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SYA 013 analogs as sigma-2 (σ_2) selective ligands: structure-affinity relationship studies

Lamya Al-Ghanim^a, Xue Y. Zhu^a, Gladys Asong^a, and Seth Y. Ablordeppey^a

^aDivision of Basic Pharmaceutical Sciences, Florida A&M University, College of Pharmacy and Pharmaceutical Sciences, Tallahassee, FL 32307, USA

Abstract

Several lines of evidence suggest that selective sigma-2 (σ_2) ligands might be useful for the treatment of solid tumors. However, very few selective σ_2 ligands have been identified. This study was aimed at identifying new selective σ_2 receptor ligands using a previously identified agent, SYA 013 as a lead. Four groups, homopiperazine, piperazine, tropane and selected oxime analogs of the homopiperazines were identified, synthesized and subsequently screened at the σ_1 and σ_2 receptors. The results demonstrate that these scaffolds can be modified to obtain selective σ_2 receptor ligands. 1-(5-Chloropyridin-2-yl)-4-(3-((4-fluorophenyl)thio)propyl)-1,4-diazepane, **7** and 3-(4-chlorophenyl)-8-(3-((2-fluorophenyl)thio)propyl)-8-azabicyclo[3.2.1]octan-3-ol, **21** were identified as the highest binding affinity ligands ($\sigma_2 Ki = 2.2$ nM) and (4-(4-(5-chloropyridin-2-yl)-1,4-diazepan-1-yl)-1-(4-fluorophenyl)-butan-1-one oxime, **22** as a high affinity and the most selective ligand for the σ_2 receptor ($\sigma_1 Ki / \sigma_2 Ki = 41.8$).

Graphical Abstract

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Receptor binding studies

Binding affinities (K_i , nM) reported in Tables 1–4 were conducted by the National Institute of Mental Health Psychoactive Drug Screening Program (NIMH-PDSP) unless otherwise stated. Details of the methods and the radioligands used for the binding assays at each receptor were previously reported.⁴⁰

1. Introduction

Initially, sigma (σ) receptors were designated as a subtype of the opioid receptor family,¹ but were shown later to be distinctive proteins incorporated in plasma, mitochondrial and endoplasmic reticulum membranes of tissues in the brain, kidneys, endocrine system, liver, immune system, and reproductive organs.^{2, 3} Historically, the opioid family included the mu (μ), kappa (κ), and sigma (σ) receptors with morphine as a prototype for the μ receptor, ketocyclazocine for the κ receptor, and SKF-10,047 ((N-allylnormetazocine), for the σ receptor.¹ However, Martin et al., 1976, noted that while morphine (μ) caused excessive pupil constriction, bradycardia, hypothermia and decreases in responsiveness to nerve pain, the ketocyclazocine (κ) syndrome was typified with sedation but did not significantly affect pulse rate. SKF-10,047(σ) on the other hand, produced tachycardia, dilation of pupils, tachypnea, and was insensitive to naloxone, a typical antagonist to opioid receptors. These responses were all in contrast to morphine and ketocyclazocine. The later discovery of ligands more selective to sigma sites such as 1,3-di-o-tolylguanidine (DTG) and phencyclidine, 1-(1-phenylcyclohexyl)piperidine (PCP), indicated that they were distinctive from the binding sites in the central nervous system, confirming that they were non-opioid receptors.^{4, 5} Based on extensive binding studies, it has now been established that σ receptors are distinct from other known neurotransmitter receptors since they have high affinity for 1,3-di(2-tolyl) guanidine (DTG), (+)-3-(3-hydroxyphenyl)-N-(1-propyl)piperidine, [(+)-3-PPP] and haloperidol and therefore, are defined as non-opioid binding sites.⁶ Even though biochemical and pharmacological studies proposed that there are several subtypes of sigma receptors, only two well-defined sigma receptor subtypes, sigma-1 (σ_1) and sigma-2 (σ_2), have been characterized.^{7–10}

The sigma-1 receptor (σ_1 R) has been characterized as a 25 kDa protein, whereas the sigma-2 receptor (σ_2 R) has a molecular weight of 18–21 kDa.^{11, 12} The σ_1 R was cloned in 1996¹³ and crystallized in 2016,¹⁴ while, σ_2 R was cloned in 2017.¹⁵ The σ_2 R was identified as a fundamental membrane protein residing at the endoplasmic reticulum (ER). The cloning also revealed σ_2 R as a four transmembrane domain protein with cytosolic N and C termini.^{15, 16} Until recently, attention was directed to the role of sigma receptors in the brain,¹² however, pharmacological studies have revealed that both σ_1 and σ_2 receptors are widely expressed in various cell lines. Non-malignant cells from the same tissue displayed less sigma receptor expression than malignant cells^{17–19} with increased levels of σ_2 receptors over the σ_1 receptor subtype in general.¹⁸ In addition, several lines of evidence have suggested that the ratio of σ_2 receptors in proliferating tumors is higher than in dormant cells with fast multiplying cells expressing ten times more σ_2 receptors than resting cells.^{18, 20} For example, it was noted that σ receptors were abundant in human breast tumor biopsy tissue, but practically lacking in normal breast tissue.²⁰ Furthermore, the cloning of σ_2 R confirmed its overexpression in epithelial, colorectal, ovarian, lung, and breast cancers.^{21–25} The σ_2 R has also been suggested as a possible drug target in cancer therapy^{26, 27} due to its association with tumor biology.²⁸ Pharmacological targeting of the σ_2 receptor in human cancer cell lines has been shown to have anti-proliferative properties.¹² In addition, σ_2 radiotracers have been developed for tumor imaging.¹⁵ Taken together, the σ_2 R offers a great potential as a target for anticancer drug development for cancers such as triple negative

