single-series focus and does not require analogs to have very similar potency progression against the given targets. In addition, 3D-QSAR modeling has also been applied to extract SAR information for a given active compound^{4,5} but not *S_SAR* transfer series.

We have investigated *S_SAR* transfer in a systematic manner through compound data mining. It is presently unknown if and to what extent *S_SAR* transfer events might occur across

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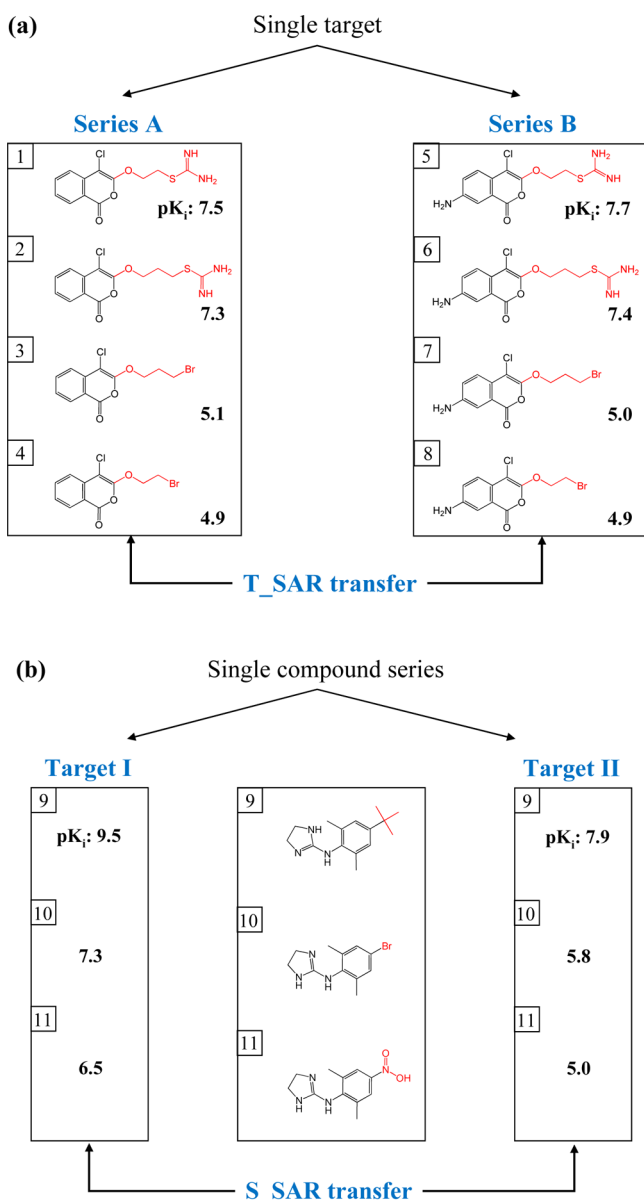


Figure 1. SAR transfer categories. The schematic representation illustrates different types of SAR transfer events. (a) *T_SAR transfer*. Compound series with different core structures and corresponding pairs of analogs yield comparable potency progression against a given target. Corresponding substituents in analogs forming the two series are colored red. (b) *S_SAR transfer*. Analogs comprising a single series display comparable potency progression against multiple targets. R-groups in analogs are colored red. Compound structures are consecutively numbered in Figures 1, 3, 4, and 5.

different targets and how many targets might be involved in *S_SAR transfer*. Herein, we report a generally applicable approach for the detection of *S_SAR transfer* and the results of a systematic search for *S_SAR transfer* series.

MATERIALS AND METHODS

Compound Data Set. From ChEMBL⁶ (release 14), the currently most comprehensive source of compound data from medicinal chemistry, compounds directly interacting (i.e., ChEMBL target relationship type “D”) at the highest confidence level (i.e., confidence score 9) with two, three, or four human targets were systematically extracted following a

previously described protocol.⁷ Only equilibrium constants were considered as potency measurements. Assay-dependent IC_{50} values were not considered. Approximate potency values such as “>”, “<”, and “~” were discarded. If multiple K_i measurements were available for a compound and a target, the geometric mean of these values was calculated as the final potency annotation. Data sets were required to contain a minimum of six compounds. Many targets participated in multiple sets, depending on the number of other targets they shared at least six active compounds with.

