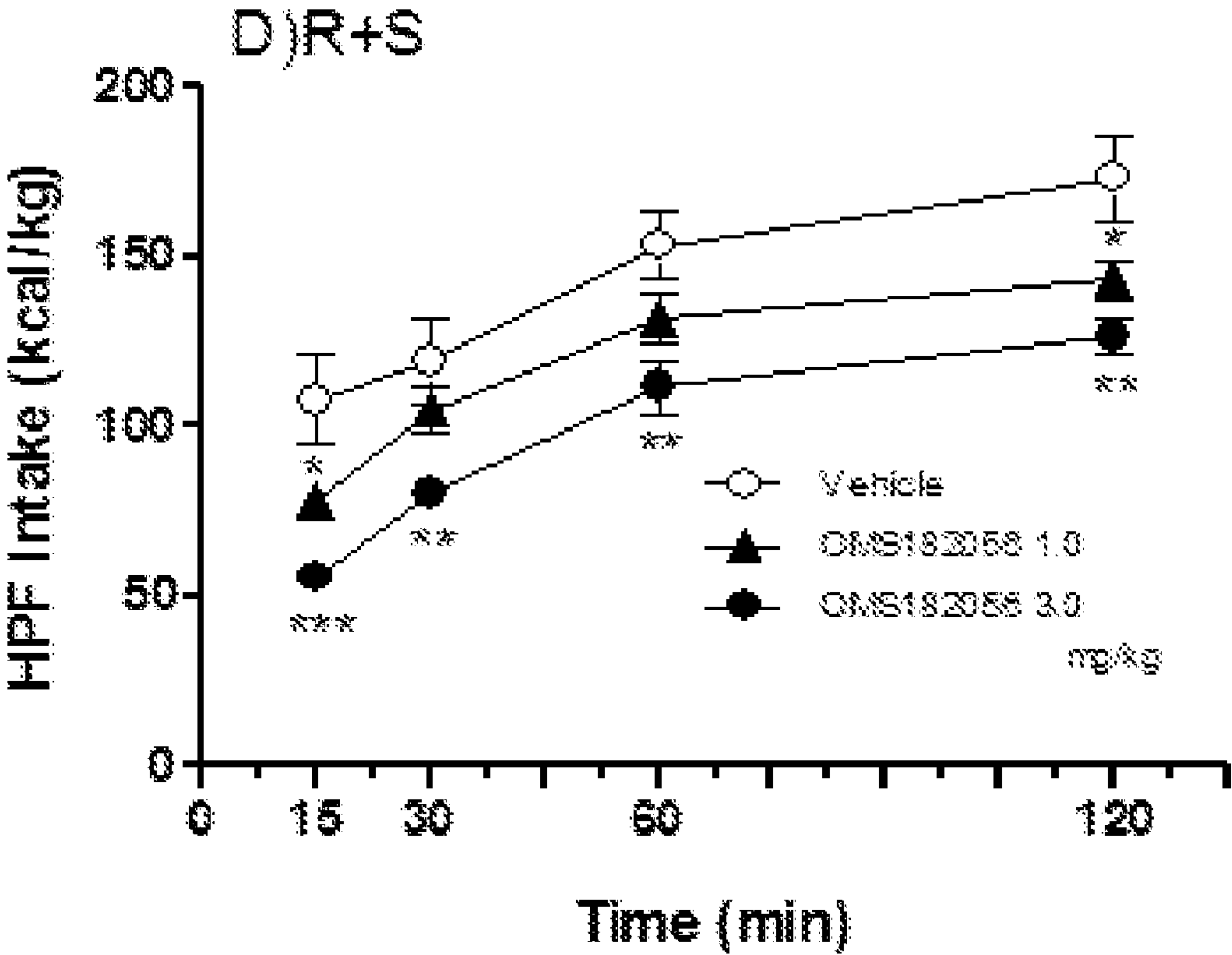




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(54) **Titre :** TRAITEMENT DE LA DEPENDANCE ET DES TROUBLES DU CONTROLE DES IMPULSIONS A L'AIDE D'INHIBITEURS
DE PDE7
(54) **Title:** TREATMENT OF ADDICTION AND IMPULSE-CONTROL DISORDERS USING PDE7 INHIBITORS



(57) **Abrégé/Abstract:**
This disclosure is directed to treatment of addictions and primary impulse- control disorders using phosphodiesterase 7 (PDE7) inhibitors, alone or in combination with other therapeutic agents.

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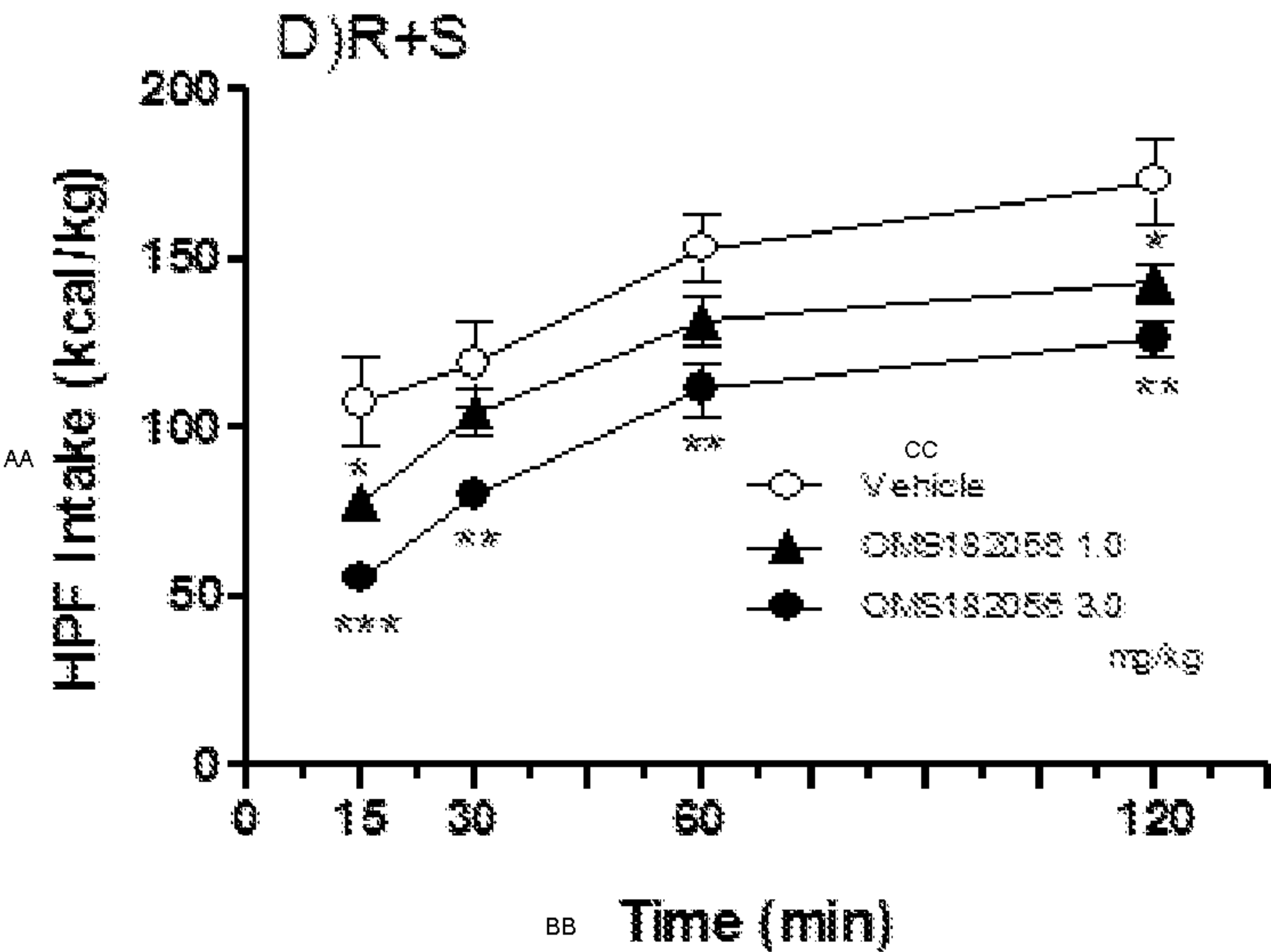
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(57) Abstract: This disclosure is directed to treatment of addictions and primary impulse- control disorders using phosphodiesterase 7 (PDE7) inhibitors, alone or in combination with other therapeutic agents.

FIGURE 24D



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**TREATMENT OF ADDICTION AND IMPULSE-CONTROL DISORDERS
USING PDE7 INHIBITORS**

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I. Field of the Invention

This disclosure is directed to prevention and treatment of substance and behavioral addictions using phosphodiesterase 7 (PDE7) inhibitors, alone or in combination with other therapeutic agents or addictive agents.

II. Background of the Invention

15

The World Health Organization (WHO) defines substance addiction as using a substance repeatedly, despite knowing and experiencing harmful effects. Substance addiction is a chronic, relapsing disease characterized by a loss of control over drug use, compulsive drug seeking and craving for a substance, use that persists despite negative consequences, and physical and/or psychological dependence on the substance. Substance addiction typically

20

follows a course of tolerance, withdrawal, compulsive drug taking behavior, drug seeking

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behavior, practice of addictive behavior, and relapse. Substance abuse and addiction are public health issues with significant social and economic impact on both the addict and society by playing a major role in violent crime and the spread of infectious diseases. Addictive substances include alcohol, caffeine, nicotine, cannabis (marijuana) and cannabis derivatives, opiates and other morphine-like opioid agonists such as heroin, phencyclidine and phencyclidine-like compounds, sedative hypnotics such as benzodiazepines and barbiturates and psychostimulants such as cocaine, amphetamines and amphetamine-related drugs such as dextroamphetamine and methylamphetamine.

Alcohol is one of the most commonly abused substances at a global level. Additionally, alcoholism leads to serious liver and cardiovascular disease and generates dependence resulting in severe mental disorders, social problems and adverse consequences including the division of families, tragic accidents and the reduction of work performance. According to the WHO, alcohol consumption is responsible for 20-30% of oesophageal and liver cancer, liver cirrhosis, homicides, epilepsy, and motor vehicle accidents worldwide. Globally, alcohol abuse leads to about 1.8 million deaths per year. Compulsive behavior towards the consumption of alcohol is a core symptom of the disorder. In recent years several approaches have been investigated to help alcoholic patients to not only control alcohol drinking but also alcohol cravings and relapse (Monti et al., *J Stud Alcohol* 54:235-45 (1993); Volpicelli et al., *Arch Gen Psychiatry* 49:876-880 (1992); and O'Brien *Science* 278 : 66-70 (1997)).

Medications such as naltrexone, acamprosate, ondansetron, disulfiram, gamma hydroxybutyrate (GHB), and topiramate tested for their potential therapeutic effect on alcohol abuse belong to several classes (Volpicelli et al. 1992; O'Brien et al. 1997). Few of these pharmacotherapeutics, such as naltrexone, acamprosate, and disulfiram, have been proven to be of a certain utility and approved for the treatment of alcoholism. Among these medications, the non-selective opioid antagonist naltrexone is currently considered the

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pharmacological best option. However, despite some promising results none of these medications, including naltrexone, is of sufficient efficacy in alcoholism and prognosis remains poor.

Nicotine is one of the most widely used addictive drugs, and nicotine abuse is the most common form of substance abuse. The WHO estimates that there are 1.25 billion smokers worldwide, representing one third of the global population over the age of 15. The WHO further estimates that 5 million deaths occur each year as a direct result of tobacco use, making nicotine abuse the largest single preventable cause of death worldwide. In industrialized countries, 70-90% of lung cancer, 56-80% of chronic respiratory disease, and 22% of cardiovascular disease instances are attributed to nicotine addiction. Cigarette smoking is associated with 430,000 deaths per year in the US alone and is estimated to cost the nation 80 billion dollars yearly in health care costs. Tobacco use accounts for one third of all cancers, including cancer of the lung, mouth, pharynx, larynx, esophagus, cervix, kidney, ureter, and bladder. The overall rates of death from cancer are twice as high among smokers as among nonsmokers. Smoking also causes lung diseases such as chronic bronchitis and emphysema; exacerbates asthma symptoms; and increases the risk of heart disease, including stroke, heart attack, vascular disease, and aneurysm. An estimated 20% of the deaths from heart disease are attributable to smoking. Expectant women who smoke are at greater risk than nonsmokers for premature delivery, spontaneous abortion, and infants with decreased birth weight.