breast cancer (TNBC) which is without clear targets and for several tumor cell types with fast proliferation.^{29, 30} In this article, we report the design and synthesis of several homopiperazine, piperazine and tropane analogs and their evaluation at the sigma receptors.

2. Chemistry

Compounds **1**, **5**, **6**, **11–15**, **17–21** were synthesized in our lab and previously reported.^{31–35} Compound **9** was synthesized and reported.³⁶ Homopiperazine analogs **2**, **3**, **4** were synthesized as described in Scheme 1 by refluxing a mixture of 4-chloro-4'-fluorobutyrophenone **25**, homopiperazines **26a-c**, KI, and NaHCO₃ in isopropanol. Refluxing each of homopiperazines **2**, **3** and **4** with hydroxylamine hydrochloride under basic conditions in EtOH afforded the corresponding oximes **22**, **23**, and **24**.

Analog **7** was synthesized using the synthetic route we previously reported.³⁷ 1-(5-chloropyridin-2-yl)piperazine and 1-(5-chloropyridin-2-yl)-1,4-diazepane were prepared by reaction of the corresponding diamine with 2,5-dichloropyridine. Piperazine analogs **8** and **10** were synthesized via coupling reactions of halides and 1-(5-chloropyridin-2-yl)piperazine. Alkylating agent **27**, which was prepared from butyrophenone **25**,³² was used to prepare analog **10**. The coupling reaction proceeded under basic conditions in the presence of KI as depicted in Scheme 2.

3. Results and Discussion

To identify new σ_2 R selective ligands we reviewed our CNS database and identified the previously reported 4-(4-(4-chlorophenyl)-1,4-diazepan-1-yl)-1-(4-fluorophenyl)butan-1-one (**1**), a homopiperazine analog of haloperidol (SYA013, **1**),³¹ as binding selectively to σ_2 receptors ($\sigma_1 K_i=24$ nM and $\sigma_2 K_i=5.6$ nM, $K_i(\sigma_1 R)/K_i(\sigma_2 R) = 4.3$ nM). The aim of this research was to synthesize a limited number of SYA013 analogs, evaluate the structural elements that impact σ_2 selectivity, and optimize their binding affinity to the σ_2 receptor. We now report several such analogs of SYA013 that selectively bind to σ_2 receptors. The structure of SYA013 and several designed analogs are shown in Fig. 1.

To obtain selective σ_2 receptor ligands using SYA013 as a lead compound, four groups of analogs were identified for evaluation: homopiperazine analogs (group 1), piperazine analogs (group 2), tropane analogs (group 3), and indanone analogs (group 4). In group 1, initially, the 4-chlorophenyl moiety was replaced by 4-chloropyridine **2**, pyridine **3** and pyrimidine **4** moieties. Subsequently, the ketone on the buta-1-one linker was deoxygenated to form compound **5**, replaced with an oxygen to form ether **6**, and the carbonyl in compound **2** was replaced with sulfur to obtain thioether **7**.

Replacing the 4-chlorophenyl moiety with the chloro-pyridine to obtain **2** did not significantly diminish affinity while still retaining selectivity for the σ_2 receptor. Removing the chloro from **2**, led to the pyridine analog **3** with significantly diminished affinity as well as the selectivity for σ_2 receptor, suggesting the chloro plays an important role in binding affinity. Introduction of an additional nitrogen to form the pyrimidine analog, **4** also decreased binding at the σ_2 receptor. Thus, it would appear that decreasing lipophilicity is

associated with reduction in binding to the σ_2 R. Deoxygenation of the carbonyl of compound **1** to form **5** or replacement of the carbonyl group with an oxygen to form **6** both improved affinity overall but led to reversal of selectivity for the σ_2 receptor. However, replacement of the carbonyl in compound **2** with a sulfur atom to form thioether **7**, improved affinity at both sigma receptors and also retained selectivity (Table 1).