A total of 118 target pair data sets comprising 6,562 compounds were obtained. Eight of the 118 sets contained more than 200 compounds. In addition, 62 data sets of compounds active against three and 34 data sets with activity against four targets were selected. Targets were assigned to families on the basis of the ChEMBL target classification scheme⁶ and the UniProt⁸ family organization.

Matched Molecular Pairs. We have applied the matched molecular pair (MMP) concept⁹ to identify *S_SAR transfer* series. An MMP is defined as a pair of compounds that only differ by the exchange of a substructure at a single site.⁹ This substructure exchange can be understood as a chemical transformation.¹⁰ MMPs were generated as follows. Compounds were systematically fragmented through deletion of one, two, or three nonring single bonds attached to a ring using our implementation of the Hussain and Rea algorithm.¹⁰ Fragments were organized as canonical SMILES strings.¹¹ Deletion of one bond produced two fragments. The larger fragment represented the key and the smaller the corresponding value, which were stored in an MMP index table. Fragments having the same size were each stored once as the key fragment and once as the value. For deletion of two and three bonds, core fragments and two or three terminal fragments were obtained, respectively. Connectivity information was recorded. In each case, the largest fragment was stored as the key and the remaining fragments as values.

S_SAR Transfer Assessment. In each data set, a search was carried out for compound series with at least three analogs. In the MMP index table, analogs shared the same key but had different value(s). The analogs were required to cover at least 2 orders of magnitude in potency against the targets comprising the set. These prequalifying compound series represented our candidates for the exploration of *S_SAR transfer* events.

Compounds from each candidate series were arranged in the order of decreasing potency values against one of their targets, e.g., target A. Therefore, the compound at ranking position i was more potent than the compound at position $i+1$ (or at least equally potent). For the comparison of potency progression, the order of the compounds was retained for all targets. Hence, for a target B, the analogs had to display a potency progression comparable to target A following the preassigned order. If this was the case, the analog series qualified as an *S_SAR transfer* series.

Potency progression across ordered analogs was assessed by calculation of two potency-dependent values. First, pairwise potency differences of the neighboring analogs in a series were calculated for each target, yielding ΔP values. Second, differences between these pairwise potency differences were calculated across the different targets, thus providing $\Delta\Delta P$ values. The ordering of analogs and calculation of ΔP and $\Delta\Delta P$ values are illustrated for two targets in Figure 2 (for larger target numbers, corresponding pairwise comparisons were carried out).

