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Targeting sigma receptors: novel medication development for drug abuse and addiction

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Abstract

Psychostimulant abuse is a serious health and societal problem in industrialized and developing countries. However, the identification of an effective pharmacotherapy to treat it has remained elusive. It has long been known that many psychostimulant drugs, including cocaine and methamphetamine, interact with sigma receptors in the brain and heart, offering a logical target for medication development efforts. However, selective pharmacological agents and molecular biological tools have only recently become available to rigorously evaluate these receptors as viable medication development targets. The current review will summarize provocative preclinical data, demonstrating the ability of sigma receptor antagonists and antisense oligonucleotides to ameliorate cocaine-induced convulsions, lethality, locomotor activity and sensitization, and conditioned place-preference in rodents. Recent studies suggest that the protective effects of sigma receptor antagonists also extend to actions produced by methamphetamine, 3,4-methylenedioxymethamphetamine, ethanol and other abused substances. Together, the data indicate that targeting sigma receptors, particularly the σ_1 -subtype, may offer an innovative approach for combating the effects of cocaine, and perhaps other abused substances.

Keywords

cocaine; ethanol; MDMA; methamphetamine; morphine; phencyclidine; sigma receptors

Sigma receptors

Sigma receptors were first postulated in 1976 by Martin and coworkers based on the actions of SKF 10,047 (*N*-allylnormetazocine) and related benzomorphans [1]. The name sigma is derived from the first letter 'S' in SKF 10,047, which is now known to be a nonselective ligand that binds to multiple receptor proteins. Consequently, sigma receptors were once thought to be an opioid receptor subtype, and then later, the phencyclidine (PCP) binding site on the NMDA receptor [2]. Today, sigma receptors are recognized as unique proteins with a distinct anatomical distribution, drug selectivity pattern and molecular biological profile from other mammalian proteins [2].

Sigma receptors are found in the brain and many peripheral organs that serve as targets for psychostimulant drugs, including the heart and lung [2]. In the brain, significant levels of sigma receptors are found in motor, limbic and endocrine regions [3–5]. These receptors have also been reported on monoaminergic and glutamatergic neurons, where they can modulate the synthesis and release of classical neurotransmitters, as well as cellular activity [4,6–10].

Many drugs of abuse interact with sigma receptors, including cocaine, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), some opioids and PCP, at concentrations that are achievable in the body [2,11–15]. In addition, many typical neuroleptics, antihistamines, antidepressant drugs, dissociative anesthetics and neuroactive steroids have been shown to have significant affinity for sigma receptors [15–17].

Consistent with the different classes of synthetic ligands that bind to sigma receptors, diverse compounds appear to serve as endogenous ligands at these receptors. Three types of studies support the existence of endogenous sigma ligands. First, screening of known endogenous ligands using receptor-binding assays reveals select neuroactive steroids (e.g., progesterone) and trace amines (e.g., N,N-dimethyltryptamine) as naturally occurring candidates [18,19]. Both classes of compounds have been shown to produce some functional effects in addition to binding, further supporting a potential role as endogenous ligands for sigma receptors [18–20]. Second, fractionation studies in a number of laboratories have uncovered tissue extracts that displace binding to sigma receptors. Although the structures of the active constituents in the fractions remain undetermined, some of them are believed to be peptides, since their binding could be obliterated by trypsin digestion or proteolysis [21,22]. Other extract fractions were not affected by pronase digestion [23], suggesting that the active constituents were not peptides and emphasizing the diversity of ligands that can interact with sigma receptors. Third, physiological studies in brain slices have demonstrated the release of endogenous compounds when either potassium or electrical stimulation was used to depolarize the tissue. Under depolarized conditions, sigma receptor radioligand binding was displaced from the tissue slices, indicating the release of endogenous substances that subsequently competed for binding to these sites [24,25]. Together, the data provide converging lines of support for the existence of endogenous sigma ligands.

