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Structure activity relationship study of benzo[*d*]thiazol-2(*3H*)one based σ receptor ligands

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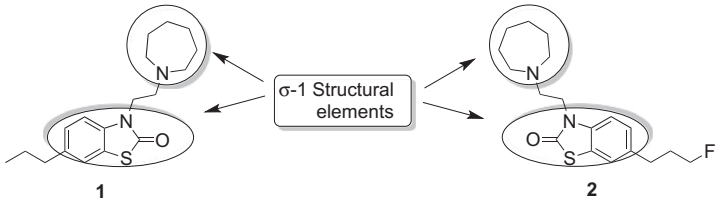
ABSTRACT

Herein we report the SAR study which involved structural modifications to the linker length, aryl substitution and alkylamine ring size of the benzo[*d*]thiazol-2(*3H*)one based sigma receptor (σ) ligands. Many compounds in this series displayed low nanomolar affinity for the σ receptor subtypes. In particular, **8a** showed high affinity (σ-1 K_i = 4.5 nM) for σ-1 receptors and moderately high selectivity (483-fold) over σ-2 receptors.

σ Receptors represent a unique family of proteins that have been classified into two subtypes: σ-1 and σ-2. These two subtypes are distinguished on the basis of protein size, tissue distribution and drug selectivity pattern.[1] The σ-1 receptor has been identified as a ligand regulated chaperone protein that modulates Ca^{2+} signaling at the interface of endoplasmic reticulumn and mitochondria.[2] The σ-1 receptor has been implicated in the behavioral and motivational effects of psychostimulants[3–8] as well as in the pathophysiology of depression,[9,10] Alzheimer's disease[11,12] and pain.[13–15] The σ-2 receptor is widely expressed on many tumor cells and it is believed to play an important role in tumor cell proliferation.[16,17] The σ-2 receptor has also been reported to be involved in the pathophysiology of depression,[18] anxiety[3] and drug abuse.[19,20] Therefore, σ receptors are attractive targets for



1

σ-1 K_i = 0.56 nM; σ-2 K_i > 1000 nM
K_i σ-2/K_i σ-1 > 2000
(Guinea-pig Brain Membranes)

σ-1 K_i = 1.6 ± 0.1 nM; σ-2 K_i = 270 ± 4.7 nM
K_i σ-2/K_i σ-1 = 169
(Rat Liver Membranes)

2

σ-1 K_i = 0.0025 nM; σ-2 K_i = 364 nM
K_i σ-2/K_i σ-1 > 100,000
(Rat Brain Membranes)

σ-1 K_i = 0.96 ± 0.21 nM; σ-2 K_i = 467 ± 60 nM
K_i σ-2/K_i σ-1 = 486
(Rat Liver Membranes)

Figure 1. σ Receptor ligands based on benzo[*d*]thiazol-2(3*H*)one scaffold.