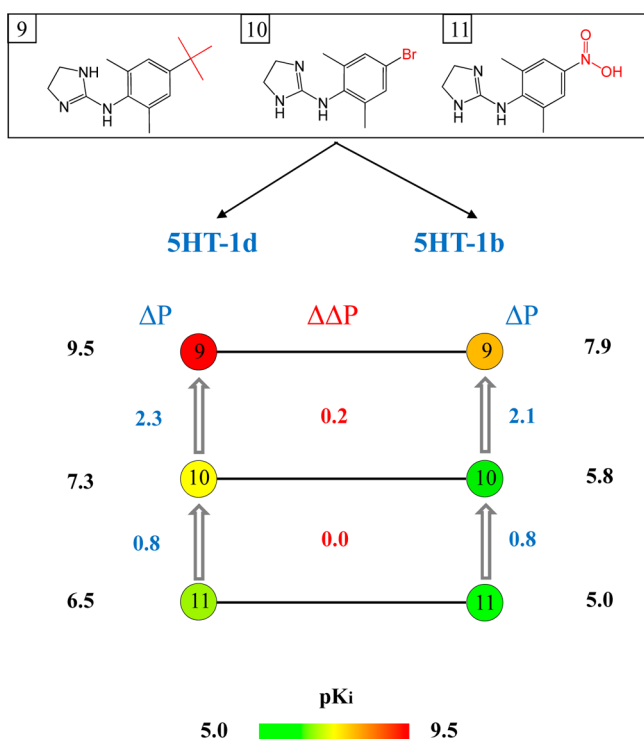


Figure 2. Detection of S_{SAR} transfer. The identification of S_{SAR} transfer series is illustrated. The same compound example is shown as in Figure 1b. Analogs 9–11 are active against two serotonin receptors (5HT-1d and 5HT-1b). A continuous potency spectrum reflecting the potency distribution in the source data set is displayed ranging from green (lowest potency) over yellow to red (highest potency). Potency values against the two targets are represented as color-coded nodes. Compound potency values are aligned with corresponding nodes and vertically calculated ΔP values (blue) and horizontally calculated $\Delta\Delta P$ values (red) are reported.

On the basis of these calculations, a candidate series qualified as an S_{SAR} transfer series if the following three criteria were met:

- No ΔP values were smaller than -0.5 (e.g., -0.6).
- No more than two ΔP values were smaller than -0.25 .
- All $\Delta\Delta P$ values were less than 1.0 order of magnitude (i.e., 1.0 pK_i unit).

According to the compound ordering illustrated in Figure 2, negative ΔP values indicate the presence of a potency increase between two analogs for target A and a corresponding potency decrease for target B, i.e., nonregular potency progression. Thus, setting criteria (i) and (ii) balanced strict regular local potency progression and ensuing boundary effects. However, criterion (i) also ensured that no significant departure from regular potency progression was permitted at any stage and criterion (ii) that only a maximum of two small pairwise potency discrepancies were allowed, regardless of the size of a series. In addition, criterion (iii) ensured the presence of potency progression of comparable magnitude for multiple targets across all analog pairs.

RESULTS AND DISCUSSION

Series-Based SAR Transfer Concept. The analysis of S_{SAR} transfer concentrates on individual analog series with multitarget activities, assesses the potency progression of the series against each target, and compares the pairwise potency progression of ordered analogs across different targets. The

major goal of S_{SAR} transfer analysis is the identification of analog series with corresponding SAR characteristics for different targets.

A detailed analysis of SAR transfer events requires the availability of high-confidence activity data and potency measurements, which rationalizes our stringent compound selection criteria. In the absence of such data, SAR transfer cannot be accurately described.

The application of the S_{SAR} transfer criteria (i)–(iii) detailed in the Materials and Methods section ensured that analogs within a series had regular/continuous potency progression against each target, as assessed by calculation of pairwise ΔP values (vertical progression in Figure 2) as well as comparable stepwise potency progression against pairs of targets, as assessed on the basis of $\Delta\Delta P$ values between targets (horizontal direction in Figure 2). Analogs within a series could be active against multiple targets at different potency levels but had to display regular potency progression against each target and closely comparable potency increases for ordered analogs against all targets.

Combining MMP-based compound series detection and ΔP / $\Delta\Delta P$ potency value-based S_{SAR} transfer analysis made it possible to systematically search compound data sets with multitarget activities for S_{SAR} transfer events.

Identification of S_{SAR} Transfer Series. On the basis of our data selection criteria, we obtained a total of 214 compound sets with multitarget activity data involving two to four targets, which were subjected to the search of S_{SAR} transfer events.

A total of 648 candidate series were identified in 50 of the 118 dual-target data sets. On average, these series consisted of 15 analogs with a standard deviation of 11.4 compounds. Hence, the size of candidate series varied significantly. A total of 63 of these candidate series ($\sim 9.7\%$) met our S_{SAR} transfer criteria and were thus classified as transfer series. In Figure 3a, the size distribution of the dual-target S_{SAR} transfer series is reported. Although 17 series consisted of only three analogs, individual transfer series with up to 20 analogs were detected. On average, a dual-target S_{SAR} transfer series consisted of six analogs with a standard deviation of 2.9 compounds. The target distribution of the dual-target series is reported in Table 1. Although various data sets involving compounds from different families were present in our selection, none of the 63 dual-target S_{SAR} transfer events we detected involved targets from different families. Most S_{SAR} transfer series were identified in the muscarinic acetylcholine receptor M2 vs M3 and the cannabinoid receptor CB1 vs CB2 data sets, which yielded 10 series each. Overall, different types of G protein coupled receptors (GPCRs) dominated the target pair distribution of S_{SAR} transfer events. However, targets from other receptor and enzyme families were also represented including, for example, multiple S_{SAR} transfer series with activity against serine proteases or nuclear hormone receptors.