Sigma receptor subtypes

Pharmacological and biochemical studies have demonstrated the existence of at least two subtypes of sigma receptors, which are designated σ_1 and σ_2 [2,12,26]. σ_1 -receptors have been cloned with high homology and identity from several species, including rodents and humans [2,12,26–28]. The σ_1 -subtype is a 223-amino acid protein with two transmembrane domains [2,29]. It represents a unique structural class of proteins that possess chaperone-like functions [30]. Within cells, σ_1 -receptors can be found on the endoplasmic reticulum, mitochondria, nuclear membrane envelope and plasma membrane [2]; their localization at the interface of the endoplasmic reticulum and mitochondria has become the focus of recent research [30]. Following the binding of ligands to it, the σ_1 -receptor can translocate between different cellular compartments and form protein–protein interactions to modulate the activities of G-protein-coupled receptors (GPCR), ion channels and signaling molecules [2,12,30–32].

By contrast, σ_2 -receptors are 18–22-kDa proteins, representing a slightly smaller entity than σ_1 -receptors [33]. Similar to σ_1 -receptors, the σ_2 -subtype is found in many different cellular locations, including the mitochondria, endoplasmic reticulum, lysosomes and plasma membrane [34]. They are particularly enriched in lipid rafts, where they are involved in calcium signaling via sphingolipid products [35,36]. They have been implicated in cell cycle functions, as well as cell survival and death processes [2,37]. σ_2 -receptors have yet to be cloned, and although pharmacological agents with preferential affinity for these receptors have been identified, truly selective compounds are unavailable [2]. Therefore, much less is known about σ_2 -receptor function compared with the σ_1 -subtype.

Putative interactions between sigma receptors & drugs of abuse

There are several mechanisms of action through which sigma receptor ligands may modulate the actions of drugs of abuse. Therefore, a conceptual framework is summarized here for the data that is presented in subsequent sections. When information relating to specific subtypes is available, the sigma receptor subtype is specified. Otherwise, the term sigma receptor, with no subtype designation, is used.

First, many drugs of abuse, including cocaine and methamphetamine, bind to sigma receptors. Cocaine and methamphetamine interact with both sigma receptor subtypes, and have an approximately tenfold better affinity for the σ_1 -compared with the σ_2 -receptor [12,13]. Therefore, interfering with their access to these sites using antagonists or antisense oligonucleotides would be expected to reduce the actions of these psychostimulant drugs.

Second, sigma-active drugs of abuse appear to act as agonists at sigma receptors. Therefore, in addition to directly competing for binding to sigma receptors, sigma receptor antagonists can mitigate the agonist actions of drugs of abuse through a number of mechanisms downstream of the receptor. For example, an antagonist could prevent agonist-induced signaling cascades from being activated. Binding of an antagonist to sigma receptors could also interfere with their ability to interact with relevant protein partners that are necessary for signaling events. Each of these effects would result in inactivation of sigma-mediated mechanisms of drugs of abuse.

Third, sigma receptors, particularly the σ_1 -subtype, modulate nonsigma-mediated cellular processes, such as dopaminergic, serotonergic and glutamatergic mechanisms, as well as the activity of ion channels [2]. Although the specific mechanisms vary from situation to situation, a general pattern appears to involve the binding of a ligand to the σ_1 -receptor and a subsequent translocation or uncoupling event to modulate the activity of another cellular element, such as a GPCR or ion channel. As part of the process, additional protein partners are picked up (or stabilized/dissociated) by σ_1 -receptors to assist with the modulation of the nonsigma cellular target (e.g., dopamine transporter). It is hypothesized that the type of ligand that binds to the σ_1 -receptor serves as a signal to direct the type of protein partners and cellular targets to which the modulation is directed. Within this conceptual framework, there are numerous ways in which a σ_1 -receptor ligand can modulate downstream effects of drugs of abuse that are mediated through nonsigma targets. It can alter the translocation of the σ_1 -receptor to any number of subsequent targets; it can alter the ability of the σ_1 -receptor to interact with relevant protein partners. Both of these effects could modulate the nonsigma agonist actions of drugs of abuse, such as indirect dopamine agonist activity.

Fourth, sigma receptor ligands can modulate drug-induced changes in gene and protein expression. Repeated exposure to drugs of abuse cause persistent neuroadaptations in the brain. Sigma ligands have been shown to alter the expression of immediate early genes [38–41], which can cause persistent changes in nervous system function through transcriptional regulation of late gene targets and their corresponding proteins. One of these late gene targets may, in fact, be σ_1 -receptors, which are upregulated in select brain regions following repeated exposure to cocaine or methamphetamine [40,42–44].