Nicotine use results in increased levels of the neurotransmitter dopamine, which activates the reward pathways to regulate feelings of pleasure and to mediate the desire to consume nicotine. Symptoms associated with nicotine withdrawal include craving, irritability, anger, hostility, aggression, fatigue, depression, and cognitive impairment, which lead the abuser to seek more nicotine. Environmental conditioning factors and exposure to psychological stress represent additional factors motivating nicotine use in smokers.

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Repeated nicotine use results in the development of tolerance, requiring higher doses of nicotine to produce the same initial stimulation.

Most therapies developed for nicotine addiction have shown only moderate success in preventing relapse, leading to a high failure rate in attempts to quit smoking. Treatments
5 include the use of nicotine replacement products, anti-depressants, anti-hypersensitives, and behavioral therapy.

The National Institute on Drug Abuse estimates that 72 million Americans, about one third of the population, have tried marijuana. Acute effects of marijuana use include memory and learning problems, distorted perception, difficulty problem solving, loss of coordination,
10 and increased heart rate. Long term abuse can cause the same respiratory problems observed in tobacco smokers, such as daily cough, phlegm production, increased risk of lung infections, and an increased chance of developing cancer of the head, neck and lungs. Depression, anxiety, and job-related problems have been associated with marijuana use. Long term marijuana use can result in addiction with compulsive use that interferes with daily
15 activities. Cravings and withdrawal symptoms, such as irritability, increased aggression, sleeplessness, and anxiety make it difficult for addicts to stop using marijuana. There are no pharmaceutical treatments available for treating marijuana addiction and relapse.

According to the WHO, an estimated 13 million people abuse opioids worldwide, including 9 million heroin addicts. More than 25% of opioid abusers die from suicide,
20 homicide, or an infectious disease, such as HIV and hepatitis, within 10-20 years of becoming addicted. Tolerance and physical dependence can develop within two to three days. While abuse and addiction to opioid agents is a known phenomenon, what is new is the worsening of this problem in the recent years (Compton and Volkow, *Drug Alcohol Depend* 83 Suppl 1: S4-7 (2006A) and Compton and Volkow, *Drug Alcohol Depend* 81(2): 103-7
25 (2006B)). Epidemiological surveys of youth in the United States in 2003 indicated that opioid analgesics were among the most frequently abused illicit drugs among secondary

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students (12th graders), second only to marijuana (Delva et al., *Am J Public Health* 95(4): 696-702 (2005)). Furthermore, the past few years have seen a marked increase in the use of opioid medications in the United States and an even greater increase in problems associated with such use. This upsurge in use and problems is particularly concerning because it seems
5 to represent an expanded pathway to opioid addiction (Siegal et al., *Am Fam Physician* 67: 942- 945 (2003)).

According to recent epidemiological data, 4.7% (i.e., 11.0 million) United States household residents over the age of twelve abused an opioid medication in 2002 and 13.7% of these persons (i.e., 1.5 million) met the criteria of a DSM-IV opioid use disorder
10 (American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. (1994); Substance Abuse and Mental Health Services Administration, Mortality Data from the Drug Abuse Warning Network, 2002, (2004)). As recently reviewed by Compton and Volkow, the annual incidence of opioid analgesic abuse increased from 628,000 initiates in 1990 to 2.4 million initiates in 2001 (Substance Abuse and Mental Health
15 Services Administration, Overview of Findings from the 2002 National Survey on Drug Use and Health, (2003); Substance Abuse and Mental Health Services Administration, Emergency Department Trends From the Drug Abuse Warning Network, Final Estimates 1995-2002, (2003)). One of the reasons fostering the expansion of opioid addiction is the increased use of analgesic secondary to medical prescription. Short-term use of opioid medication is rarely
20 associated with addiction. Conversely, protracted treatments with these agents have been associated with development of addiction in up to 18% of patients.

The goals for treatment of opiate addiction, as with other types of substance addictions, are to discontinue the use of the opioid while minimizing painful withdrawal symptoms and preventing relapse. Current treatments involve replacing the addictive drug
25 with a substitution of an opioid receptor agonist or mixed agonist/antagonist. An alternative approach consists of the use of an opioid receptor antagonist to block the effect of the

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agonist. Antagonists provide no relief from pain or other withdrawal symptoms; rather, they can precipitate withdrawal, and their therapeutic use was associated with increased accidental opioid agonists overdosing and increased lethality. Use of agonists with a lower affinity for the receptors results in the least severe withdrawal symptoms, but it can lead to a dependence
5 on the substitute opiate. Also, many substitution therapies take 3-6 months, allowing time for addicts to stop treatment midway.

Psychostimulants, such as cocaine and amphetamines, temporarily cause euphoria, increased alertness, and increased physical capacity in humans. These substances first increase dopamine transmission, but long term drug usage results in a reduction of dopamine
10 activity, leading to dysregulation of the brain reward system and dysphoria. The WHO estimates 33 million people around the world abuse amphetamines.

Chronic cocaine abuse can result in hyperstimulation, tachycardia, hypertension, mydriasis, muscle twitching, sleeplessness, extreme nervousness, hallucinations, paranoia, aggressive behavior, and depression. Cocaine overdose may lead to tremors, convulsions,
15 delirium, and death resulting from heart arrhythmias and cardiovascular failure. Desipramine, amantadine and bromocriptine have been shown to decrease cocaine withdrawal symptoms.

Amphetamine withdrawal symptoms include EEG changes, fatigue, and mental depression. Tolerance develops over time and may be associated with tachycardia, auditory and visual hallucinations, delusions, anxiety reactions, paranoid psychosis, exhaustion,
20 confusion, memory loss, and prolonged depression with suicidal tendencies. Current treatments for amphetamine addiction include phenothiazines, haloperidol, and chlorpromazine for hallucinations, but potential side effects of these drugs include postural hypotension and severe extrapyramidal motor disorders. Subjects who are addicted to psychostimulants will sometimes go through psychological withdrawal as well as
25 physiological withdrawal, making relapse potentially more likely.

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In the past, treatment for substance addictions focused on behavioral therapy, but dependence on many of these highly addictive substances is hard to break. In particular, addictions to alcohol, cocaine, and heroin are considered chronic, relapsing disorders. Also, concurrent abuse of multiple substances, such as nicotine, heroin, cocaine and alcohol, is
5 common.

The long-lasting, chronic nature of many addictions and high rates of recidivism present a considerable challenge for the treatment of drug and alcohol addiction, such that understanding of the neurobiological basis of relapse has emerged as a central issue in addiction research. Emotional and environmental factors (conditioning stimuli) were listed
10 among the main causes of relapse. For example, it is known that specific stress conditions such as loss of work and economic difficulties, or stimuli predictive of the presence of alcohol previously associated with its use such as a bottle of the preferred wine and a bar-like environment, may strongly facilitate relapse in detoxified former alcoholics.

The growing incidence of obesity in the United States, Europe and other westernized
15 societies also is indicative of the prevalence of food addiction-like behavior. As distinguished from normal eating behaviors, food addiction is a maladaptive behavior, making people who eat in response to addiction rather than hunger feel worse rather than better. The overeating of a food addict is also persistent and habitual, eating an excessive amount of food on a regular basis, and often eating excessive quantities of unhealthy foods.
20 Food addiction not only leads to obesity, but paradoxically may also lead to malnutrition. There are several similarities between food addiction and drug substance addiction, including effects on mood, external cues causing the addictive behavior, expectancies, restraint, ambivalence and attribution.

Two major theoretical positions exist to explain the persistence of addictive behavior
25 and vulnerability to relapse associated with drug and alcohol addiction, homeostatic hypotheses and conditioning hypotheses.

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Homeostatic hypotheses relate relapse risk to neuroadaptive changes and disruption of neuroendocrine homeostasis that are thought to underlie anxiety, mood dysregulation and somatic symptoms that accompany acute withdrawal, and that can persist for considerable periods of time during what has been referred to as the “protracted withdrawal” phase. This view, therefore, implicates alleviation of discomfort and negative affect as a motivational basis for relapse.

Conditioning hypotheses are based on observations that relapse is often associated with exposure to drug-related environmental stimuli. This view holds that specific environmental stimuli that have become associated with the rewarding actions of a drug by means of classical conditioning can elicit subjective states that trigger resumption of drug use. The homeostatic and conditioning hypotheses are not mutually exclusive. In fact, homeostatic and conditioning factors are likely to exert additive effects in that exposure to drug-related environmental stimuli may augment vulnerability to relapse conveyed by homeostatic disturbances.

Clearly, there is a need in the art for new methods for treating and preventing addiction and the relapse use of addictive agents. The present invention meets these needs by providing methods and pharmaceutical combinations useful in treating and preventing addiction and recidivism.

III. Summary of the Invention

The present invention provides a method of treating or preventing an addiction by determining that a subject has an addiction or is at risk of developing an addiction and then administering an inhibitor of a phosphodiesterase 7 (PDE7) effective to the subject for the treatment or prevention of the addiction.

In one aspect of the invention, the subject is addicted to an addictive agent. Examples of addictive agents include alcohol, nicotine, marijuana, a marijuana derivatives, opioid agonists, benzodiazepines, barbiturates, and psychostimulants. In one embodiment, the

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addictive agent is alcohol. In another embodiment, the addictive agent is nicotine. In a further embodiment, the addictive agent is an opioid, e.g., morphine, methadone, fentanyl, sufentanil, codeine, oxycodone, and heroin. In a further embodiment, the addictive agent is a psychostimulant, e.g., cocaine, amphetamine or an amphetamine derivative. In another
5 embodiment, the addictive agent is cocaine.

In one aspect of the invention, the subject is addicted to an addictive or compulsive behavior or suffers from an impulse-control disorder. In another aspect of the invention, the subject suffers from a primary impulse-control disorder, i.e., an impulse-control disorder in which the disorder is a primary disorder rather than a disorder that is either iatrogenic
10 (secondary to medical treatment) or that is secondary to another primary disease or disorder. Addictive or compulsive behaviors that are primary impulse-control disorders include the following: binge eating, pathological gambling, pathological use of electronic devices, pathological use of electronic video games, pathological use of electronic communication devices, pathological use of cellular telephones, addiction to pornography, sex addiction,
15 compulsive spending, anorexia, bulimia, intermittent explosive disorder, kleptomania, pyromania, trichotillomania, compulsive over-exercising, and compulsive overworking. In another embodiment, the addictive or compulsive behavior is a food addiction. In another embodiment, the addictive or compulsive behavior is binge eating. In another aspect of the invention, the addictive or compulsive disorder is an obsessive-compulsive disorder.

20 In one aspect of the invention, the PDE7 inhibitory agents for treatment of addiction are selected from the following disclosed herein: formula 1A, formula 1B, formula 29, formula 30, formula 31, formula 32, formula 33, formula 34, formula 35, formula 36, formula 37, formula 38, formula 39, formula 40, formula 41, formula 42, formula 43A, formula 43B, formula 44, formula 45, formula 46, formula 47, formula 48, formula 49,
25 formula 50, formula 51, formula 52, formula 53, formula 54, formula 6A, formula 6B,

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formula 6C, formula 6D, formula 6E, formula 6F, formula 6G, formula 6H, formula 16A, compound 1, compound 2, compound 3, and compound 4.