From 20 of the 62 triple-target data sets, a total of 373 candidate series were obtained, which yielded 26 S_{SAR} transfer series ($\sim 7\%$). Figure 3b reports the size distribution of these triple-target S_{SAR} transfer series, which covered a range from three to 12 analogs. On average, a triple-target S_{SAR} transfer series consisted of five analogs with a standard deviation of 2.4 compounds. In Table 2, the target distribution is reported for the triple-target series. Similar to the dual-target series, GPCRs also dominated the distribution in this case. With 11 series, most triple-target S_{SAR} transfer series were obtained for the opioid receptor μ vs δ vs κ data set, followed

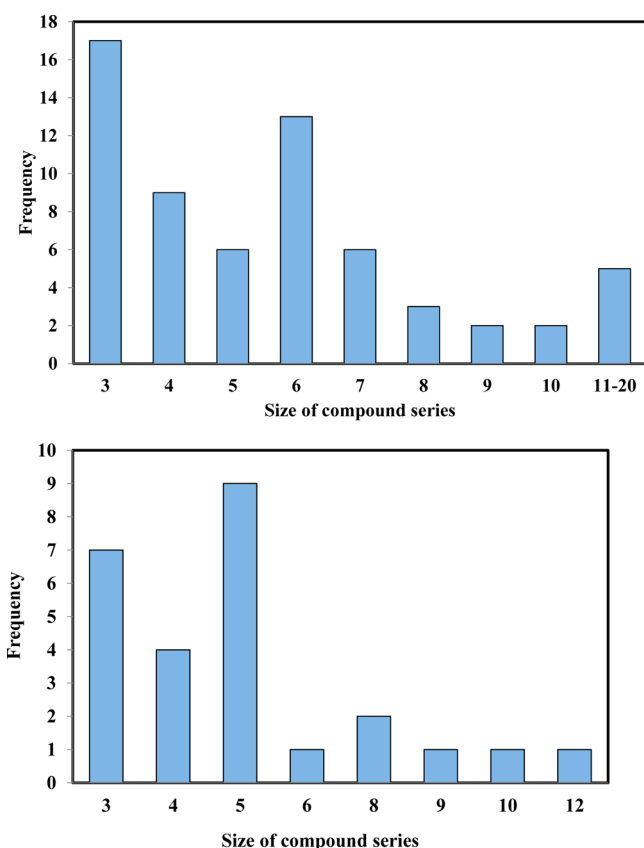


Figure 3. Composition of S_SAR transfer series. The size distribution of (a) dual-target and (b) triple-target S_SAR transfer series is reported in a histogram format.

Table 1. Dual-Target S_SAR Transfer Series^a

data set	#cpds	targets	#S_SAR transfer series
1	92	muscarinic acetylcholine receptor M2 M3	10
2	892	cannabinoid receptor CB1 CB2	10
3	29	orexin receptor 1 2	7
4	268	carbonic anhydrase II I	6
5	14	peroxisome proliferator-activated receptor γ α	6
6	620	adenosine receptor A1 A2a	5
7	15	neuropeptide Y receptor type 1 5	3
8	122	opioid receptor μ κ	3
9	382	dopamine receptor D2 D3	2
10	214	melatonin receptor 1A 1B	2
11	200	thrombin coagulation factor X	2
12	42	serotonin receptor 1d 1b	2
13	72	coagulation factor IX X	1
14	29	serotonin receptor 1a 1b	1
15	70	adenosine receptor A1 A2b	1
16	53	opioid receptor δ κ	1
17	19	adrenergic receptor α -2a α -2c	1

^aDual-target S_SAR transfer series we identified are reported together with the sizes of the data sets (#cpds) from which they originated. Different receptor isoforms or enzymes are separated by vertical lines. For example, “adenosine receptor A1 | A2a” refers to adenosine receptors A1 and A2a.