Cocaine & sigma receptors

Cocaine abuse and dependence is a serious health and societal problem. In the USA, it is estimated that nearly 36 million Americans have used cocaine at least once and that over 2 million individuals consider themselves current users of the drug [101]. Previous medication development efforts to combat cocaine abuse have been limited in success, and sigma

receptors have emerged as a promising target for pharmacotherapies to aid in breaking the cycle of abuse.

Many studies have now demonstrated the ability of putative sigma receptor antagonists (Table 1) to attenuate the acute effects of cocaine (convulsions, lethality, locomotor activity), subchronic effects of cocaine (sensitization, place conditioning) and conditioned reinstatement of behaviors motivated by cocaine (self-administration, place conditioning) in animals [12,40,42,45–47]. The role of σ_1 -receptors in these effects has been confirmed by the use of subtype selective antagonists, such as BD1063, BD1047 and NE-100, as well as sequence-specific antisense oligonucleotides [12,40,42,45–48]. Moreover, neuroactive steroids that function as putative σ_1 -receptor agonists and antagonists display cross-pharmacology with selective ligands in a number of animal models, including place conditioning [49]. The role of σ_2 -receptors is less definitive, as this subtype has not yet been cloned and no truly selective ligands have been developed. Nonetheless, studies involving σ_2 receptor-preferring putative antagonists, such as SM21 and SN79, support a role for this subtype in a number of cocaine-induced behaviors, including convulsions, locomotor activity and sensitization [50,51].

In contrast to sigma receptor antagonists that produce protective effects against the actions of cocaine, sigma receptor agonists, such as DTG, BD1031, BD1052, igmesine and SA4503 (Table 1), shift the cocaine dose–response curve to the left, indicative of an exacerbation of the effects of cocaine [12,47,49]. This has been demonstrated against cocaine-induced convulsions, locomotor activity and conditioned place preference. When administered alone, sigma receptor agonists do not produce convulsions or conditioned place preference [12,47,49]. Some sigma receptor agonists, such as (+)-pentazocine, (+)-SKF10,047 and pregnanolone, produce discriminative stimulus effects or are self-administered when given alone; under these conditions, their efficacy varies from being weaker to comparable, relative to cocaine [52–54]. However, not all sigma ligands produce similar changes in drug discrimination, sensitization and self-administration studies, suggesting that subtle differences in pharmacokinetic and pharmacodynamic parameters and training conditions could affect the overall pattern of these complex behaviors. The relative contribution of each sigma receptor subtype has not been studied systematically with regard to agonist actions, but data from compounds such as (+)-pentazocine support an involvement of σ_1 -receptors. Since most sigma receptor agonists do not produce robust cocaine-like effects on their own [12,47,49,52–54], they would not be expected to possess significant abuse liability, although they could exacerbate the effects of cocaine if used together. It is important to recognize this because many marketed medications, including the following examples, elicit sigma agonist effects as part of their myriad of actions: fluvoxamine and imipramine (antidepressant drugs), Talwin Nx (pain medication) and bupropion (smoking cessation).

In addition to behavioral changes, cocaine exposure has also been shown to trigger neuroadaptations in the brain that can be mitigated by pharmacological intervention with sigma receptor antagonists. Even after a single exposure to cocaine, numerous genes are upregulated [40,55,56]. Among them is the immediate early gene *fra-2* [39,55], which is a member of the fos family of transcription factors. Following the induction of *fra-2*, σ_1 -receptor levels become upregulated in brain regions involved in reward and addiction (striatum, cortex) [39], suggesting that σ_1 -receptors are a late gene product that is transcriptionally regulated by *fra-2*. Of particular interest is the fact that pretreatment of mice with the σ_1 -receptor antagonist BD1063 prior to cocaine significantly attenuates the ability of cocaine to induce *fra-2* as well as σ_1 -receptor gene and protein expression, in brain regions involved in reward and addiction [39].