In one aspect of the invention, the PDE7 inhibitory agent has an IC_{50} for inhibiting PDE7A and/or PDE7B activity of less than about 1 μ M. In one embodiment, the PDE7
5 inhibitory agent has an IC_{50} for inhibiting PDE7A and/or PDE7B activity of less than about 100 nM. In another embodiment, the PDE7 inhibitory agent has an IC_{50} for inhibiting PDE1B activity of greater than 5 times the lesser of the IC_{50} for inhibiting PDE7A activity and the IC_{50} for inhibiting PDE7B activity. In another embodiment, the PDE7 inhibitory agent has an IC_{50} for inhibiting PDE10 activity of greater than 5 times the lesser of the IC_{50}
10 for inhibiting PDE7A activity and the IC_{50} for inhibiting PDE7B activity. In a further embodiment, the PDE7 inhibitory agent has an IC_{50} for inhibiting PDE3 activity of greater than 10 times the lesser of the IC_{50} for inhibiting PDE7A activity and/or the IC_{50} for inhibiting PDE7B activity. In another embodiment, the PDE7 inhibitory agent has an IC_{50} for inhibiting PDE3 and PDE4 activity of greater than 10 times the lesser of the IC_{50} for
15 inhibiting PDE7A activity and the IC_{50} for inhibiting PDE7B activity. In a further embodiment, the PDE7 inhibitory agent has an IC_{50} for inhibiting PDE 4 and PDE 8 activity of greater than 10 times the lesser of the IC_{50} for inhibiting PDE7A activity and the IC_{50} for inhibiting PDE7B activity. In another embodiment, the PDE7 agent has an IC_{50} for inhibiting PDE1, PDE2, PDE3, PDE 4, PDE 8, PDE10, and PDE11 activity of greater than 10 times the
20 lesser of the IC_{50} for inhibiting PDE7A activity and the IC_{50} for inhibiting PDE7B activity. In a further embodiment, the PDE7 inhibitory agent is a selective PDE7 inhibitor for which the lesser of the IC_{50} for inhibiting PDE7A activity and the IC_{50} for inhibiting PDE7B activity is less than one tenth the IC_{50} that the agent has for inhibiting the activity of any other PDE enzyme from the PDE1-6 and PDE8-11 enzyme families. In another embodiment, the PDE7
25 inhibitory agent is a highly selective PDE7 inhibitor for which the lesser of the IC_{50} for inhibiting PDE7A activity and the IC_{50} for inhibiting PDE7B activity is less than one fiftieth

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the IC_{50} that the agent has for inhibiting the activity of any other PDE enzyme from the PDE1-6 and PDE8-11 enzyme families. In a further embodiment, the PDE7 inhibitory agent has a molecular weight of less than about 450 g/mole. In another embodiment, the PDE7 inhibitory agent is able to cross the blood/brain barrier.

5 The present invention provides a method of treating or preventing an addiction by determining that a subject has an addiction or is at risk of developing an addiction and then administering a chemical compound that inhibits PDE7 activity. The chemical compound has the following characteristics: (i) an IC_{50} for inhibiting PDE7A and/or PDE7B activity of less than about 1 μM ; and (ii) an IC_{50} for inhibiting PDE 3 greater than 10 times the lesser of the
10 IC_{50} for inhibiting PDE7A activity and/or the IC_{50} for inhibiting PDE7B activity.

 In one embodiment, the chemical compound has an IC_{50} for inhibiting PDE7A and/or PDE7B activity of less than about 100 nM. In another embodiment, the PDE7 inhibitory agent has an IC_{50} for inhibiting PDE1B activity of greater than 5 times the lesser of the IC_{50} for inhibiting PDE7A activity and the IC_{50} for inhibiting PDE7B activity. In another
15 embodiment, the PDE7 inhibitory agent has an IC_{50} for inhibiting PDE10 activity of greater than 5 times the lesser of the IC_{50} for inhibiting PDE7A activity and the IC_{50} for inhibiting PDE7B activity. In another embodiment, the PDE7 inhibitory agent has an IC_{50} for inhibiting PDE4 activity of greater than 10 times the lesser of the IC_{50} for inhibiting PDE7A activity and the IC_{50} for inhibiting PDE7B activity. In a further embodiment, the PDE7 inhibitory
20 agent has an IC_{50} for inhibiting PDE8 activity of greater than 10 times the lesser of the IC_{50} for inhibiting PDE7A activity and the IC_{50} for inhibiting PDE7B activity. In another embodiment, the PDE7 agent has an IC_{50} for inhibiting PDE1, PDE2, PDE3, PDE 4, PDE 8, PDE10, and PDE11 activity of greater than 10 times the lesser of the IC_{50} for inhibiting PDE7A activity and the IC_{50} for inhibiting PDE7B activity. In a further embodiment, the
25 PDE7 inhibitory agent is a selective PDE7 inhibitor for which the lesser of the IC_{50} for inhibiting PDE7A activity and the IC_{50} for inhibiting PDE7B activity is less than one tenth

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the IC_{50} that the agent has for inhibiting the activity of any other PDE enzyme from the PDE1-6 and PDE8-11 enzyme families. In another embodiment, the PDE7 inhibitory agent is a highly selective PDE7 inhibitor for which the lesser of the IC_{50} for inhibiting PDE7A activity and the IC_{50} for inhibiting PDE7B activity is less than one fiftieth the IC_{50} that the agent has for inhibiting the activity of any other PDE enzyme from the PDE1-6 and PDE8-11 enzyme families. In a further embodiment, the PDE7 inhibitory agent has a molecular weight of less than about 450 g/mole. In another embodiment, the PDE7 inhibitory agent is able to cross the blood/brain barrier.

In one aspect of the invention, the subject is addicted to an addictive agent. Examples of addictive agents include alcohol, nicotine, marijuana, a marijuana derivatives, opioid agonists, benzodiazepines, barbiturates, and psychostimulants. In one embodiment, the addictive agent is alcohol. In another embodiment, the addictive agent is nicotine. In a further embodiment, the addictive agent is an opioid, e.g., morphine, methadone, fentanyl, sufentanil and heroin. In a further embodiment, the addictive agent is a psychostimulant, e.g., cocaine, amphetamine or an amphetamine derivative. In another embodiment, the addictive agent is cocaine.

In one aspect of the invention, the subject treated with a PDE7 inhibitor is addicted to an addictive or compulsive behavior or suffers from an impulse-control disorder. In another aspect of the invention, the subject suffers from a primary impulse-control disorder, i.e., an impulse-control disorder in which the disorder is a primary disorder rather than a disorder that is either iatrogenic (secondary to medical treatment) or that is secondary to another primary disease or disorder. Addictive or compulsive behaviors that are primary impulse-control disorders include the following: binge eating, pathological gambling, pathological use of electronic devices, pathological use of electronic video games, pathological use of electronic communication devices, pathological use of cellular telephones, addiction to pornography, sex addiction, compulsive spending, anorexia, bulimia, intermittent explosive

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disorder, kleptomania, pyromania, trichotillomania, compulsive over-exercising, and compulsive overworking. In another embodiment, the subject suffers from food addiction. In another embodiment, the addictive or compulsive behavior is binge eating. In another aspect of the invention, the subject to be treated in accordance with the present invention has
5 an obsessive-compulsive disorder.

The present invention also provides a method of treating or preventing an addiction, comprising providing to a subject having an addiction, an inhibitor of a phosphodiesterase 7 (PDE7) and an additional therapeutic agent, wherein each of the PDE7 inhibitor and the additional therapeutic agent contribute to the effective treatment or prevention of the
10 addiction. Additional therapeutic agents include, e.g., opioid antagonists, mixed opioid partial agonist/antagonists, antidepressants, antiepileptics, antiemetics, corticotrophin-releasing factor-1 (CRF-1) receptor antagonists, selective serotonin-3 (5-HT3) antagonists, 5-HT2A/2C antagonists, cannabinoid-1 (CB1) receptor antagonists and dopamine receptor agonists or other dopaminergic agents.

15 Exemplary opioid antagonists include naltrexone and nalmefene. Exemplary antidepressants include fluoxetine, mirtazapine, and bupropion. Exemplary antiepileptics include topiramate, levetiracetam, and gabapentin. Antalarmin is an exemplary CRF-1 receptor antagonist. Ondansetron is an exemplary selective serotonin-3 (5-HT3) antagonist. Exemplary cannabinoid-1 (CB1) receptor antagonists are rimonabant and taranabant.
20 Buprenorphine is an exemplary mixed opioid agonist/antagonist. Exemplary opioid agonists include morphine, methadone, fentanyl, sufentanil and heroin.

Exemplary dopaminergic agents include, for example, levodopa (also referred to as "L-dopa"), carbidopa, and dopamine receptor agonists and precursors such as bromocriptine, pergolide, pramipexole, ropinirole, cabergoline, apomorphine, lisuride,
25 rotigotine and quinagolide, as well as fenoldopam, which is selective for dopamine receptor D1.

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In one aspect, the subject is addicted to an addictive agent, e.g., alcohol, nicotine, marijuana, a marijuana derivative, an opioid agonist, a benzodiazepine, a barbiturate, and a psychostimulant. In one embodiment, the addictive agent is alcohol and the additional therapeutic agent is an opioid antagonist, such as naltrexone, or a mixed opioid
5 antagonist/partial agonist, such as buprenorphine. In another embodiment, the subject is addicted to a psychostimulant such as cocaine, amphetamine, an amphetamine derivative, or methamphetamine and the additional therapeutic agent is an antidepressant, such as bupropion. In a further embodiment, the subject is addicted nicotine and the additional therapeutic agent is an antidepressant, such as bupropion.

10 In another aspect, the subject is addicted to an addictive or compulsive behavior, such as a primary impulse-control disorder, including, for example, pathological gambling, binge eating, pathological use of electronic devices, pathological use of electronic video games, pathological use of electronic communication devices, pathological use of cellular
15 telephones, addiction to pornography, sex addiction, compulsive spending, anorexia, bulimia, intermittent explosive disorder, kleptomania, pyromania, trichotillomania, compulsive over-exercising, and compulsive overworking. In one embodiment, the addictive or compulsive behavior is binge eating and the additional therapeutic agent is topiramate. In another aspect of the invention, the subject to be treated in accordance with the present invention has an obsessive-compulsive disorder.

20 The present invention provides a method of preventing relapse use of an addictive agent or practice of an addictive or compulsive behavior, by treating a subject who has undergone a period of abstinence from, or limited or reduced use of, the addictive agent or the addictive or compulsive behavior by administering a PDE7 inhibitor to the subject. The present invention also provides a method of preventing relapse of an addictive or compulsive
25 behavior associated with a primary impulse-control disorder, by treating a subject who has undergone a period of remission from, or limited or reduced practice of, the addictive or

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compulsive behavior associated with the primary impulse-control disorder by administering a PDE7 inhibitor to the subject. The present invention also provides a method of preventing relapse of addictive or compulsive behavior associated with an obsessive-compulsive disorder, by treating a subject who has undergone a period of remission from, or limited or reduced practice of, the addictive or compulsive behavior associated with the obsessive-compulsive disorder by administering a PDE7 inhibitor to the subject. Additional therapeutic agents that contribute to the effect prevention of relapse can be administered with the PDE7 inhibitor. This treatment can be administered to subjects that have previously been treated with a different anti-addiction treatment that is no longer being used.

10 In one aspect, the relapse use of addictive agents such as alcohol, nicotine, marijuana, marijuana derivatives, opioid agonists, benzodiazepines, barbiturates, and psychostimulants is prevented through the administration of PDE7 inhibitors. In a preferred embodiment, the relapse use of cocaine, amphetamine, or methamphetamine is prevented.

 In another aspect, the relapse of an addictive or compulsive behavior, in particular
15 addictive or compulsive behavior associated with a primary impulse-control disorders, is prevented through the administration of PDE7 inhibitors. In a preferred embodiment, the relapse of the following behaviors is prevented: binge eating, pathological gambling, pathological use of electronic devices, pathological use of electronic video games, pathological use of electronic communication devices, pathological use of cellular
20 telephones, addiction to pornography, sex addiction, compulsive spending, anorexia, bulimia, intermittent explosive disorder, kleptomania, pyromania, trichotillomania, compulsive over-exercising, and compulsive overworking. In one embodiment, the addictive or compulsive behavior is binge eating that has been induced by stress. In another embodiment, the subject is treated to prevent relapse of addictive or compulsive behavior associated with an
25 obsessive-compulsive disorder.

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The present invention provides a pharmaceutical composition that includes a PDE7 inhibitor and an additional therapeutic agent, where both the PDE7 inhibitor and the additional therapeutic agent contribute to the effective treatment or prevention of an addiction. Unit dosages of the pharmaceutical composition are also provided.

5 In one aspect of the invention, the subject is addicted to an addictive agent. Examples of addictive agents include alcohol, nicotine, marijuana, marijuana derivatives, opioid agonists, benzodiazepines, barbiturates, cocaine and other psychostimulants. In one embodiment, the addictive agent is alcohol. In another embodiment, the addictive agent is nicotine. In a further embodiment, the addictive agent is an opioid, e.g., morphine,
10 methadone, fentanyl, sufentanil and heroin. In a further embodiment, the addictive agent is a psychostimulant, e.g., cocaine, amphetamine or an amphetamine derivative. In a preferred embodiment, the addictive agent is cocaine.