To evaluate the contribution of the homopiperazine ring to binding affinity and selectivity, and to identify other isosteres of the homopiperazine, we evaluated the piperazine analogs of several compounds in group 1 to form group 2 analogs as shown in Fig. 2. First, we evaluated the piperazine analog of compound **2** that is compound **8**, and its deschloro equivalent **9**. Consistent with the group 1 agents, compound **8** maintained binding similar to compound **2**, while **9**, like compound **3**, resulted in significant reduction in binding affinity at both sigma receptors. Next we evaluated the deoxygenation of compound **8** to obtain **10**. Compound **10** showed a 4 to 5-fold reduction of binding to both receptors. Compound **11**, the piperazine analog of compound **5**, also showed a diminished affinity and a reversed receptor selectivity as in **5**. When the carbonyl in compound **8** was replaced with a sulfoxide to form compound **12**, there was a greater than 45- and 71-fold loss of affinity at the σ_1 and σ_2 receptors respectively; suggesting the sulfoxide is an undesirable moiety at either of the sigma receptors. Compounds **13** – **15** are ether analogs in which the role of the chloro and fluoro were evaluated. Compound **13**, is a desfluoro equivalent of compound **11** with insignificant change in binding affinity, although reversal of selectivity is noted. The deschloro equivalent, compound **14**, surprisingly produced an increased binding affinity for both receptors and selectivity for the σ_2 receptor. Removal of both chloro and fluoro substituents to form **15** produced a 2–5 fold decrease in binding affinity at both receptors, as expected (Table 2). Comparing the highest affinity piperazine in group 2, that is compound ($\sigma_2 Ki=5.12$ nM), with PB28 ($\sigma_2 Ki=0.68$ nM), one of the highest binding affinity ligands in the literature,³⁸ reveals a 7.5 fold lower binding affinity to the σ_2 R.

In an attempt to identify other isosteres of the homopiperazine ring, we evaluated the tropane analogs (Fig. 3) in group 3. The results of the screening are reported in Table 3.

Compound **17** is the tropanol analog of compound **5**. Compound **17** has a 6- and 3-fold lower affinity for the σ_1 and σ_2 receptors respectively. Compounds **18** and **19**, the ether and thioether analogs of compound **17** respectively, display less affinity for the sigma receptors while compounds **20** and **21**, the *meta* and *ortho*-substituted fluoro analogs show increased affinity and selectivity for the σ_2 receptor. In fact, compound **21** has the strongest affinity ($\sigma_2 Ki=2.2$ nM) and selectivity ($\sigma_1 Ki/\sigma_2 Ki=25.9$) for the σ_2 receptor among all the compounds evaluated including the lead compound SYA013.

Given the literature precedent that oximes may enhance activity of a compound's antitumor activity³⁹ we synthesized the oximes of compounds **2**, **3** and **4** and obtained compounds **22**, **23** and **24** as shown in Fig 4. The results of the screening of these compounds at the sigma receptors is reported in Table 4, showing that the oximes maintain their sigma binding affinity and selectivity for the σ_2 receptor.

As indicated in Table 4, and consistent with an overall increase in lipophilicity, all the oximes increased their binding affinities at the σ_2 receptor as compared to their carbonyl counterparts in group 1. The reverse was the case for binding at the σ_1 receptor. In addition, **22**, the oxime of compound **2**, produced the highest selectivity for the σ_2 receptor ($\sigma_1 K_i/\sigma_2 K_i=41.8$) among all the compounds evaluated in this study.

3. Conclusions

In this article, we have evaluated four groups of compounds: homopiperazine, piperazine, tropane and oxime analogs of SYA013. Among these groups, the homopiperazine and tropane groups have the highest affinity ligands at the σ_2 receptor (**7** and **21**; $K_i = 2.2$ nM), and **21** displays a high selectivity ($\sigma_1 K_i/\sigma_2 K_i=25.9$ nM) as well. Overall, oxime **22**, displayed the highest selectivity ($\sigma_1 K_i/\sigma_2 K_i=41.8$) among all the compounds evaluated in this study. Compared with PB28, one of the highest affinity ligands at the $\sigma_2 R$ ($K_i = 0.68$ nM),³⁸ compound **22** compares favorably but has a higher selectivity for the σ_2 receptor.

4. Experimental

4.1. General Information

Melting points were determined on a Gallenkamp (UK) apparatus and are uncorrected. All NMR spectra were obtained on either a Varian 300 MHz Mercury Spectrometer or 600 MHz Bruker Spectrometer. Elemental analyses were carried out by Atlantic Microlab, Inc., Norcross, GA, and are within 0.4% of theory unless otherwise noted. Flash chromatography was performed with Davisil grade 634 silica gel. Starting materials were obtained from Sigma–Aldrich and were used without further purification.

4.2. Preparation of 1-(5-chloropyridin-2-yl)-1,4-diazepane (**26a**) and 1-(5-chloropyridin-2-yl)piperazine (**28**)

4.2.1. 1-(5-chloropyridin-2-yl)-1,4-diazepane (26a)—A one to one mixture of homopiperazine and 2, 5-dichloropyridine in ethylene glycol was heated at 150 C for 12 hrs. After cooling to room temperature, the mixture was diluted with EtOAc (200 mL) followed by washing with saturated NaHCO_3 (2×200 mL). The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo to dryness, followed by column chromatography on silica gel to afford 1-(5-chloropyridin-2-yl)-1,4-diazepane as an oily residue in a yield of 65%. ^1H NMR (300 MHz, CDCl_3): δ 7.94 (1H, d, $J = 2.4$ Hz), 7.44 (1H, brs), 7.25 (1H, dd, $J = 2.4, 9.0$ Hz), 6.33 (1H, d, $J = 9.0$ Hz), 3.89 (2H, t, $J = 5.8$ Hz), 3.67 (2H, t, $J = 5.8$ Hz), 3.15 (2H, t, $J = 5.8$ Hz), 3.01 (2H, t, $J = 6.0$ Hz), 2.12 (2H, m).