by five series for the serotonin receptor 2a vs 2b vs 2c set. In this case, four series were also identified that displayed S_SAR

Table 2. Triple-Target S_SAR Transfer Series^a

data set	#cpds	targets	#S_SAR transfer series
18	634	opioid receptor μ δ κ	11
19	162	serotonin receptor 2a 2b 2c	5
20	440	NOR SER DOP transporters	4
21	87	melanocortin receptor 1 3 4	3
22	419	adenosine receptor A1 A2a A3	1
23	232	dopamine receptor D2 D3 D4	1
24	323	carbonic anhydrase I II IX	1

^aTriple-target S_SAR transfer series are reported according to Table 1. “NOR | SER | DOP transporters” stands for “norepinephrine | serotonin | dopamine transporters”. The data set numbers in Tables 1 and 2 correspond to the ones provided for download via the following URL: <http://lifescienceinformatics.uni-bonn.de/downloads>. For each data set, transfer series are designated as follows for download, e.g., for set 1: series 1.1.–1.10.

transfer for the norepinephrine, serotonin, and dopamine transporters.

We also obtained 34 compound data sets with activity against four targets, which yielded a total of 112 compound series (originating from 14 data sets). However, none of these candidate series met the S_SAR transfer criteria.

The dual- and triple-target S_SAR transfer series we identified spanned a wide range of structural classes with different molecular size and complexity. All series and the corresponding data sets reported in Tables 1 and 2 are made freely available (access information is provided in the legend of Table 2).

Exemplary Series. In Figure 4, examples of dual-target S_SAR transfer series are provided, which illustrate the closely corresponding potency progression of chemically diverse series and pairs of targets. The orexin receptor 1 vs 2 S_SAR transfer series in Figure 4a consists of four analogs that are distinguished by different ring substituents. These analogs have similar potency against both receptors, span a potency range of roughly 2 orders of magnitude, and display very similar potency progression. In Figure 4b, the chemically complex muscarinic acetylcholine receptor M2 vs M3 S_SAR transfer series, taken from one of the two sets yielding most series, also consists of four analogs that are differentiated by corresponding halogen or methyl substitutions at two sites. These compounds are slightly more potent against the M3 than the M2 receptor, and there is a notable but closely corresponding increase in potency between analogs 18 and 17. In this series, the SAR transfer is clearly determined by decreasing bulk of the halogen substituents, which steadily increases potency. The most active halogen-free analog in this series reaches subnanomolar potency against both receptors. Furthermore, the dopamine receptor D2 vs D3 S_SAR transfer series in Figure 4c contains six analogs with structurally diverse and in part large substituents at two sites. These compounds are by more than 1 order of magnitude more potent against the D3 receptor, but the potency progression against the two receptors is again very similar. In Figure 4d, a cannabinoid receptor CB1 vs CB2 S_SAR transfer series is shown that also consists of six analogs. With 892 compounds, this data set was the largest one containing S_SAR transfer events and yielded 10 different series. In the displayed series, compounds are distinguished by different ring substitutions at a single site, displaying an interesting and closely corresponding SAR progression. Despite a structurally nonconservative ring replacement, analogs 29 and