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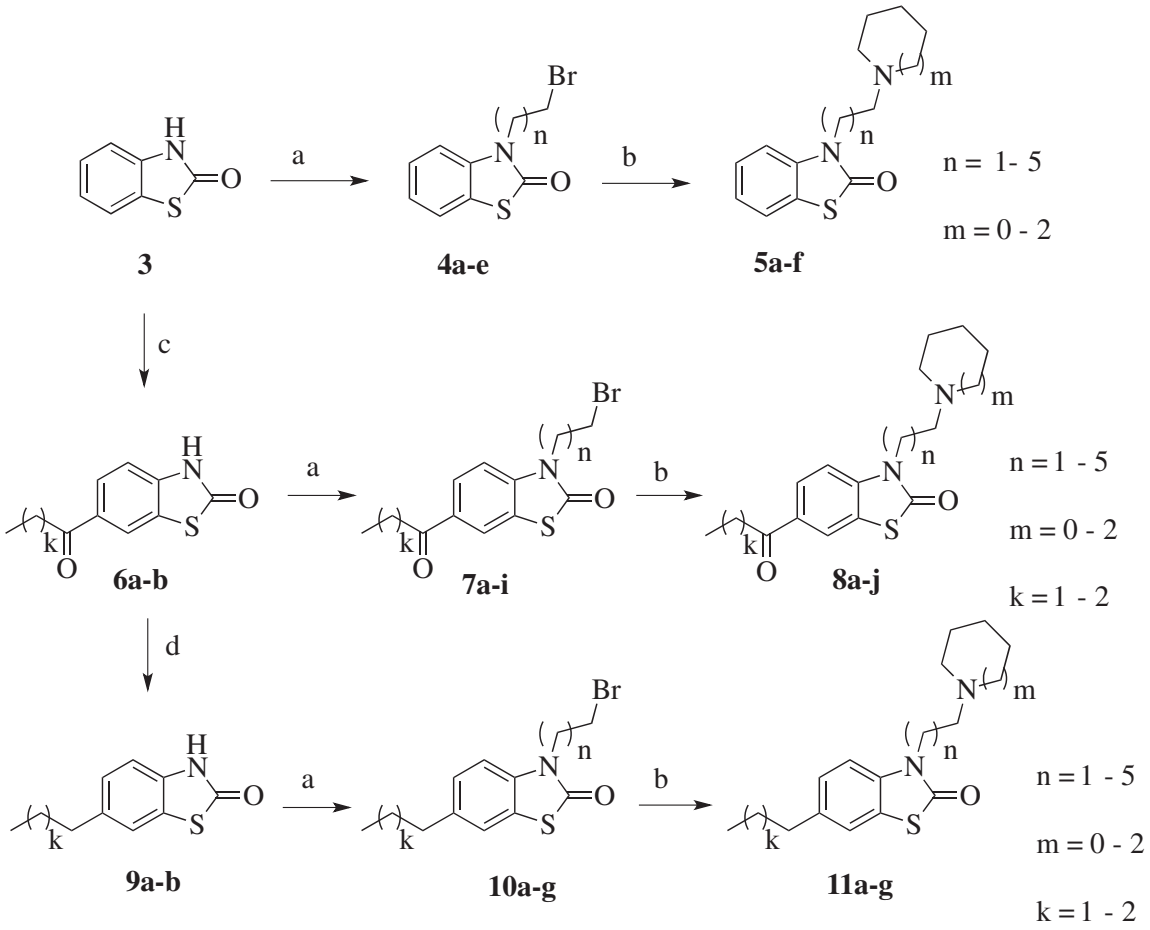
Table 1
Binding affinities (K_i) of benzo[*d*]thiazol-2(3*H*)one compounds at σ receptor subtypes

Compd no.	*k*	*n*	*m*	σ-1 K_i (nM)	σ-2 K_i (nM)	K_i σ-2/K_i σ-1
5a	—	2	2	4.1 ± 0.3	177 ± 26	43
5b	—	3	2	3.2 ± 0.02	101 ± 14	31
5c	—	4	2	7.0 ± 0.3	2.5 ± 0.3	0.4
5d	—	5	2	7.5 ± 0.6	2.4 ± 0.4	0.3
5e	—	1	0	578 ± 41	8264 ± 500	14
5f	—	1	3	9.7 ± 0.6	716 ± 30	74
8a	1	1	2	4.5 ± 0.2	2181 ± 127	484
8b	1	2	2	3.7 ± 0.3	305 ± 7.0	83
8c	1	3	2	10.3 ± 0.9	30.3 ± 2.0	3.0
8d	1	4	2	12.2 ± 1.1	8.3 ± 0.8	0.7
8e	1	5	2	10.4 ± 0.1	1.1 ± 0.1	0.1
8f	1	1	0	116 ± 15	4787 ± 101	41
8g	2	2	2	2.6 ± 0.4	104 ± 1.9	39
8h	2	3	2	4.8 ± 0.1	21.6 ± 4.2	4.5
8i	2	4	2	16.3 ± 0.6	5.7 ± 0.5	0.4
8j	2	5	2	10.8 ± 0.4	2.3 ± 0.3	0.2
11a	1	2	2	1.4 ± 0.1	17.2 ± 1.0	13
11b	1	3	2	6.1 ± 1.2	4.3 ± 0.3	0.7
11c	1	4	2	4.6 ± 0.4	1.6 ± 0.1	0.3
11d	1	5	2	6.3 ± 0.9	2.3 ± 0.2	0.4
11e	2	2	2	2.2 ± 0.4	15.3 ± 0.9	7.0
11f	2	3	2	1.9 ± 0.2	4.4 ± 0.3	2.4
11g	2	5	2	12 ± 0.7	4.1 ± 0.6	0.3
1	1	1	2	1.6 ± 0.1	270 ± 4.7	169

