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# New tetrahydroisoquinoline-based $D_3R$ ligands with an *o*-xylenyl linker motif

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ABSTRACT

The effect of rigidification of the *n*-butyl linker region of tetrahydroisoquinoline-containing $D_3R$ ligands via inclusion of an *o*-xylenyl motif was examined in this study. Generally, rigidification with an *o*-xylenyl linker group reduces $D_3R$ affinity and negatively impacts selectivity versus $D_2R$ for compounds possessing a 6-methoxy-1,2,3,4,-tetrahydroisoquinolin-7-ol primary pharmacophore group. However, $D_3R$ affinity appears to be regulated by the primary pharmacophore group and high affinity $D_3R$ ligands with 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline primary pharmacophore groups were identified. The results of this study also indicate that $D_3R$ selectivity versus the $\sigma_2R$ is dictated by the benzamide secondary pharmacophore group, this being facilitated with 4-substituted benzamides. Compounds **5s** and **5t** were identified as high affinity ($K_i < 4$ nM) $D_3R$ ligands. Docking studies revealed that the added phenyl ring moiety interacts with the Cys181 in $D_3R$ which partially accounts for the strong $D_3R$ affinity of the ligands.

There are five subtypes of dopamine receptor ($D_1R$-$D_5R$) and these are divided based on structural similarity and pharmacological properties into two subgroups – $D_1$-like which comprises $D_1R$ and $D_5R$ and $D_2$-like which includes $D_2R$, $D_3R$ and $D_4R$. All dopamine receptors are G-protein-receptor coupled and recognize the endogenous neurotransmitter dopamine. $D_1$-like receptors signal via activation of $G_s$ pathways whereas $D_2$-like receptors couple to $G_i$ inhibitory proteins.[1–3] Activation of dopamine receptors endogenously is known to play a role in a myriad of physiological effects including movement, cognition and addiction-related behaviors.[4,5] There is a high density of $D_3R$ in the mesolimbic region of the brain, an area associated with motivation and drug seeking behaviors.[6] Thus, the $D_3R$ has received considerable attention, especially over the 2 past decades as a potential target for the treatment of psychostimulant addiction.[7] In that regard, antagonism or partial agonism by selective $D_3R$ ligands is desirable.[8] $D_3R$ antagonists have also been shown to increase cognitive performance and reverse cognitive deficits in animal studies and are thus promising as antipsychotic agents.[9–11]

Over years of research, there have been significant challenges with obtaining $D_3R$ ligands that are suitable for translational research. Selectivity, especially versus the closely related $D_2R$ and $D_4R$ is one such issue, although there are now available several $D_3R$ subtype selective ligands.[12] However, several $D_3R$ ligands have other drawbacks such as poor oral bioavailability which limits their utility as therapeutics.

Several $D_3R$ ligands have been obtained that conform to a classical $D_3R$ pharmacophore which consists of three main regions: (i) an amine-containing primary pharmacophore region, (ii) a linker region – typically an *n*-butyl chain and (iii) an arylamide secondary pharmacophore moiety (Fig. 1). Various amine-containing primary pharmacophore groups have been used, among which the phenylpiperazine moiety has been fairly common (e.g. BP 897 and NGB2904, Fig. 1). A number of $D_3R$ ligands have been discovered that contain a 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline primary pharmacophore group. However, in addition to binding to $D_3R$, compounds with this motif have also been reported to possess significant affinity for the $\sigma_2$ receptor ($\sigma_2R$).[13] In fact, a number of these 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-containing compounds have been explored as $\sigma_2R$ selective ligands and as positron emission tomography (PET) cancer imaging agents.[14–18] We

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recently reported new $D_3R$ ligands that contain a slight variation of this template in containing a 6-methoxy-1,2,3,4,-tetrahydroisoquinolin-7-ol motif.[19] We found that compounds with this motif (e.g. compound **1**, Fig. 2) exhibited good selectivity for $D_3R$ over $\sigma_2R$ (see Ref. 19 and Table S1 in Supporting Information) and may thus be advantageous as compared to compounds with the 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline moiety with regards to retaining $D_3R$ selectivity.