In one aspect of the invention, the subject is addicted to an addictive or compulsive behavior or suffers from an impulse-control disorder. In another aspect of the invention, the
15 subject suffers from a primary impulse-control disorder, i.e., an impulse-control disorder in which the disorder is a primary disorder rather than a disorder that is either iatrogenic (secondary to medical treatment) or that is secondary to another primary disease or disorder. Addictive or compulsive behaviors that are primary impulse-control disorders include the following: binge eating, pathological gambling, pathological use of electronic devices,
20 pathological use of electronic video games, pathological use of electronic communication devices, pathological use of cellular telephones, addiction to pornography, sex addiction, compulsive spending, anorexia, bulimia, intermittent explosive disorder, kleptomania, pyromania, trichotillomania, compulsive over-exercising, and compulsive over-working. In a preferred embodiment, the addictive or compulsive behavior is binge eating. In another
25 aspect of the invention, the subject to be treated in accordance with the present invention has an obsessive-compulsive disorder.

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In one embodiment, the additional therapeutic agent of the pharmaceutical composition is an opioid antagonist, a mixed opioid partial agonist/antagonist, an antidepressant, an antiepileptic, an antiemetic, a corticotrophin-releasing factor-1 (CRF-1) receptor antagonist, a selective serotonin-3 (5-HT3) antagonist, a 5-HT2A/2C antagonist, or a
5 cannabinoid-1 (CB1) receptor antagonist.

Exemplary opioid antagonists include naltrexone or nalmefene. Exemplary antidepressants include fluoxetine, mirtazapine, or bupropion. Exemplary antiepileptics include topiramate, levetiracetam, and gabapentin. Antalarmin is an exemplary CRF-1 receptor antagonist. Ondansetron is an exemplary selective serotonin-3 (5-HT3) antagonist.
10 Exemplary cannabinoid-1 (CB1) receptor antagonists are rimonabant and taranabant. Buprenorphine is an exemplary mixed opioid agonist/antagonist.

In one aspect, the subject is addicted to an addictive agent, e.g., alcohol, nicotine, marijuana, a marijuana derivative, an opioid agonist, a benzodiazepine, a barbiturate, and a psychostimulant. In one embodiment, the addictive agent is alcohol and the additional
15 therapeutic agent is an opioid antagonist, such as naltrexone, or a mixed opioid antagonist/partial agonist, such as buprenorphine. In another embodiment, the addictive agent is nicotine and the additional therapeutic agent is varenicline. In another embodiment, the subject is addicted to a psychostimulant such as cocaine, amphetamine, an amphetamine derivative, or methamphetamine and the additional therapeutic agent is an antidepressant,
20 such as bupropion. In a further embodiment, the subject is addicted nicotine and the additional therapeutic agent is an antidepressant, such as bupropion. In another embodiment, the subject is addicted to more than one addictive agents and the additional therapeutic agent is an opioid antagonist, such as naltrexone, or a mixed opioid antagonist/partial agonist, such as buprenorphine.

25 The present invention provides a kit for the treatment or prevention of an addiction. The kit includes a first container containing a PDE7 inhibitor and a second container

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containing an additional therapeutic agent. Both the PDE7 inhibitor and the additional therapeutic agent contribute to the effective treatment or prevention of an addiction.

In one embodiment, the additional therapeutic agent of the pharmaceutical composition is an opioid antagonist, a mixed opioid partial agonist/antagonist, an antidepressant, an antiepileptic, an antiemetic, a corticotrophin-releasing factor-1 (CRF-1)
5 receptor antagonist, a selective serotonin-3 (5-HT3) antagonist, a 5-HT2A/2C antagonist, or a cannabinoid-1 (CB1) receptor antagonist.

Exemplary opioid antagonists include naltrexone and nalmeferone. Exemplary antidepressants include fluoxetine, mirtazapine, and bupropion. Exemplary antiepileptics
10 include topiramate, levetiracetam, and gabapentin. Antalarmin is an exemplary CRF-1 receptor antagonist. Ondansetron is an exemplary selective serotonin-3 (5-HT3) antagonist. Exemplary cannabinoid-1 (CB1) receptor antagonists are rimonabant and taranabant. Buprenorphine is an exemplary mixed opioid agonist/antagonist.

In one aspect, the subject is addicted to an addictive agent, e.g., alcohol, nicotine,
15 marijuana, a marijuana derivative, an opioid agonist, a benzodiazepine, a barbiturate, and a psychostimulant. In one embodiment, the addictive agent is alcohol and the additional therapeutic agent is an opioid antagonist, such as naltrexone, or a mixed opioid antagonist/partial agonist, such as buprenorphine. In another embodiment, the subject is addicted to a psychostimulant such as cocaine, amphetamine, an amphetamine derivative, or
20 methamphetamine and the additional therapeutic agent is an antidepressant, such as bupropion. In a further embodiment, the subject is addicted nicotine and the additional therapeutic agent is an antidepressant, such as bupropion. In another embodiment, the subject is addicted to more than one addictive agents and the additional therapeutic agent is an opioid antagonist, such as naltrexone, or a mixed opioid antagonist/partial agonist, such as
25 buprenorphine.

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In another aspect of the invention, a subject at risk of addiction to an addictive substance is administered the addictive substance in combination with a PDE7 inhibitor. For example, a subject that will be administered an opioid agonist for the relief of acute or chronic pain is administered an opioid agonist in combination with a PDE7 inhibitor such that

5 non-addictive or less addictive analgesia is provided. Examples of addictive agents that may be administered in combination with a PDE7 inhibitor, as either a fixed-dose combination or as a kit, include benzodiazepines, barbiturates, and pain medications including alfentanil, allylprodine, alphaprodine, anileridine benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide,

10 dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacylmorphan, lofenitanil, meperidine, meptazinol, metazocine,

15 methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, OXYCONTIN®, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propiram, propoxyphene sufentanil, tramadol, tilidine, salts

20 thereof, mixtures of any of the foregoing, and mixed μ -agonists/antagonists.

In some embodiments, for any of the methods and compositions described herein, the following PDE7 inhibitors are used formula 1A, formula 1B, formula 29, formula 30, formula 31, formula 32, formula 33, formula 34, formula 35, formula 36, formula 37, formula 38, formula 39, formula 40, formula 41, formula 42, formula 43A, formula 43B,

25 formula 44, formula 45, formula 46, formula 47, formula 48, formula 49, formula 50, formula 51, formula 52, formula 53, formula 54, formula 6A, formula 6B, formula 6C,

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formula 6D, formula 6E, formula 6F, formula 6G, formula 6H, formula 16A, compound 1, compound 2, compound 3, and compound 4.

In another embodiment of the invention, a PDE7 inhibitor is provided to a subject that is addicted or at risk of becoming addicted to an addictive substance to reduce the motivation
5 of the subject to seek or acquire the addictive substance.

IV. Brief Description of the Drawings

The present invention will now be described in greater detail, by way of example, with reference to the accompanying drawings in which:

10 FIGURE 1 demonstrates the effect of OMS182056, a PDE7 inhibitor, on cocaine self-administration by rats.

FIGURE 2 demonstrates the effect of OMS181869, a PDE7 inhibitor, on cocaine self-administration by rats.

15 FIGURE 3 demonstrates the effect of OMS182401, a PDE7 inhibitor, on cocaine self-administration by rats.

FIGURE 4 demonstrates the effect of SKF82958, a dopamine D1 agonist, on cocaine self-administration by rats.

FIGURE 5 demonstrates the effect of OMS182056, a PDE7 inhibitor, on non-reinforced lever-press response by rats.

20 FIGURE 6 demonstrates the effect of SKF82958, a dopamine D1 agonist, on non-reinforced lever-press response by rats.

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FIGURE 7 demonstrates the chronic effect of OMS182401, a PDE7 inhibitor, on cocaine self-administration in rats.

FIGURE 8 demonstrates the effect of OMS182056, a PDE7 inhibitor, on lever-press response by rats on the first day of extinction following cocaine addiction.

5 FIGURE 9 demonstrates the effect of OMS182056, a PDE7 inhibitor, on yohimbine-induced relapse to cocaine seeking by rats.

FIGURE 10 demonstrates the effect of OMS182401, a PDE7 inhibitor, on yohimbine-induced relapse to cocaine seeking by rats.

10 FIGURE 11 demonstrates the effect of OMS182056, a PDE7 inhibitor, on cue-induced relapse to cocaine seeking by rats.

FIGURE 12 demonstrates the effect of OMS182401, a PDE7 inhibitor, on cue-induced relapse to cocaine seeking by rats.

FIGURE 13 demonstrates the effect of OMS182056, a PDE7 inhibitor, on cocaine priming-induced relapse by rats.

15 FIGURE 14 demonstrates the effect of SKF82958, a dopamine D1 agonist, on cocaine priming-induced relapse by rats.

FIGURE 15 demonstrates the effect of OMS182401, a PDE7 inhibitor, on nicotine self-administration in rats using a short access model.

20 FIGURE 16 demonstrates the effect of OMS182401, a PDE7 inhibitor, on nicotine self-administration in rats using a long access model.

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FIGURE 17 demonstrates the effect of OMS182399, a PDE7 inhibitor, on nicotine self-administration in rats using a short access model.

FIGURES 18A and 18B demonstrate that the PDE7 inhibitors OMS182399 and OMS182401, respectively, do not have an effect on food self-administration.

5 FIGURES 19A-19C demonstrate the effect of OMS182401, a PDE7 inhibitor, on motivation of nicotine-addicted mice to acquire nicotine in a self-administration progressive ratio study.

FIGURE 20 demonstrates the effect of OMS182401, a PDE7 inhibitor, on the first day of extinction of nicotine self-administration.

10 FIGURE 21 demonstrates the effect of OMS182401, a PDE7 inhibitor, on cue-induced reinstatement of nicotine seeking behavior.

FIGURE 22 demonstrates the effect of OMS182401, a PDE7 inhibitor, on yohimbine-induced reinstatement of nicotine seeking behavior.

15 FIGURES 23A-23D demonstrates the effect of OMS182401, a PDE7 inhibitor, on stress induce binge eating by rats. FIGURE 23A shows the results for control animals, which were not stressed or subjected to dietary restriction. FIGURE 23B shows the results for experimental animals that were not stressed and were subjected to dietary restriction. FIGURE 23C shows the results for experimental animals that were stressed and were not subjected to dietary restriction. FIGURE 23D shows the results for experimental animals that
20 were stressed and were subjected to dietary restriction.

FIGURES 24A-24D demonstrates the effect of OMS182056, a PDE7 inhibitor, on stress induce binge eating by rats. FIGURE 24A shows the results for control animals, which were not stressed or subjected to dietary restriction. FIGURE 24B shows the results for

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experimental animals that were not stressed and were subjected to dietary restriction. FIGURE 24C shows the results for experimental animals that were stressed and were not subjected to dietary restriction. FIGURE 24D shows the results for experimental animals that were stressed and were subjected to dietary restriction.

5 FIGURES 25A-25D demonstrates the effect of topiramate, as a comparator, on stress induce binge eating by rats. FIGURE 25A shows the results for control animals, which were not stressed or subjected to dietary restriction. FIGURE 25B shows the results for experimental animals that were not stressed and were subjected to dietary restriction. FIGURE 25C shows the results for experimental animals that were stressed and were not
10 subjected to dietary restriction. FIGURE 25D shows the results for experimental animals that were stressed and were subjected to dietary restriction.

FIGURE 26 demonstrates the effect of the PDE7 inhibitor OMS182399 on yohimbine-induced relapse to food seeking in a food addiction model.

FIGURE 27 and 28 demonstrates the effect of OMS182399, a PDE7 inhibitor, on
15 basal and nicotine-induced, respectively, dopamine release in the nucleus and accumbens of Wistar rats by an *in vivo* microdialysis study.

FIGURES 29A-29B demonstrate that OMS182401, a PDE7 inhibitor, inhibits spontaneous activity of dopaminergic ventral tegmental area (VTA) neurons, and potentiates the inhibitory effect of SKF82958, a dopamine D1 agonist.

20 FIGURE 30 demonstrates the effect of the PDE7 inhibitor OMS182401 on VTA GABA release.

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FIGURE 31 demonstrates that the PDE7 inhibitor OMS182401 inhibits the activation of dopaminergic VTA neurons by nicotine and acts synergistically with the dopamine D1 agonist SKF82958.

FIGURE 32 demonstrates the effect of direct administration of the PDE7 inhibitor
5 OMS182401 into rat VTA.

FIGURE 33 demonstrates that the PDE7 inhibitor OMS182399 dose-dependently blocks morphine-induced excitation of VTA dopamine cells.

FIGURE 34 demonstrates that acute application of the PDE7 inhibitor OMS182399 dose-dependently blocks ethanol-induced excitation of VTA dopamine cells.

10 FIGURE 35 demonstrates that acute application of the PDE7 inhibitor OMS182399 dose-dependently reverts cocaine-induced excitation of VTA dopamine cells.