^{13}C (75 MHz, CD_3OD): δ 156.0, 145.8, 137.2, 119.3, 106.8, 45.9, 45.7, 45.2, 43.6, 25.3.

4.2.2. 1-(5-chloropyridin-2-yl)piperazine (28)—A one to one mixture of piperazine and 2, 5-dichloropyridine in ethylene glycol was heated at 150 C for 12 hrs. After cooling to room temperature, the mixture was diluted with EtOAc (200 mL) followed by washing with saturated NaHCO_3 (2×200 mL). The organic layer was dried over Na_2SO_4 , and filtered. The filtrate was concentrated in vacuo to dryness to obtain a residue that was purified by column

chromatography on silica gel to afford 1-(5-chloropyridin-2-yl)piperazine as an oily residue in a yield of 78%.

^1H NMR (300 MHz, CDCl_3): δ 8.10 (1H, d, J = 6.0 Hz), 7.41 (1H, dd, J = 6.0, 9.0 Hz), 6.57 (1H, d, J = 9.0 Hz), 3.46–3.49 (4H, m), 2.96–3.00 (4H, m), 2.67 (1H, brs).

^{13}C (75 MHz, CDCl_3): δ 157.6, 146.3, 137.1, 120.4, 107.8, 45.3, 44.8.

4.3. Synthesis of homopiperazine analogs 2, 3, 4 and piperazine analogs (8 and 10)

General Procedure I: A mixture of 4-chloro-1-(4-fluorophenyl)butan-1-one (1.0 g, 5.0 mmol), 1-(5-chloropyridin-2-yl)-1,4-diazepane (1.2 g, 5.7 mmol), KI (250 mg), NaHCO_3 (1.0 g, 11.9 mmol) in $i\text{PrOH}$ (10 mL) was heated to reflux under N_2 for 12 h. After cooling to rt, the mixture was diluted with EtOAc (500 mL) and washed with water (2×300 mL). The organic layer was dried over Na_2SO_4 , filtered and the filtrate was concentrated in vacuo to dryness to obtain a residue which was purified by column chromatography on silica gel to afford 4-(4-(5-chloropyridin-2-yl)-1,4-diazepan-1-yl)-1-(4-fluorophenyl)butan-1-one **2** as a free base.

4.3.1. 4-(4-(5-chloropyridin-2-yl)-1,4-diazepan-1-yl)-1-(4-fluorophenyl)butan-1-one (2·2HCl)—The free base of **2** was converted into the HCl salt by the addition of ethereal HCl and the salt was purified by recrystallization from MeOH-Et₂O to afford the pure salt in a yield of 32%. Mp 185–187 °C, *Calcd for* $\text{C}_{20}\text{H}_{25}\text{Cl}_3\text{FN}_3\text{O} \cdot 0.4 \text{H}_2\text{O}$: C 52.68, H 5.70, N 9.22; *Found*: C 52.64, H 5.81, N 9.14.

^1H NMR (300 MHz, DMSO- d_6): δ 10.70 (1H, brs), 8.09 (1H, d, J = 2.4 Hz), 8.00–8.07 (2H, m), 7.63 (1H, dd, J = 2.7, 9.0 Hz), 7.31–7.38 (2H, t, J = 9.0 Hz), 6.76 (1H, d, J = 9.0 Hz), 4.26 (1H, dd, J = 4.2, 14.2 Hz), 3.75 (1H, dd, J = 8.4, 15.3 Hz), 3.47–3.61 (4H, m), 3.06–3.18 (6H, m), 2.32–2.43 (1H, m), 2.09–2.17 (1H, m), 1.96–2.06 (2H, m).

^{13}C NMR (75 MHz, DMSO- d_6): δ 197.8, 165.7 (d, J = 250.1 Hz), 155.5, 143.5, 139.0, 133.6 (d, J = 3.0 Hz), 131.3 (d, J = 9.3 Hz), 118.7, 116.2 (d, J = 21.4 Hz), 109.4, 55.9, 54.2, 53.4, 46.5, 41.8, 35.7, 23.4, 18.5.

4.3.2. 1-(4-fluorophenyl)-4-(4-(pyridin-2-yl)-1,4-diazepan-1-yl)butan-1-one (3·2HCl)—The free base was converted into the HCl salt by the addition of ethereal HCl, followed by recrystallization from MeOH-Et₂O to afford the pure salt in a yield of 34.7%. Mp 198–199 °C, *Calcd for* $\text{C}_{20}\text{H}_{26}\text{Cl}_2\text{FN}_3\text{O} \cdot 0.5 \text{H}_2\text{O}$: C 56.74, H 6.43, N 9.93; *Found*: C 56.86, H 6.36, N 9.76.