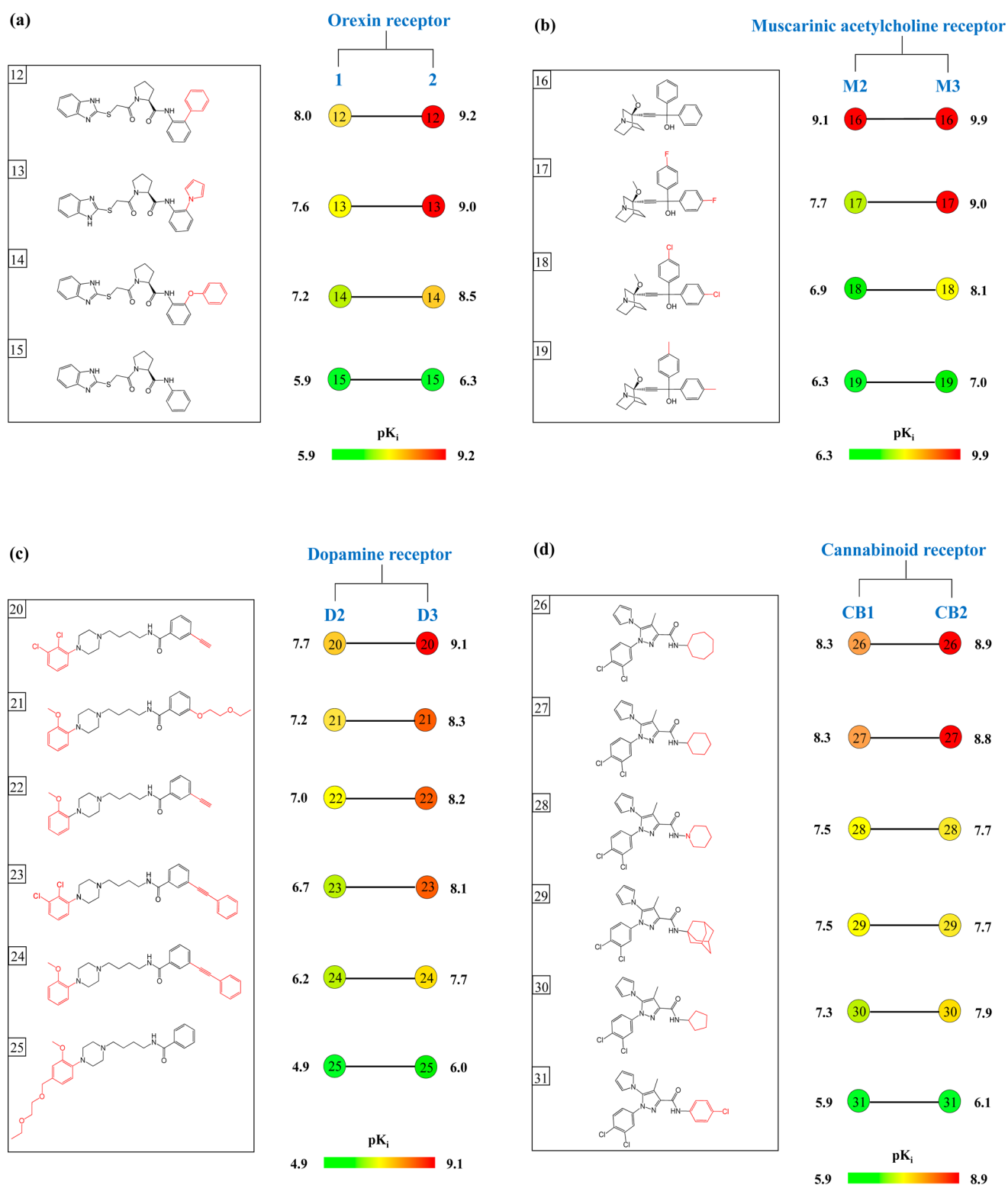


Figure 4. Exemplary dual-target series. In (a)–(d), different examples of dual-target S_{SAR} transfer series are provided. The color-coded node-based representation of the potency progression of analogs for the two targets is according to Figure 2.

28 have the same potency. However, a single-atom replacement in the aliphatic ring moiety of analog 28 then leads to an increase in potency of nearly (CB1) and more than one (CB2) order of magnitude for analog 27, hence providing a clear example of SAR discontinuity as a part of this S_{SAR} transfer event.

In Figure 5, examples of triple-target S_{SAR} transfer series are shown. The dopamine receptor D2–D4 transfer series in Figure 5a consists of three analogs with alkynyl substituents of decreasing size, which lead to substantial and comparable potency increases of 1 to 2 orders of magnitude per step, albeit at different potency levels. The most potent analog spans a potency range of 2 orders of magnitude for the three receptors.