Previous studies have investigated rigidification of the flexible *n*-butyl linker region of other $D_3R$ scaffolds (particularly those containing phenyl piperazine-based primary pharmacophore groups) with moieties including *cis*-alkenyl, *trans*-alkenyl, alkynyl, xylenyl and cycloalkyl motifs with varying results.[21–24] We were curious to find out the extent to which rigidification of the *n*-butyl linker unit of a $D_3R$ scaffold containing a 6-methoxy-1,2,3,4,-tetrahydroisoquinolin-7-ol and related tetrahydroisoquinolyl primary pharmacophore groups may lead to improvements in $D_3R$ affinity and potentially increased selectivity versus $\sigma_2R$. We considered rigidification with an *o*-xylenyl motif as this would: i) preserve the 4-atom connectivity between the amine of the primary pharmacophore group and the nitrogen of the arylamide group and ii) preserve the basicity of the nitrogen in the tetrahydroisoquinoline region which is deemed to be necessary towards formation of a critical salt bridge interaction with $D_3R$.[19] The synthesized compounds were pharmacologically characterized at dopamine $D_1R$ – $D_5R$ and at the $\sigma_2R$. Data on these evaluations as well as receptor docking studies of the ligands at $D_3R$ are discussed herein.

In terms of structural diversity of the designed analogues, we targeted the synthesis of compounds with the following structural variations: i) *primary pharmacophore group* – either a 6-methoxy-1,2,3,4,-tetrahydroisoquinolin-7-ol, 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline motif, ii) *linker* – *o*-xylene unit and iii) *secondary pharmacophore region* – a variety of arylamide units, including some found in previously identified $D_3R$ ligands. The compounds were synthesized as outlined in Scheme 1.

To commence the synthesis of compounds containing a 6-methoxy-1,2,3,4,-tetrahydroisoquinolin-7-ol motif in tandem with the *o*-xylenyl linker unit, readily available compound **2a** was subjected to reductive amination conditions with 2-formylbenzonitrile yielding **3a**. Compound **3a** was subsequently reduced with lithium aluminium hydride to afford the amine **4a**. Compound **4a** in turn underwent acid–amine coupling with various carboxylic acid groups to afford intermediate amides which were debenzylated under acidic conditions (without purification of the intermediate amide) to give the target analogues **5a**–**r**. Analogues **5s** and **5t** with the 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline motif were prepared from **2b** in an analogous route to that described for analogues **5a**–**r** (except for the acidic cleavage step). Compounds **5g**, **5s** and **5t** were treated with $BBr_3$ to effect *O*-demethylation, thus yielding catechol analogues **6a**, **6b** and **6c** respectively.

The results of radioligand binding evaluations on analogues containing the *o*-xylenyl linker unit are compiled in Table 1. In general, compounds in this series lacked affinity for $D_1R$ and $D_5R$. Compound **5a** which contains a 4-fluorophenyl arylamide motif was devoid of affinity at all receptors tested. The 2-naphthylamide-containing **5b** had only moderate affinity for $D_3R$ ($K_i = 780$ nM); affinity was still moderate but approximately twice as high at $D_2R$. No affinity was detected for the $\sigma_2R$. Compounds with a 2-chloro, 2-bromo and 2-methoxy mono-substituted benzamide motif (i.e. **5c**–**5e**) displayed moderate affinity for $D_3R$ ($K_i$ = 120–540 nM). In all cases these compounds were slightly more selective for $D_2R$. Affinities generally increased in the order $D_4R < D_3R < D_2R$. These analogues also had moderate affinity for the $\sigma_2R$. Compounds **5f**–**5 h** with the 3-chloro, 3-bromo and 3-methoxy benzamide motifs, displayed a similar binding profile and selectivity trends at $D_2R$, $D_3R$, $D_4R$ and $\sigma_2R$ as their previously described 2-substituted congeners. Compound **5i**, with a 3-cyano substituent however displayed strong affinity for $D_3R$ ($K_i = 26$ nM) with comparable affinity for $D_2R$ and good selectivity versus $D_4R$ (>100-fold). This compound lacked any appreciable affinity for the $\sigma_2R$. Compounds **5j**–**5m** with a 4-halophenyl moiety in the benzamide motif, had similar binding profiles in that they all lacked affinity for $D_4R$ and the $\sigma_2R$. Compounds **5j**–**5m** showed good affinity for $D_2R$ and $D_3R$; compound **5m** had good $D_2R$ affinity (84 nM) but lacked $D_3R$ affinity and was the compound with the best $D_2R$ selectivity identified in this study. Replacement of the 4-halo substituent groups with 4-methoxy or 4-cyano groups (compounds **5n** and **5o** respectively) resulted in a rebound in (albeit weak: $K_i$ = 1040–2800 nM) $D_4R$ affinity. The 2,3-dichloro benzamide analogue **5p** displayed a binding profile that was reminiscent of the 2- and 3-substituted analogues described above. Interestingly, the 2,3-dimethoxy benzamide analogue (**5q**) showed complete selectivity for $D_3R$ ($K_i = 57$ nM) with no affinity at the other receptors evaluated. This compound has the best $D_3R$ selectivity profile of all compounds evaluated in this study. The sole 3,4-disubstituted benzamide tested (**5r**) showed strong affinity at $D_3R$ ($K_i = 24$ nM), comparable to that at $D_2R$ and with low $D_1R$ affinity ($K_i$ = 1970 nM).