^1H NMR (300 MHz, DMSO- d_6): δ 11.27 (1H, s), 8.00–8.06 (3H, m), 7.94–7.99 (1H, m), 7.34 (2H, t, J = 9.0 Hz), 7.25 (1H, brs), 6.91–6.95 (1H, m), 4.20–4.26 (1H, m), 4.00–4.10 (1H, m), 3.62–3.75 (2H, m), 3.53–3.61 (2H, m), 3.09–3.29 (6H, m), 2.50–2.56 (2H, m), 2.14–2.20 (1H, m), 1.96–2.02 (2H, m).

^{13}C NMR (75 MHz, DMSO- d_6): δ 197.8, 165.5 (d, J = 250.7 Hz), 152.5, 143.8, 137.7, 133.5 (d, J = 2.3 Hz), 131.3 (d, J = 9.1 Hz), 116.2 (d, J = 21.8 Hz), 113.0, 112.6, 56.2, 53.3, 52.8, 48.1, 43.3, 35.7, 23.0, 18.5.

4.3.3. 1-(4-fluorophenyl)-4-(4-(pyrimidin-2-yl)-1,4-diazepan-1-yl)butan-1-one (4·2HBr)—The free base was treated with ethereal HBr to form a salt. Recrystallization from MeOH:Et₂O, afforded 1-(4-fluorophenyl)-4-(4-(pyrimidin-2-yl)-1,4-diazepan-1-yl)butan-1-one **4**, dihydrobromide, in yield of 33%, Mp 225–230 °C. *Calculated for* C₁₉H₂₅Br₂FN₄O: C 45.26, H 5, N 11.11; *Found*: C 45.47, H 5.07, N 11.02.

¹H NMR (600 MHz, DMSO-d₆): δ 9.80 (1H, s), 8.51 (2H, d, *J* = 4.9 Hz), 8.21–7.92 (2H, m), 7.52–7.25 (2H, m), 6.81 (1H, t, *J* = 4.9 Hz), 4.49–4.21 (1H, m), 3.93–3.81 (2H, m), 3.78–3.74 (1H, m), 3.72–3.65 (1H, m), 3.62–3.52 (1H, m), 3.34–3.23 (2H, m), 3.23–3.14 (4H, m), 2.37–2.3 (1H, m), 2.25–2.13 (1H, m), 2.08–1.99 (2H, m).

¹³C NMR (151 MHz, DMSO-d₆): δ 197.7, 165.1 (d, *J* = 250.0 Hz), 161.5, 157.6, 133.6, 131.4 (d, *J* = 9.4 Hz), 116.2 (d, *J* = 21.7 Hz), 110.7, 56.8, 55.4, 54.78, 4.36, 45.9, 36.0, 27.4, 22.2.

4.3.4. 4-(4-(5-chloropyridin-2-yl)piperazin-1-yl)-1-(4-fluorophenyl)butan-1-one (8·HCl)—The free base was converted into the salt by addition of ethereal HCl and the salt was purified by recrystallization from MeOH-Et₂O to afford the pure salt in a yield of 25%, Mp 183–185 °C. *Calcd for* C₁₉H₂₂Cl₂FN₃O · 1.0 H₂O: C 54.81, H 5.81, N 10.09; *Found*: C 54.89, H 5.47, N 10.09.

¹H NMR (300 MHz, DMSO-d₆): δ 10.47 (1H, brs), 8.15 (1H, d, *J* = 2.7 Hz), 8.06 (1H, d, *J* = 5.7 Hz), 8.03 (1H, d, *J* = 5.7 Hz), 7.68 (1H, dd, *J* = 2.7, 9.0 Hz), 7.36 (2H, t, *J* = 9.0 Hz), 6.98 (1H, d, *J* = 9.3 Hz), 4.33 (2H, d, *J* = 14.1 Hz), 3.56 (2H, d, *J* = 14.1 Hz), 3.21–3.32 (2H, m), 3.00–3.21 (6H, m), 1.91–2.06 (2H, m).

¹³C NMR (75 MHz, DMSO-d₆): δ 197.7, 165.5 (d, *J* = 250.1 Hz), 157.0, 145.8, 138.1, 133.6, 131.3 (d, *J* = 9.3 Hz), 120.5, 116.2 (d, *J* = 21.4 Hz), 109.8, 55.5, 50.6, 42.3, 35.7, 18.1.

4.3.5. 1-(5-chloropyridin-2-yl)-4-(4-(4-fluorophenyl)butyl)piperazine (10·HCl)—The free base was converted into the salt by addition of ethereal HCl and the residue was purified by recrystallization from MeOH-Et₂O to afford the pure salt in a yield of 31%, Mp 195–196 °C. *Calcd for* C₁₉H₂₄Cl₂FN₃: C 59.38, H 6.29, N 10.93; *Found*: C 59.22, H 6.04, N 10.90.