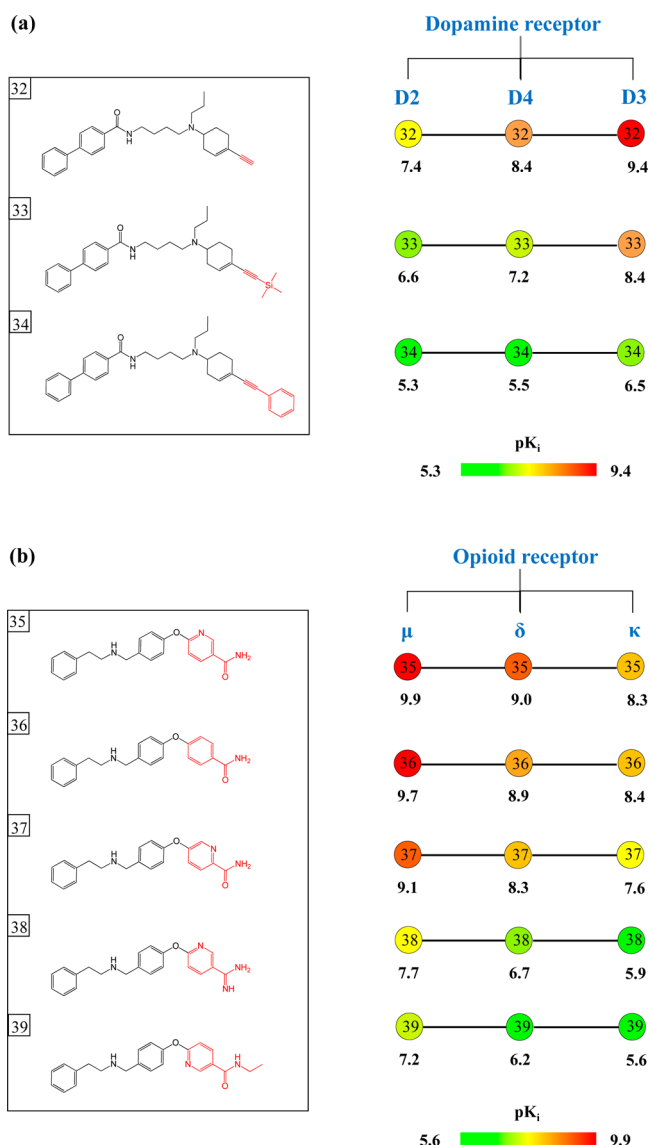


Figure 5. Exemplary triple-target series. In (a) and (b), two triple-target S_{SAR} transfer series are shown (represented as in Figure 4).

The opioid receptor μ vs δ vs κ transfer series in Figure 5b contains five analogs that are distinguished by a differently substituted aromatic ring at a single site. These analogs are also active at different potency levels against the three receptors but display a very similar potency progression that conserves the original relative potency differences of close to 1 order of magnitude between the opioid receptors across the series up to the most potent analog.

CONCLUDING REMARKS

Herein, compound series-based SAR transfer events involving different targets have been systematically investigated. The availability of high-quality compound activity data is a prerequisite for a detailed comparative analysis of SAR progression. Therefore, we have initially assembled high-quality data sets of compounds with multitarget activity from the public domain and then searched these data sets for S_{SAR} transfer series. A limited number of previous studies have focused on target-based SAR transfer, i.e., the search for multiple compound series with similar SAR progression against

a given target. Taken together, these studies have identified structurally diverse T_{SAR} transfer series with relatively high frequency for targets from a wide range of families. Our current analysis has revealed that S_{SAR} transfer events also occur, albeit less frequently than T_{SAR} transfer. We have identified a total of 63 dual-target (~10% of all candidate series) and 26 triple-target (~7%) S_{SAR} transfer series that consisted on average of five to six analogs and displayed closely corresponding potency progression. These S_{SAR} transfer events involved closely related targets. S_{SAR} transfer across different target families or involving more than three targets was not observed in our data sets. The majority of the S_{SAR} transfer series involved different GPCRs. We note that the S_{SAR} transfer events we detected covered different SAR phenotypes including largely continuous and also discontinuous SARs, which renders the corresponding compound series interesting for further chemical exploration and the evaluation on additional targets. Considering the ~7–10% overall frequency with which S_{SAR} transfer series were detected among qualifying candidate series, there should be opportunities to generate additional S_{SAR} transfer series, especially for GPCR ligands.

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Notes

The authors declare no competing financial interest.

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