Two compounds with a 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline motif were evaluated – the 3-cyano and 4-cyano benzamide derivatives **5s** and **5t** respectively. These compounds displayed very high affinity for $D_3R$ ($K_i$ = 1.2 and 3.4 nM; among the most potent $D_3R$ ligands in this study) and exhibited selectivities ranging from 15- to 420-fold versus the other dopamine receptors tested. Interestingly, both compounds lacked $\sigma_2R$ affinity.

Among the compounds with a 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline unit, compound **6a** and **6c** displayed the highest $D_3R$ affinity. In fact, compound **6a** had one of the highest $D_3R$ affinities (2 nM) of all compounds evaluated and had no affinity for $D_5R$ and $\sigma_2R$. Selectivity of **6a** versus $D_1R$, $D_2R$ and $D_4R$ was modest (<50-fold). In comparing the catechol-containing analogues **6b** and **6c** with their dimethoxy counterparts (**5s** and **5t** respectively) and 7-hydroxy-6-methoxy congeners

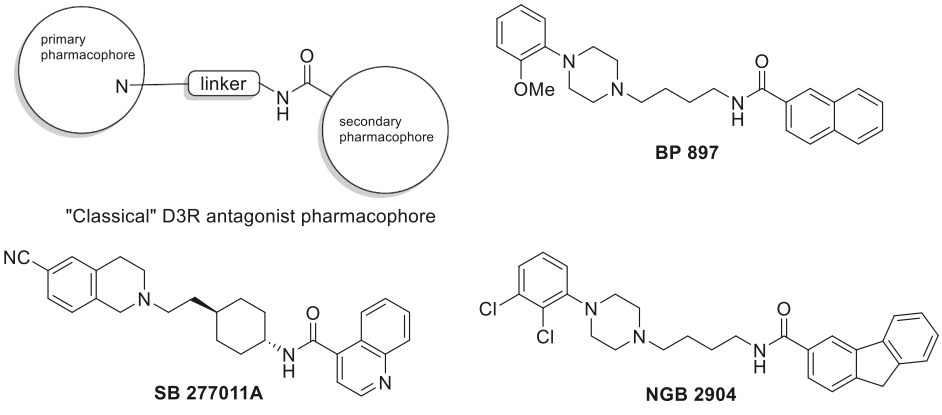



**Fig. 1.** Structures of the $D_3R$ antagonist pharmacophore and selected $D_3R$ antagonist ligands.

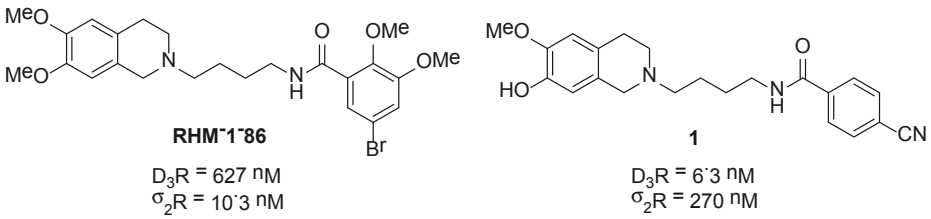