¹H NMR (300 MHz, DMSO-d₆): δ 10.30 (1H, brs), 8.15 (1H, d, *J* = 1.8 Hz), 7.68 (1H, dd, *J* = 2.7, 9.0 Hz), 7.21–7.26 (2H, m), 7.09 (2H, t, *J* = 9.0 Hz), 6.97 (1H, d, *J* = 8.4 Hz), 4.32 (2H, d, *J* = 14.2 Hz), 3.47–3.51 (2H, m), 3.17–3.26 (2H, m), 2.93–3.12 (4H, m), 2.56–2.61 (2H, m), 1.62–1.71 (2H, m), 1.52–1.60 (2H, m).

¹³C NMR (75 MHz, DMSO-d₆): δ 161.1 (d, *J* = 239.5 Hz), 157.0, 146.1, 138.2, 138.0, 130.5 (d, *J* = 7.7 Hz), 120.5, 115.4 (d, *J* = 20.3 Hz), 109.6, 55.6, 50.6, 42.2, 34.1, 28.6, 23.0.

4.4. Synthesis of 1-(5-chloropyridin-2-yl)-4-(3-((4-fluorophenyl)thio)propyl)-1,4-diazepane hydrochloride (7·HCl)

The method previously reported in Sampson et al.³⁴ was used. A mixture of 3-((4-fluorophenyl)thio)propyl methanesulfonate (0.86 g, 3.5 mmol), 1-(5-chloropyridin-2-yl)-1,4-diazepane (0.85 g, 4.0 mmol) **26a**, KI (150 mg), NaHCO₃ (1.0 g, 11.9 mmol) in *i*-PrOH (10 mL) was heated to reflux under N₂ for 12 h. After cooling to rt, the mixture was diluted with EtOAc (500 mL), followed by washing with water (2×300 mL), the organic layer was separated, dried over Na₂SO₄, and filtered. The filtrate was concentrated in vacuo to dryness, followed by column chromatography on silica gel to afford 1-(5-chloropyridin-2-yl)-4-(3-((4-fluorophenyl)thio)propyl)-1,4-diazepane **7**. The product was converted into the salt by the addition of ethereal HCl and the salt was purified by recrystallization from MeOH-Et₂O to afford the HCl salt, in a yield of 42%, Mp 191–193 °C. *Calcd for* C₁₉H₂₅Cl₃FN₃S·0.5 H₂O: C 49.41, H 5.67, N 9.10; *Found*: C 49.41, H 5.65, N 9.08.

¹H NMR (300 MHz, DMSO-d₆): δ 10.91 (1H, brs), 8.08 (1H, d, *J* = 2.4 Hz), 7.63 (1H, dd, *J* = 3.0, 9.0 Hz), 7.38–7.45 (2H, m), 7.14–7.21 (2H, m), 6.75 (1H, d, *J* = 9.0 Hz), 4.20–4.27 (1H, m), 3.67–3.75 (1H, m), 3.41–3.53 (4H, m), 3.11–3.17 (2H, m), 3.03–3.07 (2H, m), 2.95–3.00 (2H, m), 2.31–2.41 (1H, m), 2.04–2.16 (1H, m), 1.90–2.00 (2H, m).

¹³C NMR (75 MHz, DMSO-d₆): δ 161.4 (d, *J* = 241.7 Hz), 154.5, 141.4, 140.1, 131.9 (d, *J* = 7.6 Hz), 131.1 (d, *J* = 2.8 Hz), 118.7, 116.7 (d, *J* = 21.4 Hz), 110.6, 52.3, 54.0, 53.5, 47.0, 42.2, 30.9, 23.6, 23.3.

4.5. Synthesis of oximes 22–24

General Procedure II: A mixture of 4-(4-(5-chloropyridin-2-yl)-1,4-diazepan-1-yl)-1-(4-fluorophenyl)butan-1-one **2** (0.65g, 1.73 mmol), hydroxylamine hydrochloride (0.25g, 3.46 mmol), KOH (0.19g, 3.46 mmol) in EtOH (10 mL) was heated to reflux at 90 °C for 5 h. After cooling to room temperature, H₂O was added to the reaction mixture to precipitate the compound. The residue was washed with water and EtOAc and the aqueous layer was extracted twice with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄ and filtered. The filtrate was evaporated and the residue purified by flash chromatography using (90:10% EtOAc: Hexane).

4.5.1. (4-(4-(5-chloropyridin-2-yl)-1,4-diazepan-1-yl)-1-(4-fluorophenyl)butan-1-one oxime (22)—The product was recrystallized using EtOAc/Hexane to afford (4-(4-(5-chloropyridin-2-yl)-1,4-diazepan-1-yl)-1-(4-fluorophenyl)butan-1-one oxime **22** in a yield of 37%, Mp 148–150 °C. *Calculated for* C₂₀H₂₄ClFN₄O: C 61.46, H 6.19, N 14.33; *Found*: C 61.68, H 6.28, N 14.33. ¹H NMR (600 MHz, DMSO-d₆): δ 11.16 (1H, s), 8.03 (1H, d, *J* = 2.7 Hz), 7.83–7.58 (2H, m), 7.51 (1H, dd, *J* = 2.7, 9.1 Hz), 7.42–6.94 (2H, m), 6.63 (1H, d, *J* = 9.2 Hz), 3.71–3.59 (2H, m), 3.56 (2H, t, *J* = 6.1 Hz), 2.72–2.65 (2H, m), 2.65–2.60 (2H, m), 2.49–2.44 (2H, m), 2.43 (2H, dd, *J* = 8.7, 15.6 Hz), 1.92–1.69 (2H, m), 1.69–1.49 (2H, m).