Recent studies have further shown that the upregulation of *fra-2* and σ_1 recently receptors following cocaine exposure has functional consequences for subsequent responses to further cocaine exposure. Repeated, intermittent exposure to cocaine has long been known to produce behavioral sensitization in animals [57]. Using a cocaine-induced behavioral sensitization model coupled with gene and protein expression studies in mice, we have shown recently that cocaine induces the expression of the immediate early gene *fra-2*, which leads to a progressive increase in σ_1 -receptor gene and protein expression over a period of days [40]. This progressive increase in σ_1 -expression corresponds to the steady increase in the locomotor response to repeated cocaine administration in mice [40]. The cocaine-induced changes in σ_1 -receptor gene and protein expression occur in brain regions subserving drug abuse, such as the cortex and striatum, but not the cerebellum [40]. Moreover, the prototypic σ_1 -receptor antagonist BD1063 significantly attenuates both the molecular adaptations and behavioral sensitization induced by cocaine [40]. The ability of σ_1 -receptor expression to predict alterations in the behavioral responses of animals to cocaine, and the ability of antagonists to mitigate both the molecular and behavioral changes induced by repeated exposure to cocaine, provides a compelling target for further evaluation as a potential biomarker of responsiveness to cocaine.

Methamphetamine & sigma receptors

Methamphetamine is one of the most widely abused drugs worldwide, second only to cannabis [58]. In the USA, over 13 million people have used methamphetamine at least once, and over 500,000 consider themselves current users of the drug [101], putting them at risk for convulsions, hyperthermia, respiratory problems and cardiovascular collapse, all of which can be life threatening. In addition, repeated use of methamphetamine can lead to serious adverse health consequences, such as addiction and neurodegenerative damage [58]. There are currently no effective pharmacotherapies to aid in the treatment of methamphetamine abuse, and its escalating use has created an urgent need to address this problem. We propose that sigma receptors are promising drug development targets for achieving this goal.

Earlier studies have demonstrated that sigma receptor antagonism can mitigate the stimulant actions of methamphetamine. The acute locomotor stimulant effects of methamphetamine are reduced by pretreatment with sigma receptor antagonists [13,59]. Knockdown of the σ_1 -subtype in adult animals using antisense oligonucleotides also mitigates the stimulant actions of methamphetamine [13], although σ_1 -receptor-knockout mice still respond to methamphetamine [18]. Since complete genetic ablation often elicits compensatory changes during development, the data suggest that in the absence of σ_1 receptors throughout life, adaptations occur in non- σ_1 -mechanisms that allow methamphetamine to maintain its robust stimulant effects through alternative means (e.g., perhaps through σ_2 - or dopaminergic mechanisms). However, if development proceeds normally, impeding access to σ_1 -receptors in adult animals can interfere with the psychostimulant effects of methamphetamine. A specific role for the σ_2 -subtype in methamphetamine-induced effects awaits direct confirmation.

The involvement of sigma receptors in the actions of methamphetamine is also supported by sensitization studies, in which sigma receptor antagonists, such as MS-377 and BMY 14802, attenuate the sensitized behavioral response to methamphetamine [60,61]. In addition, sigma receptors can mediate more subtle modulation of methamphetamine-induced behaviors as shown by the ability of sigma receptor antagonists, such as BMY 14802 and BD1047, to shift the types of stereotyped responses induced by the psychostimulant without affecting the overall frequency of these behaviors [62].

Chronic exposure to stimulant doses of methamphetamine has also been reported to result in the upregulation of σ_1 -receptors in the midbrain in two separate studies [43,44]. This upregulation appears to have functional relevance to drug abuse because it can occur in rats self-administering methamphetamine compared with saline-treated or yoked controls [43].

Chronic exposure to high doses of methamphetamine can result in neurotoxicity [58]. Recent studies have confirmed that sigma receptor antagonists attenuate the neurotoxic effects of methamphetamine [59,63]. Selective sigma receptor antagonists, such as AC927 and CM156, prevent methamphetamine-induced depletions in striatal dopamine and serotonin levels, striatal dopamine transporter expression and hyperthermia [59,63]. The specific sigma receptor subtype(s) that mediate these effects has yet to be elucidated.

Other drugs of abuse & sigma receptors

Other sigma-active drugs of abuse whose actions can be mitigated with sigma receptor antagonists include MDMA and PCP. Similar to cocaine and methamphetamine, MDMA has preferential affinity for σ_1 - compared with σ_2 -receptors [11]. However, MDMA discriminates between the two sigma receptor subtypes to a lesser degree than cocaine and methamphetamine. Saturation binding assays and behavioral studies suggest that MDMA interacts with σ_1 -receptors in a competitive manner. MDMA produces a significant change in K_d but not B_{max} in saturation binding studies of σ_1 -receptors [11]. The locomotor stimulant actions of MDMA are also attenuated by pretreatment with the prototypic σ_1 -receptor antagonist BD1063, whereby BD1063 produces a parallel shift to the right in the dose–response curve for MDMA [11]. The functional role of σ_2 -receptors in the actions of MDMA have yet to be studied.