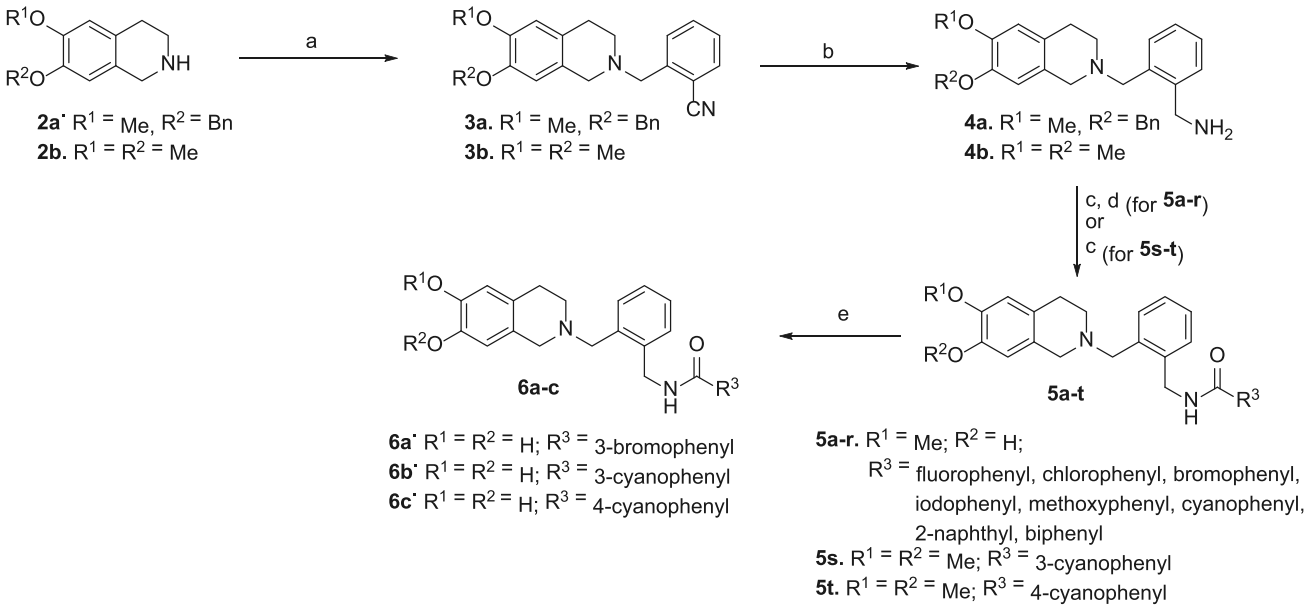



**Fig. 2.** Structures of typical tetrahydroisoquinoline-containing $D_3R$ and $\sigma_2R$ ligands – RHM-1-86[20] and compound 1.[19]




**Scheme 1.** Synthesis of analogues 5a-t and 6a-c *Reagents and conditions*: (a) Appropriate aldehyde, $NaBH(OAc)_3$, DCM, 12 h, rt, 69–72%; (b) $LiAlH_4$, THF, 1 h, rt, 60–63%; (c) HBTU, appropriate carboxylic acid, TEA, 12 h, rt; (d) conc. HCl, $CH_3COOH$, 12 h, 40 °C, 55–63% (over two steps); (e) $BBr_3$, DCM, 0 °C, 2 h, 87–90%.

(**5i** and **5o** respectively), it is apparent that $D_3R$ affinity is better tolerated with the dimethoxy functionality than either the catechol or 7-hydroxy-6-methoxy motifs.

On a whole, it appears that 4-substituents on the benzamide moiety are less likely to promote binding to the $\sigma_2R$ as compared to their 2- or 3-substituted benzamide counterparts. However, compounds with a 2,3-disubstituted benzamide motif do not necessarily follow the same trend as for 2- and 3-monosubstitued benzamides. In that regard, compound **5q** stands out in maintaining selectivity versus all other receptors including the $\sigma_2R$.