^{13}C NMR (151 MHz, DMSO- d_6): δ 162.8 (d, J = 244.3 Hz), 156.9, 156.4, 146.0, 137.3, 133.2, 128.3 (d, J = 8.3 Hz), 117.4, 115.7 (d, J = 21.6 Hz), 107.2, 57.0, 55.0, 54.5, 47.3, 46.6, 27.3, 24.4, 23.4.

4.5.2. 1-(4-fluorophenyl)-4-(4-(pyridin-2-yl)-1,4-diazepan-1-yl)butan-1-one oxime (23)—Using the general method II, 1-(4-fluorophenyl)-4-(4-(pyridin-2-yl)-1,4-diazepan-1-yl)butan-1-one, **3** was treated with hydroxylamine hydrochloride to form the product which was recrystallized from EtOAc/Hexane to afford 1-(4-fluorophenyl)-4-(4-(pyridin-2-yl)-1,4-diazepan-1-yl)butan-1-one oxime **23** in a yield of 48%, Mp 108–112 °C. *Calculated for* $\text{C}_{20}\text{H}_{25}\text{FN}_4\text{O}$: C 67.39, H 7.07, N 15.72; *Found*: C 67.43, H 6.90, N 15.66.

^1H NMR (600 MHz, DMSO- d_6): δ 11.16 (1H, s), 8.43–7.87 (1H, m), 7.89–7.54 (2H, m), 7.46–7.43 (1H, m), 7.36–7.08 (2H, m), 6.57 (1H, d, J = 8.7 Hz), 6.54–6.46 (1H, m), 3.78–3.63 (2H, m), 3.57 (2H, t, J = 6.2 Hz), 2.76–2.66 (2H, m), 2.68–2.59 (2H, m), 2.48–2.44 (2H, m), 2.43 (2H, t, J = 7.0 Hz), 1.80 (2H, dt, J = 6.0, 11.7 Hz), 1.69–1.49 (2H, m).

^{13}C NMR (151 MHz, DMSO- d_6): δ 162.8 (d, J = 244.3 Hz), 158.3, 156.4, 148.1, 137.7, 133.2 (d, J = 2.4 Hz), 128.3 (d, J = 8.3 Hz), 115.7 (d, J = 21.4 Hz), 111.5, 105.8, 57.0, 55.3, 54.6, 46.9, 46.2, 27.5, 24.4, 23.4.

4.5.3. 1-(4-fluorophenyl)-4-(4-(pyrimidin-2-yl)-1,4-diazepan-1-yl)butan-1-one oxime (24)—Using the general method II, 1-(4-fluorophenyl)-4-(4-(pyrimidin-2-yl)-1,4-diazepan-1-yl)butan-1-one **4** was treated with hydroxylamine hydrochloride to form the product which was recrystallized from EtOAc/Hexane to afford 1-(4-fluorophenyl)-4-(4-(pyrimidin-2-yl)-1,4-diazepan-1-yl)butan-1-one oxime **24** in a yield of 20%, Mp 126–128 °C. *Calculated for* $\text{C}_{19}\text{H}_{24}\text{FN}_5\text{O}$: C 63.85, H 6.77, N 19.59; *Found*: C 63.49, H 6.79, N 19.57.

^1H NMR (600 MHz, CDCl_3): δ 8.32 (2H, d, J = 4.7 Hz), 7.79–7.57 (2H, m), 7.17–7.00 (2H, m), 6.48 (1H, t, J = 4.7 Hz), 4.12–3.91 (2H, m), 3.84 (2H, t, J = 6.4 Hz), 2.80 (3H, dd, J = 4.5, 8.8 Hz), 2.75–2.62 (m, 2H), 2.62–2.50 (2H, m), 2.16–1.98 (2H, m), 1.98–1.74 (3H, m).

^{13}C NMR (151 MHz, CDCl_3): δ 163.3 (d, J = 247.3 Hz), 161.5, 158.3, 157.7, 132.1 (d, J = 3.2 Hz), 127.9 (d, J = 8.3 Hz), 115.3 (d, J = 21.7 Hz), 109.2, 56.8, 55.6, 54.6, 45.8, 29.7, 27.0, 23.9, 23.5, 4.6.

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Fig. 1.
Homopiperazine analogs of group 1.

Fig 2.
Piperazine analogs in Group 2.

Fig. 3.
Tropane analogs in group 3.

Fig 4.
Oxime analogs of group 1 agents (Group 4).

Scheme 1.