Recently, the hallucinogenic trace amine N,N-dimethyltryptamine (DMT) has been suggested as an endogenous ligand for σ_1 -receptors [18]. In addition to being found in the body, DMT can be extracted from many plants and is used in ritualistic ceremonies for its hallucinogenic properties [64]. Antagonism of σ_1 -receptors using pharmacological antagonists or knockout mice attenuates several functional effects of DMT, suggesting that at least some of its effects, including stimulant actions, are mediated through σ_1 -receptors [18]. However, the abuse liability of DMT is still unclear [64].

In addition to its interaction with NMDA receptors, PCP has significant affinity for sigma receptors. In contrast to the other drugs of abuse described thus far, PCP has preferential affinity for the σ_2 -subtype compared with σ_1 [2,65]. At least some of the actions of PCP can be attributed to sigma receptors, since pre-treatment with sigma receptor antagonists, such as MS-377 and NE-100, can attenuate the following PCP-induced effects: motor behavior, attention deficits, release of dopamine and serotonin in the rat brain, and *c-fos* and *hsp70* gene expression [41,66–71].

Accumulating data suggest that sigma receptor antagonism can also mitigate the actions of abused substances, even if the drugs do not themselves have appreciable affinity for sigma receptors. The best example is ethanol, which has not been shown to have significant affinity for sigma receptors. Yet, sigma receptor antagonists attenuate the following ethanol-induced effects: locomotor activity, place conditioning, taste conditioning, self-administration in excessive ethanol drinking models and NMDA-independent long-term potentiation in early adolescent exposed animals [72–74]. Therefore, sigma receptor antagonists are capable of modulating nonsigma receptor targets to produce favorable therapeutic actions, in addition to altering the actions of sigma-active drugs of abuse.

It should also be noted that the ability of sigma ligands to negatively modulate the effects of abused drugs is not limited to antagonist compounds. A number of studies have

demonstrated that σ_1 -receptor agonists can reduce behaviors in animals that are elicited following exposure to drugs of abuse; examples include modulation of some PCP and nicotine effects. Consistent with the body of literature showing that sigma receptor agonists have cognitive-enhancing effects [2], selective σ_1 -receptor agonists, such as (+)-pentazocine and SA4503, counteract PCP-induced impairments in learning and memory [75]. In contrast to their favorable effects under pathological conditions, sigma receptor agonists do not improve learning and memory processes in normal animals, emphasizing the modulatory impact of sigma receptors in normalizing cellular functions. In addition, nicotine, which does not have significant affinity for sigma receptors, produces conditioned place preference in animals that can, nonetheless, be attenuated by the σ_1 -receptor agonist SA4503 [76]. This pattern of response would be consistent with the effectiveness of the putative sigma receptor agonist bupropion for smoking cessation in humans [77]. Although the precise mechanisms underlying the agonist effects are not fully elucidated, one salient feature may be that under the chronic exposure conditions described above, there is impaired synaptogenesis or connectivity in the nervous system and the ability of sigma receptor agonists to promote plasticity may contribute to their effectiveness.

Expert commentary

The ability of sigma receptor antagonism to mitigate the actions of many drugs of abuse suggests that these receptors represent a common medication development target for a variety of classes of abused substances. The modulatory role of sigma receptors, particularly the σ_1 -subtype, in the body and their tendency to normalize cellular functions makes them an attractive medication development lead. The modulatory role allows σ_1 -receptor ligands to intervene in a wide variety of situations and functional states, including in the presence of drugs of abuse. At the same time, they produce few effects under normal conditions and have a low side-effect liability, resulting in a class of drugs that would be expected to have a favorable therapeutic and safety margin. The existing preclinical data indicate that sigma receptor ligands have the potential to treat various aspects of drug abuse, including the reversal of acute toxic overdoses, prevention of relapse and compensation for pathological neuroadaptations and behaviors that result from repeated drug exposures.