FIGURE 36 demonstrates that the PDE7 inhibitor OMS182401 potentiates the activity of the dopamine D1 agonist SKF82958 in an open field activity model.

15 V. Detailed Description of the Preferred Embodiment

The present invention is based upon the surprising discovery by the present inventors that selective inhibitors of the type 7 cyclic nucleotide phosphodiesterase (PDE7) cause a striking decrease in relapse of addiction. Using rat models, the decreases were demonstrated in subjects addicted to addictive agents and in subjects that exhibited
20 compulsive behaviors.

A. Methods of Treating and Preventing Addictions Using PDE7 Inhibitor(s)

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Thus, the present invention includes methods of treating or preventing an addiction, comprising administering one or more PDE7 inhibitors to a subject having an addiction or at risk for developing an addiction. In various embodiments, the subject is addicted to an addictive agent or behavior, including, but not limited to, any of the
5 addictive agents and behaviors described herein. The subject may be physically or physiologically dependent on the substance or behavior; the subject may be psychologically dependent; or the subject may be both physically and psychologically dependent. The subject may be addicted to one or more than one addictive agent or behavior.

10 As used herein, unless the context makes clear otherwise, "treat," and similar word such as "treatment," "treating" etc., is an approach for obtaining beneficial or desired results, including and preferably clinical results. Treatment can involve optionally either the reducing or amelioration of a disease or condition, (e.g., addiction or relapse use or behavior), or the delaying of the progression of the disease or condition
15 (e.g., addiction, or relapse use or behavior).

As used herein, unless the context makes clear otherwise, "prevent," and similar word such as "prevention," "preventing" etc., is an approach for preventing the onset or recurrence of a disease or condition, (e.g., addiction, or relapse use or behavior) or preventing the occurrence or recurrence of the symptoms of a disease or condition, or
20 optionally an approach for delaying the onset or recurrence of a disease or condition or delaying the occurrence or recurrence of the symptoms of a disease or condition.

As used herein the term "PDE7" is used generically to refer to all translation products coded by transcripts of either or both of these two genes: PDE7A and/or PDE7B.

25 As used herein, the term "PDE7 inhibitory agent" or "inhibitor of PDE7" refers to an agent, such as a chemical compound, a peptide, or a nucleic acid molecule, that

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directly or indirectly inhibits or blocks the phosphodiesterase activity of PDE7A, PDE7B, or PDE7A and PDE7B. In some cases, the agent may bind or interact directly with PDE7 protein. An agent that binds to PDE7 may act to inhibit or block the PDE7 activation by any suitable means, such as by inhibiting the binding of cAMP or substrate ligand with
5 PDE7. In other cases, the PDE7 inhibitory agent may inhibit PDE7 activity indirectly, such as by decreasing expression of the PDE7 protein. In some cases, the PDE7 inhibitory agent may inhibit PDE7 activity by altering the cellular distribution of PDE7, for example, by interfering with the association between PDE7 and an intracellular anchoring protein.

10 As used herein, the term "dopaminergic agent" refers to an agent that functions to enhance or replicate the effects mediated by dopamine in the central nervous system, including dopamine (if a clinically effective method of delivery should be developed), dopamine precursors, such as levodopa (L-dopa), dopamine cofactors, inhibitors of enzymes that metabolize dopamine, other dopamine receptor agonists and precursor
15 compounds that are metabolically converted to a dopamine receptor agonist, as well as dopamine reuptake inhibitors and facilitators of dopamine release.

As used herein, the term "dopamine receptor agonist" refers to any molecule that causes the activation of one or more of the subtypes of the dopamine receptor protein family.

20 As used herein, the term "mammalian subject" includes all mammals, including without limitation humans, non-human primates, dogs, cats, horses, sheep, goats, cows, rabbits, pigs, and rodents.

Generally, a subject is provided with an effective amount of a PDE7 inhibitor. As used herein, an "effective amount" or a "therapeutically effective amount" of a substance,
25 e.g., a PDE7 inhibitor, is that amount sufficient to affect a desired biological or psychological effect, such as beneficial results, including clinical results. For example, in

the context of treating addiction using the methods of the present invention, an effective amount of a PDE7 inhibitor is that amount sufficient to cause the subject to reduce or discontinue use of an addictive agent. In the case of an addictive behavior, an effective amount of a PDE7 inhibitor is that amount sufficient to cause the subject to reduce or
5 discontinue the addictive behavior.

In one embodiment, a therapeutically effective dose is an amount of PDE7 inhibitory agent sufficient to inhibit PDE7 enzyme activity in a neuronal cell. In another embodiment of the methods of the invention, a therapeutically effective dose is an amount of PDE7 inhibitory agent sufficient to inhibit PDE7 enzyme activity in striatal
10 neurons or nucleus acumbens. The determination of an effective dose of a PDE7 inhibitory agent sufficient to cross a cellular membrane and inhibit PDE7 enzyme activity within a cell may be determined using a cellular assay for PDE7 inhibition, such as described by Smith S.J. et al., *Molecular Pharmacology* 66(6): 1679-1689 (2004).

The determination of an effective dose of a PDE7 inhibitory
15 agent sufficient to inhibit PDE7 enzyme activity in the striatum may be determined using an assay for measuring the effect of a PDE inhibitory agent on cAMP levels in the striatum, as described in Siuciak J.A. et al., *Neuropharmacology* 51: 386-396 (2006).

According to certain embodiments of the present invention, a subject is provided
20 with a PDE7 inhibitor alone, while in other embodiments, a subject is provided with a PDE7 inhibitor in combination with an additional therapeutic agent. It is understood that the effective amount of either or both of a PDE7 inhibitor and an additional therapeutic agent may be different when either is provided alone than when provided in combination. For example, when the PDE7 inhibitor and the additional therapeutic agent act
25 synergistically, then a lower amount of the PDE7 inhibitor, a lower amount of the additional therapeutic agent, or lower amounts of both the PDE7 inhibitor or the

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additional therapeutic agent may be required to achieve the same therapeutic effect that would be provided by either the PDE7 inhibitor or the additional therapeutic agent alone. In other embodiments, the same amount of the PDE7 inhibitor and the additional therapeutic agent are used to provide an enhanced therapeutic effect relative to the therapeutic effect provided by either the PDE7 inhibitor or the additional therapeutic agent alone.

According to certain embodiments of the present invention, a subject is provided with a PDE7 inhibitor in combination with an addictive therapeutic agent, with the dosage of the addictive therapeutic agent being determined to achieve the desired therapeutic effect and the dosage of the PDE7 inhibitor being determined to eliminate or reduce the potential for addiction to the addictive therapeutic agent.

The subject may be any animal, including a mammal, and, particularly, a human.

In one aspect of the invention, the subject is first determined or diagnosed to have an addiction, or to be at risk of developing an addiction, by diagnostic testing, observation or analysis by a medical care provider. An effective amount of a PDE7 inhibitor, or an effective amount of a PDE7 inhibitor and one additional therapeutic agent, are then provided to the subject for treatment or prevention of the addiction. In another aspect of the invention, the subject is first determined or diagnosed to have an addiction, or to be at risk of developing an addiction, by diagnostic testing, observation or analysis by a medical care provider, but the subject has not been diagnosed or determined to have diabetes or other insulin disorder. An effective amount of a PDE7 inhibitor, or an effective amount of a PDE7 inhibitor and one additional therapeutic agent, are then provided to the subject for treatment or prevention of the addiction. The dosage of the PDE7 inhibitor, or the PDE7 inhibitor and the one additional therapeutic agent, may be specifically determined by the medical practitioner for treatment or prevention of the addiction rather than for any other disorder or disease.

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In particular embodiments, the subject is suffering from or at risk for addiction to any physically addictive agent or addictive or compulsive behavior, including, e.g., any of those described below. In particular embodiments, the subject is addicted to alcohol, cocaine, nicotine, marijuana, an opiate or other opioid agonist or methamphetamine or
5 other psychostimulant, or phencyclidine and phencyclidine derivatives. In another embodiment, the subject suffers from a primary impulse-control disorder. In still another embodiment, the subject suffers from obsessive-compulsive disorder. In still another embodiment, the subject has a history of repeated dieting and is at risk of binge eating.

In particular embodiments, a subject is considered at risk of addiction or relapse to
10 use of an addictive agent or practice of an addictive behavior when the subject has previously been addicted to the same or a different addictive agent or addictive or compulsive behavior. In certain embodiment, the subject is considered at risk of addiction or relapse to use of an addictive agent or practice of an addictive behavior when the subject is psychologically addicted to an addictive agent or addictive or compulsive
15 behavior, even if the subject is no longer physically addicted. In one embodiment, the subject suffers from food addiction. In other embodiments, the addictive behavior is binge eating. Subjects at risk of binge eating typically have at least one of the following in their history: recurring food restrictions or yo-yo dieting, eating in response to environmental stress, preference for highly palatable and high caloric food, eating after
20 reaching fullness, and eating to the point of discomfort. In another embodiment, the subject suffers from a primary impulse-control disorder.

In certain embodiments, the subject is addicted to or at risk of becoming addicted to a therapeutic agent provided to the patient to treat a disease or disorder, e.g., a pain medication. In a related embodiment, the subject may be at risk of abusing an addictive
25 therapeutic agent, such as a pain medication. Abusing an addictive therapeutic agent, in certain embodiments, is understood to indicate using the agent for a reason different than

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or in addition to its prescribed use. In such a situation, a subject may be provided with both an addictive therapeutic agent and a PDE7 inhibitor, alone or in combination with an additional therapeutic agent. For example, a subject suffering from pain, or at risk of pain, may be provided with an opioid agonist and a PDE7 inhibitor, to both provide
5 analgesia and prevent or treat addiction to the opioid agonist.

In various embodiments, the subject is provided with the PDE7 inhibitor at the same time that the subject is using an addictive agent, after the subject has discontinued use of an addictive agent, or before the subject begins using an addictive agent.

Addictive Agents and Impulse Control Disorders

10 The term “addiction” is used to describe a recurring compulsion by an individual to engage in some specific activity, despite harmful consequences to the individual's health, mental state or social life. The term is often reserved for drug addictions, but it is applied to other compulsions, such as problem gambling, and binge eating. Factors that have been suggested as causes of addiction include genetic, biological/pharmacological
15 and social factors.

The medical community now makes a careful theoretical distinction between physical or physiological dependence (characterized by symptoms of withdrawal) and psychological dependence (sometimes referred to simply as addiction). Addiction is now narrowly defined as “uncontrolled, compulsive use.” If there is no harm being suffered
20 by, or damage done to, the patient or another party, then clinically it may be considered compulsive, but to the definition of some it is not categorized as “addiction”. In practice, the two kinds of addiction (physiological dependence and psychological dependence) are not always easy to distinguish. Addictions often have both physical and psychological components.

25 “Physical dependence” (or “drug dependence”) refers to a state resulting from habitual use of a drug, where negative physical withdrawal symptoms result from abrupt

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discontinuation. Examples of addictive agents for which a user may develop a physical dependence include nicotine, opioids, barbiturates, benzodiazepines, alcohol, i.e., ethyl alcohol, GHB, and methaqualone.

Commonly abused stimulants such as cocaine or amphetamine class drugs are not
5 believed to cause significant physical dependence. However, their potential for extreme psychological addiction can compel the user to consume amounts which become physically damaging, but life-threatening withdrawal effects have not been observed.

As used herein, “addictive agent(s)” includes any and all agents to which a subject can become addicted, either physically or psychologically, or both. As noted above,
10 addiction includes addiction to chemical entities, such as drugs, as well as addiction to behaviors, as in impulse control disorders.

Addictive agents include addictive recreational drugs, as well as addictive medications. Examples of addictive agents include, but are not limited to, alcohol, e.g., ethyl alcohol, gamma hydroxybutyrate (GHB), caffeine, nicotine, cannabis (marijuana)
15 and cannabis derivatives, opiates and other morphine-like opioid agonists such as heroin, phencyclidine and phencyclidine-like compounds, sedative hypnotics such as benzodiazepines, methaqualone, mecloqualone, etaqualone and barbiturates and psychostimulants such as cocaine, amphetamines and amphetamine-related drugs such as dextroamphetamine and methylamphetamine. Other examples include LSD, psilocybin,
20 ecstasy and other hallucinogens. Examples of addictive medications include, e.g., benzodiazepines, barbiturates, and pain medications including alfentanil, allylprodine, alphaprodine, anileridine benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol,
25 dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydrocodone,

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hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacymorphan, lofenitanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, 5 oxycodone, OXYCONTIN®, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propiram, propoxyphene sufentanil, tramadol, tilidine, salts thereof, mixtures of any of the foregoing, mixed μ -agonists/antagonists, and the like.