Synthesis of homopiperazine analogs and their corresponding oximes. Reagents and conditions: i) KI, NaHCO₃, *t*PrOH, reflux; ii) NH₂OHHCl, KOH, EtOH, reflux.

Scheme 2.

Synthesis of piperazine analogs in Group 2. Reagents and conditions: i) KI, NaHCO₃, iPrOH, reflux.

Table 1

Binding affinity of homopiperazine analogs of SYA013 (group 1) at the sigma receptors

Compound	(σ_1R , [*] <i>Ki</i>), nM/p <i>Ki</i> $\pm$ SEM	(σ_2R , <i>Ki</i>), nM/p <i>Ki</i> $\pm$ SEM	<i>Ki</i> (σ_1R)/ <i>Ki</i> (σ_2R)
1	(24)/7.63 $\pm$ 0.07	(5.6)/8.29 $\pm$ 0.07	4.3
2	(30)/7.52 $\pm$ 0.05	(8.0)/8.1 $\pm$ 0.05	3.8
3	(453)/(6.34) $\pm$ 0.06	(32)/7.49 $\pm$ 0.09	14
4	(63)/7.20 $\pm$ 0.09	(44)/7.40 $\pm$ 0.10	1.4
5	(3.6)/8.44 $\pm$ 0.05	(8.5)/8.07 $\pm$ 0.06	0.4
6	(2.9)/8.54 $\pm$ 0.07	(5.9)/8.23 $\pm$ 0.08	0.5
7	(7.2)/8.14 $\pm$ 0.05	(2.2)/8.65 $\pm$ 0.05	3.3

* *Ki* data are within 20% of the mean value, p*Ki* data are recorded as the Mean $\pm$ SEM.

Table 2

Binding affinity constants of piperazine analogs (group 2 agents) at sigma receptors.

Compound	(σ_1R , K_i , nM/p <i>Ki</i> $\pm$ SEM)	(σ_2R , K_i , nM/p <i>Ki</i> $\pm$ SEM)	$K_i(\sigma_1R)/K_i(\sigma_2R)$
8	(25.0)/7.61 $\pm$ 0.07	(8.4)/8.07 $\pm$ 0.06	3.0
9	(403)/6.39 $\pm$ 0.05	(52.0)/7.3 $\pm$ 0.1	7.8
10	(95.0)/7.02 $\pm$ 0.07	(43.0)/7.37 $\pm$ 0.05	2.2
11	(36.0)	(51.5)	0.7
12	(1148)/5.94 $\pm$ 0.04	(600)/6.2 $\pm$ 0.01	1.9
13	(51.7)	(33.0)/7.48 $\pm$ 0.09	1.6
14	(41.5)	(5.12)	8.1
15	(77.1)	(25.1)	3.1
[#] PB 28	(0.38)	(0.68)	0.56

* K_i data are within 20% of the mean value, p*Ki* data are recorded as the Mean $\pm$ SEM.

[#] From Ref. [38].

Table 3

Binding affinity constants of tropane analogs of group 3 at sigma receptors.

Compound	(σ_1R , * Ki), nM/p <i>Ki</i> $\pm$ SEM	C(σ_2R , Ki), nM/p Ki $\pm$ SEM	$Ki(\sigma_1R)/Ki(\sigma_2R)$
17	(22.0)/7.66 $\pm$ 0.06	(27.0)/7.60 $\pm$ 0.10	0.8
18	(16.6)/6.78 $\pm$ 0.06	(18.0)/7.70 $\pm$ 0.10	3.7
19	(81.0)/7.09 $\pm$ 0.07	(29.0)/7.53 $\pm$ 0.08	2.8
20	(71.0)/7.15 $\pm$ 0.09	(8.1)/8.09 $\pm$ 0.06	8.8
21	(57.0)/7.24 $\pm$ 0.06	(2.2)/78.67 $\pm$ 0.09	25.9

* Ki data are within 20% of the mean value. p*Ki* data are recorded as the Mean $\pm$ SEM.

Table 4Binding affinity constants of oxime analogs in group 4 at σ receptors.

Compds	$(\sigma_1R, ^*Ki),$ nM/p <i>Ki</i> $\pm$ SEM	C(σ_2R, Ki), nM/p <i>Ki</i> $\pm$ SEM	$K_i(\sigma_1R)/K_i(\sigma_2R)$	Compds	$(\sigma_1R) ^* (Ki),$ nM/p <i>Ki</i> $\pm$ SEM	$(\sigma_2R) Ki,$ nM/p <i>Ki</i> $\pm$ SEM
22	(113.0)	(2.7)/8.6 $\pm$ 0.1	41.8	2	(30)77.52 $\pm$ 0.05	(8.0)/8.1 $\pm$ 0.05
23	(70)	(13.1)	5.3	3	(63)/6.34 $\pm$ 0.06	(32)77.49 $\pm$ 0.09
24	(1 4 8)	(26.0)77.6 $\pm$ 0.1	5.7	4	(63)77.20 $\pm$ 0.09	(44)77.40 $\pm$ 0.10

* *Ki* data are within 20% of the mean value. p*Ki* data are recorded as the Mean $\pm$ SEM.