developing pharmaceutical agents directed towards the treatment of psychostimulant abuse, cancer, Alzheimer's disease, pain as well as diagnostic agents for cancer and nervous system imaging.[21,22]

A derivatized 2(3*H*)-benzothiazolone (**1**, Fig. 1) was reported to have high affinity (K_i = 0.56 nM) for σ-1 receptor and over 1000-fold selectivity over σ-2 receptor in guinea-pig brain membranes.[23] When tested in the rat liver membrane binding assay, **1** demonstrated high affinity (σ-1 K_i = 1.6 ± 0.1 nM) albeit lower preference for σ-1 receptor (Table 1). A fluorinated derivative (**2**, Fig. 1) was synthesized in our laboratory and was found to have high affinity (K_i = 0.0025 nM) for σ-1 receptor and high selectivity (>100,000-fold) over σ-2 receptor in rat brain homogenates. Compound **2** was also tested in the rat liver membrane binding assay and was found to have a K_i of 0.96 ± 0.21 nM for σ-1 receptor and a K_i of 467 ± 60 nM for σ-2 receptor. This compound was converted into a ^{18}F PET imaging agent and is currently being studied in various species.[24] Both of the compounds (**1** & **2**) have a benzo[*d*]thiazol-2(3*H*)one scaffold and several other structural similarities. This prompted us to investigate the SAR of 3,6-disubstituted benzo[*d*]thiazole-2(3*H*)one's for affinity and selectivity at σ receptors. The objectives of the study were to investigate the effect of—(1) linker length between benzo[*d*]thiazol-2(3*H*)-one and cycloalkylamine ring; (2) alkyl/acyl substitution on benzo[*d*]thiazol-2(3*H*)-one; and (3) expansion or contraction of the cycloalkylamine ring on the σ receptor binding affinity and subtype preference of ligands. A library of benzo[*d*]thiazol-2(3*H*)one analogues were synthesized and their receptor binding affinities were evaluated in rat liver membranes using a 96 well format high throughput methodology.[25] The σ-1 receptors were labeled with 5 nM [^{3}H](+)-pentazocine. The σ-2 receptors were labeled with 5 nM [^{3}H]DTG in the presence of 300 nM (+)-pentazocine.



Scheme 1. Reagents and conditions: (a) dibromoalkanes, K_2CO_3, DMF, 60 °C, 3 h; (b) cyclic amines, K_2CO_3, DMF, 60 °C, 2 h; (c) $AlCl_3$–DMF, acyl halides (or anhydrides), 80 °C, 4–5 h; (d) triethylsilane, trifluoroacetic acid, rt, 5 h.

Nonspecific binding was determined in the presence of 10 μM haloperidol.