In certain embodiments, a subject may be addicted to an opioid agonist. The 10 terms “opioid agonist,” “opioid” and “opiate” are used interchangeably herein and are used to designate a group of drugs that are, to varying degrees, opium- or morphine-like in their properties. Their main use is for pain relief. These agents work by binding to opioid receptors, which are found principally in the central nervous system and the gastrointestinal tract. Opiates are also addictive agents. Opiates include alfentanil, 15 allylprodine, alphaprodine, anileridine, apomorphine, benzylmorphine, beta-hydroxy 3-methylfentanyl, bezitramide, carfentanil, clonitazene, codeine, desomorphine, dextromoramide, diacetylmorphine (heroin), diampromide, dihydrocodeine, dihydroetorphine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetylbutyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, 20 ethylmorphine, etonitazene, etorphine, fentanyl, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, LMM, levorphanol, levophenacymorphan, lofentanil, meperidine, metapon, metazocine, methadone, methadyl acetate, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, normorphine, norpipanone, opium, oxycodone, 25 oxymorphone, papaverine, phenadoxone, phenomorphan, phenoperidine, piminodine,

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piritramide, propheptazine, promedol, properidine, propoxyphene, remifentanil, sufentanil, thebaine, tildine, and tramadol.

Naturally occurring opiates include codeine, morphine, noscapine, papaverine, and thebaine. Semi-synthetic opioids include diacetylmorphine, hydrocodone, hydromorphone, levorphanol, metapon, nalorphine, naloxone, naltrexone, oxycodone, oxymorphone, and tramadol. Synthetic opioids include ethoheptazine, fentanyl, levorphanol, meperidine, methadone, phenazocine, propoxyphene and sufentanil.

Three broad classifications of opiates are phenanthrenes, phenylheptylamines, and phenylpiperidines. Examples of phenanthrenes include codeine, etorpine, hydrocodone, hydromorphone, morphine, oxycodone, and oxymorphone. Examples of phenylheptylamines include dimeheptanol, dimenoxadol, dipipanone, isomethadone, methadone, methadyl acetate, and propoxyphene. Examples of phenylpiperidines include alfentanil, alphaprodine, beta-promedol, carfentanyl, fentanyl, lofentanil, meperidine, properidine, and sufentanil.

Specific psychostimulants include, by way of example, amphetamine, cocaine, dextroamphetamine, methamphetamine, pemoline, Ritalin, Adderall and methylenedioxymethamphetamine.

As noted above, addiction includes addiction to behaviors, e.g., food addiction, binge eating disorder, pathological gambling, pathological use of electronic devices, e.g., BlackBerry®, pathological use of electronic video games, pathological use of electronic communication devices, pathological use of cellular telephones, addiction to pornography, sex addiction, obsessive-compulsive disorder, compulsive spending, intermittent explosive disorder, kleptomania, pyromania, trichotillomania, compulsive over-exercising, and compulsive overworking.

In one aspect of the invention, a subject treated with a PDE7 inhibitor suffers from food addiction or binge eating disorder, often with secondary health problems such

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as obesity due to excessive consumption of food and/or malnutrition due to excessive consumption of foods that are high in fat and/or sugar and low in vitamins and minerals.

As used herein “binge eating disorder” or “binge eating” includes at least one of the following episodic symptoms: eating large amounts of food, eating even when full, rapid eating, feeling that eating behavior is out of control, eating substantial amounts of food when not hungry, frequent dieting possibly without weight loss, eating alone, feeling depressed or disgusted about eating habits, eating in response to stress. Binge eating disorder is distinguished from other types of eating disorders, including food addiction, bulimia and binge-purge syndromes. Unlike bulimia and binge-purge syndromes, a subject suffering from binge eating disorder and food addiction-like behavior is that subjects suffering from binge eating disorder and food addiction-like behavior do not undertake compensatory behavior to attenuate excessive caloric consumption.

A body of scientific literature is building to support the characterization of certain types of problematic eating behaviors as addictions, given that binge eating and chronic excess eating share many characteristics with addictive behaviors (e.g., diminished control, continued use despite negative consequences). Despite similarities, binge eating disorder and food addiction may represent unique yet overlapping conditions. Gearhardt, A. N., et al., *Binge Eating Disorder and Food Addiction*, Curr. Drug Abuse Rev, 4:201-207 (2011).

As used herein, the term “food addiction” refers to a regular, persistent and habitual pattern of overeating characterized by craving and seeking high caloric foods, overeating in response to stimuli other than hunger, diminished control over food consumption, continued consumption despite negative consequences and diminished ability to cut down and abstain from consumption of an excess of food. Food addiction is a chronic relapsing disorder that typically follows a course of over-eating, tolerance,

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withdrawal, high caloric food seeking behavior and relapse (initiation of overeating after a period of abstinence).

A natural preference for highly palatable foods rich in fat and carbohydrate has developed for evolutionary reasons due to the high caloric support associated with such foods. Although it is indisputable that feeding behavior is regulated by homeostatic mechanisms, eating and overeating are also regulated by emotional, affective and learning processes. Polivy, et al., "Food restriction and binge eating: a study of a former prisoner of war," *J Abnorm Psychol* **103**:409-411 (1994). In this respect several commonalities exist between excessive eating and drug abuse (reward, reinforcement, effects on mood, external cue-control of appetite, stress-induced motivation). Evidence is accumulating that excessive intake of certain foods under specific conditions produces behaviors and changes in the brain that resemble an addiction-like state. Gold, et al., "Overeating, binge eating, and eating disorders as addictions," *Psychiatr Ann* **33**:112-116 (2003); Kenny, et al., "Common cellular and molecular mechanisms in obesity and drug addiction," *Nat Rev Neurosci* **12**:638-651 (2011); Pelchat, et al., "Images of desire: food-craving activation during fMRI," *Neuroimage* **23**:1486-1493 (2004); Avena, et al., "Evidence for sugar addiction: behavioral and neurochemical effects of intermittent, excessive sugar intake," *Neurosci Biobehav Rev* **32**:20-39 (2008); Ifland, et al., "Refined food addiction: a classic substance use disorder," *Med Hypotheses* **72**:518-526 (2009); Gearhardt, et al., "Food addiction: an examination of the diagnostic criteria for dependence," *J Addict Med* **3**:1-7 (2011).

Drug addiction can be characterized by progressive escalation in drug use, tolerance development, abstinence following abrupt cessation of their use and recurrent relapse, and similar phenomena have been described for high sucrose high fat food. For example, rats fed with highly palatable sucrose solution experience opiate-like withdrawal symptoms following sucrose removal. Cross sensitization between sucrose

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and drugs of abuse has also been described. Avena, et al., “Evidence for sugar addiction: behavioral and neurochemical effects of intermittent, excessive sugar intake,” *Neurosci Biobehav Rev* **32**:20–39 (2008); Avena, et al., “Dysregulation of brain reward systems in eating disorders: Neurochemical information from animal models of binge eating, bulimia nervosa, and anorexia nervosa,” *Neuropharmacology* (Epub ahead of print) (Nov. 27, 2011). Moreover, it has been well documented that psychological stress and dysphoric mood states play a major role in facilitating overeating as well as excessive drug use, and contribute to the high rate of recidivism typical of both disorders. Corwin, et al., “Feeling and reward: perspective from three rat models of binge eating,” *Physiol Behav* **104**:87-97 (2011); Ghitza, et al., “The anxiogenic drug yohimbine reinstates palatable food seeking in a rat relapse model: a role of CRF1 receptors,” *Neuropsychopharmacology* **31(10)**:2188-2196 (2006); Mizes, et al., “Bulimia: A review of its symptomatology and treatment,” *Adv. Behav. Res. Ther.* **7**:91–142 (1985); Crowther, et al., “The role of daily hassles in binge eating,” *Int J Eat Disord* **29**:449–454 (2001); Herman, et al., “Anxiety, restraint, and eating behaviour,” *J Abnorm Psychol* **84**:66–72 (1975).

Exposure to environmental conditioning stimuli has also been shown to play a critical role in eliciting drug craving in addicted individuals as well as food craving in obese patients meeting the criteria for food addiction. Gearhardt, et al., “Food addiction: an examination of the diagnostic criteria for dependence,” *J Addict Med* **3**:1-7 (2011). Consistent with studies in humans, in laboratory animals it has been shown that exposure to environmental conditioning factors and exposure to stress (i.e., yohimbine) are similarly effective in eliciting reinstatement behaviors for drugs of abuse and for highly palatable food. Cifani, et al., “Preclinical model of binge-eating elicited by yo-yo dieting and stressful exposure to food: effect of sibutramine, fluoxetine, topiramate and midazolam,” *Psychopharmacology* **204**:113–25 (2009); Cifani, et al., “Pre-exposure to

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environmental cues predictive of food availability elicits hypothalamic-pituitary-adrenal axis activation and increases operant responding for food in female rats,” *Addict Biol.* **14(4)**:397-407 (Sept. 2009); Pickens, et al., “Effect of fenfluramine on reinstatement of food seeking in female and male rats: implications for the predictive validity of the reinstatement model,” *Psychopharmacology (Berl)* **221(2)**:341-353 (May 2012). Neural systems that motivate and reinforce drug abuse have also been proposed to underlie behaviors associated with compulsive food seeking and excessive food intake. Johnson, et al., “Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats,” *Nat Neurosci* **13**:635-641 (2010); Hoebel, et al., “Brain neurotransmitters in food and drug reward,” *Am J Clin Nutr* **42(5 Suppl)**:1133–1150 (1985); Volkow, et al., “How can drug addiction help us understand obesity?” *Nat Neurosci* **8**:555–560 (2005); Corwin, et al., “Feeling and reward: perspective from three rat models of binge eating,” *Physiol Behav* **104**:87-97 (2011); Gearhardt, et al., “Neural correlates of food addiction,” *Arch Gen Psychiatry* **68**:808-816 (2011); Wang, et al., “Enhanced striatal dopamine release during food stimulation during binge eating disorder,” *Obesity* **19(8)**:1601-1608 (Aug. 2011). For example, studies suggest that like in drug addicts, an altered regulation of striatal dopamine (DA) may exist in patients with bulimia nervosa.

Interest in the concept of food addiction has recently received greater attention, in large part due to the similarities between the behavioral indicators of addiction and binge eating disorder (BED). Episodes of binge eating in humans are characterized by compulsive, non-homeostatic consumption of an unusually large quantity of highly palatable food in a short period of time. Even though they are not hungry, subjects eat more rapidly than normal until feeling uncomfortably full. As described by the DMS-IV-TR (American Psychiatric Association, “Diagnostic and statistic manual of mental disorders,” Washington, DC. (2000)), these episodes are accompanied by a subjective

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sense of loss of control over eating, and are associated with feeling of distress, disgust, depression, being guilty about overeating, and eating alone because of embarrassment.

BED, described for the first time by Stunkard, "Eating patterns and obesity," *Psychiatry Q* **33**:284-295 (1959), is probably the most prevalent eating disorder. Hudson, et al., "The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication," *Biol Psychiatry* **61**:348-58 (2007). It is characterized by repeated episodes of binge eating in the absence of compensatory behaviors to avoid weight gain. The diagnostic criteria for BED in the DSM-IV-TR include that binge eating episodes should occur at least 2 days per week for six months. BED is associated with significant medical and psychiatric co-morbidity. Javaras, et al., "Co-occurrence of binge eating disorder with psychiatric and medical disorders," *J Clin Psychiatry* **269**:266-273 (2008); Grucza, et al., "Prevalence and correlates of binge eating disorder in a community sample," *Compr Psychiatry* **48**:124-131 (2007). It is estimated that binge eating afflicts approximately 5% of the US adult population at some time during their lives (Foulds, et al., "The biology of binge eating," *Appetite* **52**:545-553 (2009)) and that it contributes to aggravate obesity and associated pathologies. Hudson, et al., "The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication," *Biol Psychiatry* **61**:348-58 (2007); Yanovski, "Binge eating disorder and obesity in 2003: could treating an eating disorder have a positive effect on the obesity epidemic?" *Int J Eat Disord* **34 Suppl**:S117-S1120 (2003).