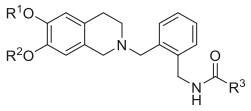
A comparison of the previously evaluated 6-methoxy-1,2,3,4,-tetrahydroisoquinolin-7-ol – containing ligands with a flexible linker group (e.g. **1**) with their congeners containing the rigidifying *o*-xylenyl motif in the present study, also allows some general conclusions to be drawn about the impact of the introduced *o*-xylenyl sub-structure on $D_3R$ affinity and selectivity. In our previous study the compounds with flexible linker groups displayed strong $D_3R$ affinity (ranging from 2 to 28 nM) with moderate or no affinity for other dopamine (See Table S1 in Supporting Information for data on comparator compounds from our previous work).[19] However, in this study the highest $D_3R$ affinity seen for a rigidified compound with the 6-methoxy-1,2,3,4,-tetrahydroisoquinolin-7-ol motif was 26 nM (compound **5i**); most such compounds in the present study had affinities >100 nM at the $D_3R$. Generally then, introduction of the *o*-xylenyl linker group resulted in a reduction in $D_3R$ affinity receptors (see Table S1). It appears that the inclusion of the *o*-xylenyl ring improves $D_2R$ affinity as most compounds with flexible linker groups (i.e. from our previous study) had low or no affinity unlike analogous rigidified compounds in the present study. Taken together, the data indicate that the rigidifying *o*-xylenyl ring motif is detrimental towards $D_3R$ versus $D_2R$ selectivity. One area where the SAR of the flexible and rigid compounds diverged in a positive sense was with regards to $D_4R$ affinity of the 4-halo-substituted benzamide derivatives. With the flexible analogues we found moderate $D_4R$ affinity (95–1500 nM) for this sub-group of compounds; for the analogous rigidified compounds there was no $D_4R$ affinity.[19] Therefore, the inclusion of the *o*-xylenyl ring in this instance is beneficial in promoting $D_3R$ selectivity versus $D_4R$. There does not seem to be any major impact on $D_1R$ or $D_5R$ affinity as both the flexible and rigidified compounds generally lacked $D_1R$ and $D_5R$ affinity.

A comparison of the 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-containing compound **5t** with its flexible counterpart from our previous study (see Table in Supporting Information), indicates that the presence of the rigidifying phenyl unit is beneficial for $D_3R$ affinity ($K_i$ at $D_3R$ = 3.4 and 410 nM for **5t** and its more flexible congener respectively). Further investigations are required in order to determine the extent to which this SAR trend holds for other 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-containing compounds.

The compounds with the highest $D_3R$ affinity contained either a 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline or 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline moiety. This suggests that the presence of an *o*-xylenyl ring linker motif in tandem with a 6-methoxy-1,2,3,4,-tetrahydroisoquinolin-7-ol moiety is less favorable for strong $D_3R$ affinity.

A molecular docking investigation was conducted to attempt to provide a structural interpretation of the effects of linker rigidification and methylation of substituents on the tetrahydroisoquinoline primary pharmacophore moiety that have been observed in this study. Our previous study showed that, with a flexible linker, compounds with the 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline primary pharmacophore

**Table 1**
Binding affinity of *o*-xylenyl ring rigidified analogues at dopamine and $\sigma_2$ receptors.



| Cmpd. | $R^1$ | $R^2$ | $R^3$ | $K_i \pm$ SEM (nM)[a] | | | | | $\sigma 2$[d] |
|---|---|---|---|---|---|---|---|---|---|
| | | | | $D_1R$[b] | $D_2R$[c] | $D_3R$[c] | $D_4R$[c] | $D_5R$[b] | |
| 5a | Me | H |  | na[e] | na | na | na | na | na |
| 5b | Me | H |  | na | 310 ± 40 | 780 ± 100 | na | na | na |
| 5c | Me | H |  | na | 190 ± 25 | 380 ± 49 | 3900 ± 500 | na | 440 ± 57 |
| 5d | Me | H |  | na | 420 ± 54 | 540 ± 70 | 880 ± 110 | na | 360 ± 46 |
| 5e | Me | H |  | na | 78 ± 10 | 120 ± 15 | 950 ± 120 | na | 140 ± 18 |
| 5f | Me | H |  | na | 100 ± 13 | 140 ± 18 | 950 ± 1 10 | na | 240 ± 31 |
| 5g | Me | H |  | na | 150 ± 19 | 170 ± 22 | na | na | 290 ± 37 |
| 5h | Me | H |  | na | 140 ± 18 | 280 ± 36 | 1070 ± 1 40 | na | 610 ± 79 |
| 5i | Me | H |  | na | 39 ± 5 | 26 ± 3.4 | 3360 ± 430 | na | >10000 |
| 5j | Me | H |  | na | 52 ± 6.7 | 140 ± 18 | na | na | na |
| 5k | Me | H |  | na | 47 ± 6.1 | 55 ± 7.1 | na | na | na |
| 5l | Me | H |  | na | 76 ± 9.8 | 160 ± 21 | na | na | na |
| 5m | Me | H |  | na | 84 ± 11 | na | na | na | na |
| 5n | Me | H |  | na | 74 ± 9.5 | 180 ± 23 | 1040 ± 130 | na | 1400 ± 180 |
| 5o | Me | H |  | na | 190 ± 25 | 310 ± 40 | 2800 ± 360 | na | na |
| 5p | Me | H |  | na | 280 ± 36 | 460 ± 5.9 | 1150 ± 150 | na | 480 ± 62 |
| 5q | Me | H |  | na | na | 57 ± 7.4 | na | na | na |
| 5r | Me | H |  | 1970 ± 250 | 27 ± 3.5 | 24 ± 3.1 | na | na | na |
| 5s | Me | Me |  | 510 ± 66 | 46 ± 5.9 | 1.2 ± 0.2 | 57 ± 7.4 | 300 ± 39 | na |
| 5t | Me | Me |  | 58 ± 7.5 | 50 ± 6.5 | 3.4 ± 0.4 | 140 ± 18 | 340 ± 44 | na |
| 6a | H | H |  | 91 ± 12 | 56 ± 7.2 | 2.0 ± 0.2 | 101 ± 13 | na | na |
| 6b | H | H |  | na | 900 ± 120 | 370 ± 48 | na | na | na |
| 6c | H | H |  | na | 83 ± 11 | 28 ± 3.6 | – | na | na |
| (+)-butaclamol | | | | 2.84 ± 0.05 | | | | | |
| Haloperidol | | | | | 2.61 ± 0.03 | | | | 7.21 ± 0.9 |
| Nemonapride | | | | | | 0.86 ± 0.04 | 0.75 ± 0.06 | | |
| SKF 83566 | | | | | | | | 1.75 ± 0.1 | |