Commercially available benzo[*d*]thiazol-2(3*H*)one (**3**, Scheme 1) was treated with dibromoalkane followed by aminocycloalkanes under base catalyzed conditions to give analogue **5a**–**f** (Scheme 1). 6-Acyl benzothiazolone intermediates (**6a** & **b**; Scheme 1) were synthesized by Friedel–Crafts acylation of benzo[*d*]thiazol-2(3*H*)one followed by reduction (acyl to alkyl) which led to regiospecific 6-alkyl derivatives (**9a** & **b**; Scheme 1). The acyl/alkyl derivatives were then treated with dibromoalkane and further treated with aminocycloalkane under base catalyzed conditions to give the analogues (**8a**–**j** and **11a**–**g**; Scheme 1). Hydrochloride salts of the compounds were prepared for biological testing.

Benzo[*d*]thiazol-2(3*H*)-one analogues (**5a**–**d**; Table 1) were synthesized to investigate the effect of spacer length between benzo[*d*]thiazol-2(3*H*)-one and azepane ring by varying it from three to six methylene units. All the derivatives displayed good affinity towards both receptor subtypes. The shorter chain analogues (**5a** & **5b**; Table 1) demonstrated high σ-1 affinity (K_i 4.1 and 3.2 nM, respectively) and moderate selectivity (43- and 31-fold, respectively) versus the σ-2 subtype. In order to study the importance of aryl substitution along with varying spacer lengths on σ receptor binding, several aryl substituted (propionyl/butyryl) analogues were synthesized with spacer length varying from two to six methylene units. Analogues with a propionyl/butyryl substitution at the aryl ring and a shorter chain length (**8a**, **8b** & **8g**; Table 1) exhibited higher affinity for σ-1 subtype. However, analogues with propionyl substitution had highest σ-1 preference as exhibited by compound **8a** (σ-1 K_i = 4.5 nM). Placing a propionyl group at the sixth position of benzothiazolone ring slightly improved the affinity and selectivity of the compounds for σ-1 subtype as compared to its non-substituted analogue. Generally, reduction of the aryl acyl moiety led to a slightly increased affinity at both the receptor subtypes (**11a**–**g**; Table 1). However, the increased affinity came at the expense of subtype selectivity. The best analogues (**11a** & **11b**; Table 1) of this series of compounds exhibited a lower selectivity for σ-1 subtype as compared to their corresponding analogues (**8a** & **8b**; Table 1) with benzylic ketone functionality. In order to elucidate the importance of ring size on σ receptor affinity and selectivity some analogues were synthesized in which the seven-membered azepane ring was replaced with a five membered pyrrolidine or eight membered octylamine ring. When the ring size was increased (**5f**; Table 1) the compound still retained good affinity for σ-1 subtype (K_i = 9.7 nM) however it lost affinity at σ-2 subtype (K_i = 716 nM). Decreasing the ring size had a detrimental effect on the affinity of the compounds (**5e** & **8f**; Table 1) for both the receptor subtypes as well as their selectivity over σ-2 subtype. Some trends observed during the SAR study—(1) Increase in linker arm length (from n = 2 to 5), reflects marginal change in affinity at σ-1 subtype and significant increase in affinity for the σ-2 subtype; (2) Modification of aryl substitution from propyl (**1**) to propionyl (**8a**) results in a dramatic decrease in σ-2 affinity with a marginal change in σ-1 affinity; (3) Reduced affinity for both σ receptor subtypes when the azepane ring (**8a**) is replaced with a pyrrolidine ring as demonstrated by **5e** and **8f**.

In Summary, we have reported the synthesis and SAR study around the linker length, aromatic substitution and alkylamine ring size of some σ receptor ligands based on the benzo[*d*]thiazol-2(3*H*)one chemotype. Several of these compounds were shown to have low nanomolar affinity for σ receptors. The linker chain length between the two hydrophobic regions of the molecule and aryl substitution was important for deciding the subtype selectivity of the ligands whereas the alkylamine ring size was important for the receptor affinity. In this study, **8a** was identified as a compound with high affinity for σ-1 subtype and appreciable selectivity over σ-2 subtype.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.06.032.

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