A large body of evidence suggests that dieting, stress and negative affective states represent important triggers of binge eating in patients suffering from BED or bulimia nervosa. Wardle, et al., "Stress, dietary restraint and food intake," *J Psychosom Res* **48**:195-202 (2000); Freeman, et al., "Daily stress, coping, and dietary restraint in binge eating," *Int J Eat Disord* **36**: 204-212 (2004). Indeed, dieting periods are common in the histories of binge eaters, although hunger itself does not appear to be enough to induce

bing eating in the absence of stress and negative affective state. Polivy, et al., "Food restriction and binge eating: a study of former prisoner of war," *J Abnorm Psychol* **103**:409-411(1994); Waters, et al., "Internal and external antecedents of binge eating episodes in a group of women with bulimia nervosa," *Int J Eat Disord* **29**:17-22 (2001).

5 Considerable evidence suggests that binge eating may be caused by a unique interaction between dieting and stress; thus, environmental stress and a history of cyclic food restrictions may be responsible for its precipitation and maintenance. Stice, et al. "Subtyping binge eating-disordered women along dieting and negative affect dimensions," *Int J Eat Disord* **30**:11-27 (2001); Crowther, et al., "The role of daily

10 hassles in binge eating," *Int J Eat Disord* **29**:449-454 (2001). Accordingly, recurring food restrictions are consistently the strongest predictor of overeating in response to stress. Wardle, et al., "Stress, dietary restraint and food intake," *J Psychosom Res* **48**:195-202 (2000).

While a subject may be addicted to a single addictive agent or behavior,

15 frequently subject is addicted to two or more addictive agents or behaviors. Addiction to two or more addictive agents or addictive behaviors is referred to as polyaddiction.

B. Methods of Treating and Preventing Addiction and Impulse Control Disorders Using PDE7 Inhibitor(s) in Combination with Other Therapeutic Agents

PDE7 inhibitors may be effectively used in combination with one or more

20 additional therapeutic agents to treat or prevent addiction, including addiction to one or more of the addictive agents described herein and compulsive or addictive behavior. Accordingly, the present invention includes methods of treating or preventing an addiction, comprising administering to a subject addicted to an addictive agent one or more PDE7 inhibitor(s) and one or more additional therapeutic agent(s), in which each of

25 the PDE7 inhibitor(s) and the additional therapeutic agent(s) contribute to the effective treatment or prevention of the addiction. In one embodiment, a subject is provided with

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or administered one PDE7 inhibitor and one additional therapeutic agent. In another embodiment, a subject is addicted to two or more addictive agents.

The PDE7 inhibitor and the additional therapeutic agent may be administered at the same time (i.e., concurrently), or either may be administered before the other (i.e., sequentially). In general, both the PDE7 inhibitor and the additional therapeutic agent are present in the subject at the same time for a duration of time and at levels sufficient to provide a therapeutic benefit to the subject, i.e., in the treatment or preventing of an addiction or the prevention of a relapse use (or reinstatement) of an addictive agent or compulsive or addictive behavior. The PDE7 inhibitor and the additional therapeutic agent may be administered by the same or different routes of administration. Typically, the PDE7 inhibitor and the additional therapeutic agent are each provided to a subject according to a standard route of administration of a commercially available or other pharmaceutical composition. In one embodiment, the PDE7 inhibitor and the additional therapeutic agent are co-administered using a composition comprising both agents.

The additional therapeutic agent provided in combination with a PDE7 inhibitor may be any therapeutic agent that contributes to an aspect of the effective treatment or prevention of the addiction. For example, the additional therapeutic agent may be a drug used to treat an addiction or a drug used to alleviate side-effects associated with physiological withdrawal from an addictive agent. In addition, the additional therapeutic agent may be any drug that affects brain serotonin neurotransmission, such as selective serotonin reuptake inhibitors (SSRIs), and tricyclic and tetracyclic serotonin and norepinephrine reuptake inhibitors (SNRIs) as described below, and serotonin agonists such as sumatriptan, ergonovine, dihydroergotamine and buspirone. In certain embodiments, the additional therapeutic agent is an opioid antagonist, including mixed opioid partial agonist/antagonists, an antidepressant, an antiepileptic, an antiemetic, a dopaminergic agent such as a dopamine D1 receptor agonist, a corticotrophin-releasing

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factor-1 (CRF-1) receptor antagonist, a selective serotonin-3 (5-HT3) antagonist, a 5-HT2A/2C antagonist such as mianserin, mirtazapine and ketanserin, or a cannabinoid-1 (CB1) receptor antagonist, including but not limited to those therapeutic agents specifically described herein.

5 In one embodiment, the addictive agent is alcohol and the additional therapeutic agent is an opioid antagonist or a mixed opioid antagonist/partial agonist. In a particular embodiment, the opioid antagonist is naltrexone. In another embodiment, the mixed opioid partial agonist/antagonist is buprenorphine.

10 In one embodiment, the addictive agent is alcohol, and the additional therapeutic agent is topiramate or levetiracetam.

 In one embodiment, the addictive agent is nicotine and the additional therapeutic agent is an antidepressant. In a particular embodiment, the antidepressant is bupropion.

 In one embodiment, the addictive agent is cocaine, and the additional therapeutic agent is buprenorphine.

15 In one embodiment, the addictive agent is a psychostimulant and the additional therapeutic agent is an antidepressant. In a particular embodiment, the antidepressant is bupropion.

 In one embodiment, the addictive behavior is binge eating and the additional therapeutic agent is an antidepressant or an antiepileptic. In one particular embodiment, 20 the antidepressant is sibutramine. In another particular embodiment, the antidepressant is fluoxetine. In one particular embodiment, the antiepileptic is topiramate.

 In one embodiment, the addictive agent is nicotine, and the additional therapeutic agent is an anti-epileptic. In a particular embodiment, the anti-epileptic is levetiracetam. In another particular embodiment, the anti-epileptic agent is naltrexone.

25 In one embodiment, the subject is addicted to two or more addictive agents and the additional therapeutic agent is an opioid antagonist or a mixed opioid partial

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agonist/antagonist. In a particular embodiment, the mixed opioid partial agonist/antagonist is buprenorphine.

In one embodiment, the subject is addicted to both alcohol and nicotine, and the additional therapeutic agent is an anti-epileptic. In a particular embodiment, the anti-epileptic is naltrexone.

For treatment of alcohol addiction, combinations to be administered in accordance with the present invention include a PDE7 inhibitor and an opioid agonist or a mixed opioid antagonist/partial antagonist, a PDE7 inhibitor and an antidepressant, a PDE7 inhibitor and a CB1 receptor antagonist/inverse agonist, a PDE7 inhibitor and varenicline, a PDE7 inhibitor and acamprosate, and a PDE7 inhibitor and disulfiram.

For treatment of a psychostimulant addiction, combinations to be administered in accordance with the present invention include, e.g., a PDE7 inhibitor and an antidepressant or a PDE7 inhibitor and a partial opioid agonist/antagonist, e.g., buprenorphine.

For treatment of nicotine addiction, combinations to be administered in accordance with the present invention include, e.g., a PDE7 inhibitor and an antidepressant, a PDE7 inhibitor and nicotine (as a replacement, in an oral, transcutaneous or other conventional formulation), a PDE7 inhibitor and an opioid antagonist, a PDE7 inhibitor and a CB1 receptor antagonist/inverse agonist, and a PDE7 inhibitor and varenicline. In one embodiment, an addictive agent, such as nicotine, and a PDE7 inhibitor are administered together using a transdermal patch delivery system. In another aspect of the invention, a kit including multiple transdermal patches, including dosages of nicotine in diminishing levels and dosages of a PDE7 inhibitor in either constant or diminishing levels, are provided for sequential use by a subject addicted to nicotine to wean the subject from nicotine addiction.

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For treatment of polysubstance addiction, combinations to be administered in accordance with the present invention include, e.g., a PDE7 inhibitor and an opioid agonist or a mixed opioid antagonist/partial antagonist.

For treatment of gambling addiction, combinations to be administered in accordance with the present invention include, e.g., a PDE7 inhibitor and an antidepressant or a PDE7 inhibitor and an agent affecting dopamine neurotransmission, e.g., a direct or indirect dopamine antagonist.

The effective amount of either or both of a PDE7 inhibitor and an additional therapeutic agent may be reduced when administered in combination than when either is provided alone. For example, when the PDE7 inhibitor and the additional therapeutic agent act additively or synergistically, then a lower amount of the PDE7 inhibitor, a lower amount of the additional therapeutic agent, or lower amounts of both the PDE7 inhibitor or the additional therapeutic agent may be required to achieve the same therapeutic effect that would be provided by either the PDE7 inhibitor or the additional therapeutic agent alone.

1. Opioid Antagonists

An opioid antagonist acts on one or more opioid receptors. At least three types of opioid receptors, mu, kappa, and delta opioid receptors, have been reported, and opioid antagonists are generally classified by their effects on the opioid receptors. Opioid antagonists may antagonize central receptors, peripheral receptors or both. Naloxone and naltrexone are commonly used opioid antagonist drugs that are competitive in that they bind to the opioid receptors with higher affinity than agonists, but do not activate the receptors. This effectively blocks the receptor, preventing the body from responding to opiates and endorphins.

Many opioid antagonists are not pure antagonists but also produce some weak opioid partial agonist effects, and can produce analgesic effects when administered in

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high doses to opioid-naive individuals. Examples of such compounds include nalorphine, and levallorphan. However, the analgesic effects from these drugs are limited and tend to be accompanied by dysphoria, most likely due to action at the kappa opioid receptor. Since they induce opioid withdrawal effects in people who are taking, or have previously used, opioid full agonists, these drugs are considered to be antagonists.

Naloxone is one example of an opioid antagonist that has no partial agonist effects. Instead, it is a weak inverse agonist at mu opioid receptors, and is used for treating opioid overdose.

Specific examples of opioid antagonists that may be used according to the invention include alvimopan, binaltorphimine, buprenorphine, cyclazocine, cyclorphan, cypridime, dinicotinate, beta-funaltrexamine, levallorphan, methylnaltrexone, nalbuphine, nalide, nalmefene, nalmexone, nalorphine, nalorphine dinicotinate, naloxone, naloxonazine, naltrendol, naltrexone, naltrindole, oxilorphan, and pentazocine.

2. Antidepressants

Antidepressants are drugs used to treat depression. The three neurotransmitters believed to be involved in depression are serotonin, dopamine, and norepinephrine. Certain types of antidepressants increase the levels of one or more of these neurotransmitters in the brain by blocking their reabsorption.

Several different classes of antidepressants have been identified, including selective serotonin reuptake inhibitors (SSRIs), tricyclic and tetracyclic serotonin and norepinephrine reuptake inhibitors (SNRIs), norepinephrine reuptake inhibitors (NRIs), norepinephrine and dopamine reuptake inhibitors (NDRIs), azaspirones, monoamine oxidase inhibitors (MAOIs), and atypical antidepressants.

SSRIs include, e.g., citalopram, clomipramine, cyanodothiepin, dapoxetine, duloxetine, escitalopram, femoxetine, fluoxetine, fluvoxamine, ifoxetine, imipramine, indalpine, indeloxazine, litoxetine, lofepramine, mianserine, milnacipran,

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mirtazapine, nefazadone, nortriptyline, paroxetine, sertraline, sibutramine, tomoxetine, trazodone, venlafaxine, and zimeldine.

Amitriptyline, amoxapine, butriptyline, clomipramine, demexiptiline, desipramine, dibenzepin, dimetacrine, dothiepin, doxepin, imipramine, iprindole,
5 lofepramine, maprotiline, melitracen, metapramine, mianserin, mirtazapine, nortriptyline, propizepine, protriptyline, quinupramine, setiptiline, tianeptine, and trimipramine are all tricyclic and tetracyclic antidepressants.

SNRIs include, e.g., amoxapine, atomoxetine, bicipadine, desipramine, desvenlafaxine, duloxetine, maprotiline, milnacipran, nefazodone, reboxetine,
10 sibutramine, and venlafaxine.

Nisoxetine, nortriptyline, reboxetine, talsupram, and tomoxetine are all examples of NRIs.

NDRI include, e.g., bupropion, hydroxybupropion, and tesofensine.

Azaspirones include, e.g., buspirone, gepirone, ipsapirone, tandospirone, and
15 tiapirone. Buspirone is an anxiolytic (partial agonist at 5-HT₁ autoreceptors) that may be provided with an anti-depressant such as an SSRI.

Specific MAOIs include, e.g., amiflamine, brofaromine, clorgyline, alpha-ethyltryptamine, iproclozide, iproniazid, isocarboxazid, mebanazine, moclobemide, nialamide, pargyline, phenelzine, pheniprazine, pirlindole, safrazine, selegiline,
20 toloxatone, and tranlcypromine.