[a] Experiments conducted in triplicate.
[b] [3*H*]-SCH23390 used as radioligand.
[c] [3*H*]*N*-methylspiperone used as radioligand.
[d] [3H]DTG used as radioligand.
[e] na- not active-ligands displayed <10% inhibition in a primary assay at a ligand concentration of 10 μM.

moiety displayed less favorable affinity to $D_3R$ relative to 6-methoxy-1,2,3,4,-tetrahydroisoquinolin-7-ol-containing analogues. Based on previous molecular modeling results, this behavior was attributed to the ability of the latter group of compounds to form two hydrogen bond interactions between the primary pharmacophore group and Ser192 of the receptor compared to only one hydrogen bond in the case of the 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-containing compounds.[19,25] A similar molecular docking study conducted here indicates that rigidification of the linker induces a mode of binding distinct from the one observed earlier and consistent with the observed SAR. As shown in Fig. 3, the three most potent compounds (**5s**, **5t**, and **6a**) dock as generally expected with the primary pharmacophore group in the orthosteric pocket and forming the key salt bridge between the alkyl protonated nitrogen and Asp110.

However, while the unmethylated compound **6a** makes a hydrogen-bond interaction with Ser192 as observed in the previous series, compounds **5s** and **5t** do not. Interestingly, these compounds offset the lack of hydrogen-bond interactions in the orthosteric pocket with an