Five-year view

Additional studies to fully explore the myriad of potential applications for sigma receptor ligands and the cellular mechanisms through which they elicit therapeutic actions represent fertile areas for new research. In the drug abuse field, studies to determine the specific situations and conditions under which pharmacological intervention with a sigma receptor ligand is most effective will help to advance medication development efforts. For example, the extent to which this class of compounds is effective in reducing craving, pathological cognitive processing and other maladaptive changes that are associated with addiction remain to be determined. In addition, studies that provide insights into basic mechanisms of sigma receptor function will promote the optimization of effective therapeutic interventions that target these receptors. Significant advances in several key areas are anticipated. First, the delineation of specific mechanisms that are involved in the modulation of function under different conditions (e.g., acute vs subchronic drug exposures) will help to identify viable therapeutic opportunities that are amenable to intervention with sigma receptor ligands. Second, the identification of endogenous ligand(s) for sigma receptors will aid in defining the manner in which sigma ligands can modulate cellular functions under normal versus pathological conditions. Third, the cloning of σ_2 -receptors and the development of subtype-selective experimental tools will help to optimize the targeting of sigma ligands with therapeutic potential. For example, additional information with regard to the σ_2 -subtype will be critical for determining whether the ideal sigma drug should be one that is subtype

selective or one that discriminates to a lesser degree between the subtypes. Fourth, it is anticipated that major advances will be made in the area of sigma receptors as biomarkers for a variety of disease states and their treatment. Finally, the use of knockout mice and other genetic manipulations offers opportunities to further explore sigma receptor function and influences on behavior with regard to drug abuse. All of these developments are anticipated to provide valuable insight that will help to shape the therapeutic development and optimization of sigma ligands for the treatment of addiction.

Key issues

- Many drugs of abuse, including cocaine and methamphetamine, interact with sigma receptors.
- Antagonism of sigma receptors attenuates an array of psychostimulant-induced effects, including neurochemical changes, gene and protein expression, and drug-related behaviors.
- The ability of sigma receptor antagonists to mitigate diverse effects of psychostimulant drugs stems from their ability to intercede in numerous cellular mechanisms, including competition for binding sites and the downstream modulation of sigma- and nonsigma-mediated signaling cascades and transcriptional processes.
- Potential therapeutic effects of sigma receptor antagonists also extend to abused substances that do not appear to directly bind to these receptors, such as ethanol.
- Additional studies to further elucidate the mechanisms through which ligands for each of the sigma receptor actions of drugs of abuse are needed.
- This information, together with additional studies of complex behavioral and neural changes associated with addiction, will be important to identify the conditions under which therapeutic intervention with sigma ligands could provide optimal benefit.

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Table 1

Select sigma ligands used in substance-abuse studies.

Ligand	Chemical name
<i>Putative agonists</i>	
BD1031	3R-1-[2-(3,4-dichlorophenyl)ethyl]-1,4-diazabicyclo[4.3.2]nonane
BD1052	<i>N</i> -[2-(3,4-dichlorophenyl)ethyl]- <i>N</i> -allyl-2-(1-pyrrolidinyl)ethylamine
DTG	1,3-di- <i>o</i> -tolylguanidine
Igmesine	(+)-cinnamyl-1-phenyl-1- <i>N</i> -methyl- <i>N</i> -cyclopropylene
SA4503	1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine
SKF-10,047	<i>N</i> -allylnormetazocine
<i>Putative antagonists</i>	
AC927	<i>N</i> -phenethylpiperidine
BD1047	<i>N</i> -[2-(3,4-dichlorophenyl)ethyl]- <i>N</i> -methyl-2-(dimethylamino)ethylamine
BD1063	1-[2-(3,4-dichlorophenyl)ethyl]-4-methylpiperazine
BMV 14802	α -(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazine-butanol
CM156	3-(4-(4-cyclohexylpiperazin-1-yl)butyl)benzo [<i>d</i>]thiazole-2(3 <i>H</i>)-thione
MS-377	(<i>R</i>)-(+)-1-(4-chlorophenyl)-3-[4-(2-methoxyethyl)piperazin-1-yl] methyl-2-pyrrolidinone
NE-100	<i>N,N</i> -dipropyl-2-[4-methoxy-3-(2-phenylethoxy)phenyl]ethylamine
SM21	tropanyl 2-(4-chlorophenoxy)butanoate
SN79	6-acetyl-3-(4-(4-(4-fluorophenyl)piperazin-1-yl)butyl)benzo[<i>d</i>]oxazol-2 (3 <i>H</i>)-one