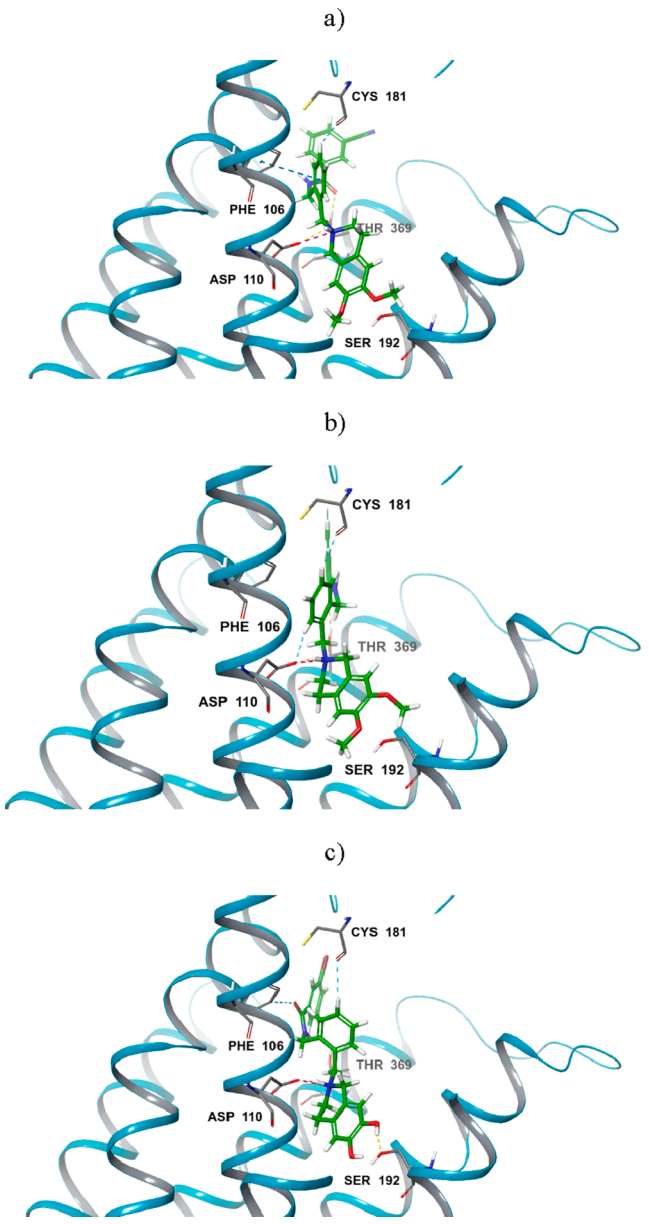



**Fig. 3.** Docked poses of compounds 5s (a), 5t (b) and 6a (c) at $D_3R$.

interaction between the linker and regions further up the $D_3R$ binding cavity. In particular, in **5s** and **5t** there is an interaction between Cys181 of $D_3R$ and the newly introduced phenyl ring of these analogues (via an aromatic H-bond interaction). A similar interaction with the introduced phenyl ring is also seen in **6a**. In compound **5s**, the phenyl ring also forms a π-π interaction with Phe106. In addition, the positioning of the phenyl ring observed for **5s** and **5t** enables additional hydrogen-bonds between the carbonyl of the aryl amide moiety and Thr369 (see Fig. 3a and b). Such interactions do not occur with compound **6a** probably because it is shifted deeper into the orthosteric pocket to establish the hydrogen bond with Ser192 as mentioned above.

Overall, the molecular docking models developed here offer useful structural interpretations of the observed affinity of the compounds with the rigid linkers. The drawback of having the *o*-xylenyl linker is the decrease in selectivity. The orthosteric binding sites of $D_2R$ and $D_3R$ are highly conserved, but the secondary binding pocket of these receptors differ significantly. Interactions with the $D_3R$ secondary binding pocket are important for achieving $D_3R$ versus $D_2R$ selectivity.[26,27] For compounds with both a 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline motif, the rigid *o*-xylenyl linker present in this new series does not allow the arylamide secondary pharmacophore of the molecules to make strong contacts with residues in the secondary binding pocket. This diminished binding of the secondary pharmacophore in the secondary binding pocket may be responsible for the lowered $D_3R$ versus $D_2R$ selectivity in this series.

In conclusion, we examined the effect of rigidification of the linker region of tetrahydroisoquinoline-containing $D_3R$ antagonist chemotypes via the inclusion of an *o*-xylenyl linker motif. Various oxygenated tetrahydroisoquinoline motifs and benzamide sub-structures were utilized for the primary and secondary pharmacophore regions respectively.

We found that in general, rigidification with an *o*-xylenyl ring is detrimental to $D_3R$ selectivity versus $D_2R$. However, selectivity versus the $\sigma_2R$ seems to be dependent on the benzamide motif employed; 4-substituted benzamide groups in particular afforded compounds with excellent selectivity versus $\sigma_2R$ (i.e. low or no affinity for $\sigma_2R$). In compounds with a 6-methoxy-1,2,3,4,-tetrahydroisoquinolin-7-ol primary pharmacophore group, $D_3R$ affinity was negatively impacted. However, we identified compounds with 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline primary pharmacophore groups with high $D_3R$ affinity. Overall, in this series of *o*-xylenyl ring rigidified compounds, it appears that the choice of the primary pharmacophore group is critical for $D_3R$ affinity while the benzamide secondary pharmacophore region is important for maintaining $D_3R$ affinity as well as selectivity versus $\sigma_2R$. Compounds **5s** and **5t** were among the most potent $D_3R$ ligands identified in this study. Docking studies indicate that the high $D_3R$ affinity of some compounds may be due to the extra interactions of the phenyl ring of the linker with, especially, Cys181.

## Author contributions

The manuscript was written through contributions of all authors.

## Notes

The authors declare no competing financial interest.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2021.128047.

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