Atypical antidepressants include, e.g., amesergide, amineptine, benactyzine, bupropion, clozapine, fezolamine, levoprotiline, lithium, medifoxamine, mianserin, minaprine, olanzapine, oxaflozane, oxitriptan, rolipram, teniloxazine, tofenacin, trazodone, tryptophan, and viloxazine.

25 3. Antiepileptics

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The anticonvulsants, also called anti-epileptic drugs (AEDs) are a diverse group of drugs used in prevention of the occurrence of epileptic seizures and bipolar disorders. AEDs suppress the rapid and excessive firing of neurons that begins a seizure and/or prevents the spread of the seizure within the brain and offer protection against possible excitotoxic effects that may result in brain damage. Many anticonvulsants block sodium channels, calcium channels, AMPA receptors, or NMDA receptors.

Anti-epileptic agents include, but are not limited to, benzodiazepines, barbituates, valproates, GABA agents, iminostilbenes, hydantoins, NMDA antagonists, sodium channel blockers and succinamides.

10 Benzodiazepines include, e.g., alprazolam, chlordiazepoxide, chlrazepate, clobazam, clonazepam, diazepam, halazepam, lorazepam, oxazepam, and prazepam.

Barbiturates used as anti-epileptics include, e.g., amobarbital, mepobarbital, methylphenobarbital, pentobarbital, phenobarbital, and primidone.

15 Valproates used as anti-epileptics include, e.g., sodium valporate, valproic acid, valproate semisodium, and valpromide.

Anti-epileptic GABA agents include, e.g., gabapentin, losigamone, pregabalin, retigabine, rufinamide, and vigabatrin.

Carbamazepine and oxcarbazepine are examples of iminostilbenes.

20 Hydantoins include, e.g., fosphenytoin sodium, mephenytoin, and phenytoin sodium.

NMDA antagonists such as harkoseramide are used as anti-epileptics.

Sodium channel blockers such as lamotrigine are also anti-epileptic agents.

Succinimides include, e.g., ethosuximide, methsuximide, and phensuximide.

25 Other anti-epileptic drugs include acetazolamide, briveracetam, CBD cannabis derivative, clomthiazole edisilate, divalproex sodium, felbamate, isovaleramide, lacosamide, lamotrigine, levetiracetam, methanesulphonamide, talampanel, tiagabine,

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topiramate, safinamide, seletracetam, soretolide, stiripentol, sultiam, valroceamide, and zonisamide.

4. Antiemetics

Antiemetics are drugs effective against vomiting and nausea. Antiemetics are typically used to treat motion sickness and the side effects of opioid analgesics, general anaesthetics, and chemotherapy.

Classifications of antiemetics include, e.g., 5-hydroxytryptamine 3 (5-HT₃) receptor antagonists, histamine receptor antagonists, dopamine receptor antagonists, muscarinic receptor antagonists, acetyl choline receptor antagonists, cannabinoid receptor antagonists, limbic system inhibitors, NK-1 receptor antagonists, corticosteroids, tachykinin antagonists, GABA agonists, cannabinoids, benzodiazepines, anticholinergics, and substance P inhibitors.

5-HT₃ receptor antagonists include, e.g., alosetron, azasetron, bemesetron, cilansetron, dolasetron, granisetron, indisetron, itasetron, ondansetron, palonosetron, propisetron, ramosetron, renzapride, tropisetron, and zatosetron.

Corticosteroid antiemetics include dexamethasone and methylprednisolone.

Limbic system inhibitors include alprazolam, lorazepam, and midazolam.

Dopamine receptor antagonists include diphenhydramine, dronabinol, haloperidol, metoclopramide, and prochlorperazine.

NK-1 receptor antagonists used as an antiemetic include aprepitant and morpholine, and an example of a GABA agonist is propofol.

Thiethylperazine is a type of histamine receptor antagonist.

Cannabinoid receptor antagonists or agonists used as antiemetics include dronabinol, nabilone, rimonabant, taraxagolol, and tetrahydrocannabinol.

Examples of other antiemetics include acetylleucine, monoethanolamine, alizapride, benzquinamide, bietanautine, bromopride, buclizine, chlorpromazine,

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clebopride, cyclizine, dimenhydrinate, dipheniodol, domperidone, dranisetrone, meclizine, methalltal, metopimazine, oxypendyl, pipamazine, piprinhydrinate, scopolamine, thioproperzaine, and trimethobenzamide.

5. Cannabinoid Receptor Antagonists

5 The cannabinoid receptors are a class of the G-protein coupled receptor superfamily. Their ligands are known as cannabinoids. There are currently two known subtypes, CB1 which is expressed mainly in the brain, but also in the lungs, liver, and kidney, and CB2, which is mainly expressed in the immune system and in hematopoietic cells. It is also believed that there are novel cannabinoid receptors that is, non-CB1 and
10 non-CB2, which are expressed in endothelial cells and in the CNS. Cannabinoid receptor antagonists may be selective for either the CB1 or CB2 receptor. The present invention contemplates the use of either or both CB1 and CB2 receptor antagonists.

Addictive agents (e.g., alcohol, opiates, Delta(9)-tetrahydrocannabinol (Delta(9)-THC) and psychostimulants, including nicotine) elicit a variety of chronically relapsing
15 disorders by interacting with endogenous neural pathways in the brain. In particular, they share the common property of activating mesolimbic dopamine brain reward systems, and virtually all abused drugs elevate dopamine levels in the nucleus accumbens. Cannabinoid-1 (CB1) receptors are expressed in this brain reward circuit and modulate the dopamine-releasing effects of Delta(9)-THC and nicotine.

20 Rimonabant (SR141716), a CB1 receptor antagonist, blocks both the dopamine-releasing and the discriminative and rewarding effects of Delta(9)-THC in animals. Although CB1 receptor blockade is generally ineffective in reducing the self-administration of cocaine in rodents and primates, it reduces the reinstatement of extinguished cocaine-seeking behavior produced by cocaine-associated conditioned
25 stimuli and cocaine priming injections. Similarly, CB1 receptor blockade is effective in reducing nicotine-seeking behavior induced by re-exposure to nicotine-associated stimuli.

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In human clinical trials, rimonabant was shown to block the subjective effects of Delta(9)-THC in humans and prevents relapse to smoking in ex-smokers.

Other examples of cannabinoid receptor CB1 antagonists include SR141716A (rimonabant), rosanabant, taranabant and CP-945598.

5 6. Dopaminergic Agents

Drug addiction is a chronic, relapsing disease characterized by a loss of control over drug use, compulsive drug seeking and craving for a substance, use that persists despite negative consequences, and physical and/or psychological dependence on the substance. A fundamental role in the pathogenesis of addiction has been attributed to
10 dopamine. Dopamine, in fact, has permeated the natural history of drug addiction at all levels, from its involvement in shaping individual response to vulnerability factors (i.e., genetics, environmental and stress) to its role in the mechanism of action of the drugs of abuse.

The mesocorticolimbic dopamine system originates in the ventral tegmental area
15 (VTA), which prominently projects to the nucleus accumbens (NAc) and the prefrontal cortex (PFC). It is a defining commonality of all addictive drugs that at least initially they stimulate dopamine transmission in the terminal areas of the mesolimbic system and in particular in the nucleus NAc shell. Nestler, E.J., "Is there a common molecular pathway for addiction?" *Nat Neurosci* **8**:1445-1449 (2005); Pierce, R.C., et al., "The
20 mesolimbic dopamine system: The final common pathway for the reinforcing effect of drugs of abuse?" *Neurosci Biobehav Rev* **30**:215-238 (2006). Brain imaging studies have extended these observations to humans. Drevets, W.C., et al., "Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria," *Biol Psychiatry* **49**:81-96 (2001); Brody A.L., et al., "Smoking-induced ventral striatum dopamine
25 release," *Am J Psychiatry* **161**:1211-1218 (2004). The release of dopamine from these projections is thought to play an important role in mediating drug reward, reinforcement

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and in the induction of compulsive addictive behaviour. Although dopamine is involved in the predisposition and in the initial stages of the development of drug addiction, this condition, once established, is associated with long-lasting changes related to the chronic exposure to the drugs themselves.

5 These changes are collectively indicated as "neuroadaptive" and are thought to be the substrate of behavioural sensitization, a long-lasting increase in the sensitivity to the behavioural stimulant properties of drugs and of changes in the baseline of hedonic state (hedonic allostasis). Berridge K.C., et al., "What is the role of dopamine in reward: Hedonic impact, reward learning, or incentive salience?" *Brain Res Rev* **28**:309-369
 10 (1998); Koob, G.F., et al., "Neurobiological mechanisms for opponent motivational processes in addiction," *Philos Trans R Soc Lond B Biol Sci.* **363**:3113-3123 (2008). Neuroadaptations occurs also at the level of the dopamine system, where a relative reduction in the basal level of activity of dopamine transmission in ventral striatal areas and a reduction in dopamine D2-receptor levels has been documented. Volkow, N.D., et
 15 al., "Dopamine in drug abuse and addiction: results from imaging studies and treatment implications," *Mol Psychiatry* **9**:557-569 (2004); Volkow, N.D., et al., "Dopamine in drug abuse and addiction: results from imaging studies and treatment implications," *Arch Neurol* **64**:1575-1579 (2007); Fehr, C., et al., "Association of low striatal dopamine d2 receptor availability with nicotine dependence similar to that seen with other drugs of
 20 abuse," *Am J Psychiatry* **165**:507-514 (2008).

The most common mechanism through which drugs of abuse result in dopamine neurotransmission is through modulation of VTA presynaptic γ -aminobutyric acid (GABA) activity. Lüscher, C., et al., "The mechanistic classification of addictive drugs," *PLoS Med* **3**:e437(2006). In the VTA, GABA neurons act as local inhibitory
 25 interneurons playing a tonic control on corticomesolimbic dopamine cells. Reduction in

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GABA neurotransmission leads to a net disinhibition of dopamine neurons and increased dopamine release in terminal areas such as the NAc and in the PFC.

A prototypical example of this mechanism is offered by opiates that following activation of μ opioid receptors located onto presynaptic GABA cells lead to a marked inhibition of GABAergic neurotransmission resulting in disinhibition of VTA dopaminergic cells. Johnson, S.W., et al., "Opioids excite dopamine neurons by hyperpolarization of local interneurons," *J Neurosci* **12**:483-488 (1992). Cannabis derivatives appear to increase VTA dopamine firing rate with a similar mechanism but through selective activation of cannabinoid receptor 1 (CB1R) located on presynaptic GABA neurons. Also nicotine, increases dopamine neurotransmission but through a complex interplay of actions of nicotinic receptors on GABA and on glutamatergic inputs to dopamine neurons. Lüscher C, et al., The mechanistic classification of addictive drugs., *PLoS Med.* **3**(11):e437 (2006). In fact, nicotine through β 2-containing nAChRs decreases presynaptic GABA release leading to a prolonged disinhibition of dopamine, at the same time acting on homomeric α 7-containing nAChRs, which are mainly expressed on synaptic terminals of excitatory glutamatergic afferents on dopamine neurons in the VTA, facilitating glutamate release. This effect may also contribute to nicotine-evoked dopamine release. Furthermore, recent evidence suggests that nicotine directly modulates dopamine release in the NAc. Ethanol and benzodiazepines also appear to stimulate VTA dopamine neurotransmission through inhibition of presynaptic GABA activity via modulation of specific GABA-A receptors subunits.

Psychostimulants like amphetamine derivatives and cocaine, comprise the only class of addictive drugs that act directly on dopaminergic terminals by inhibiting dopamine reuptake mechanisms or by facilitating dopamine release from synapses. Through these mechanisms they increase extracellular dopamine levels in terminal areas (i.e., NAc and MPF) of the brain dopamine system. Most notably, however, dopamine

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terminals are also present in the VTA where D1- and D2-like receptors are expressed on dopaminergic cell bodies (autoreceptors) as well as on glutamatergic and GABAergic presynaptic neurons. Direct application of cocaine in the VTA results in a reduction or to an increase (depending on the dose) of dopamine firing rate, an effect that could be potentially mediated by D1 receptors located onto presynaptic GABA and glutamate cells, respectively. Hence presynaptic modulation of VTA DA activity may play a role also in the regulation of the addictive properties of psychostimulants. Brodie, M.S., et al., "Cocaine effects in the ventral tegmental area: Evidence for an indirect dopaminergic mechanism of action," *Naunyn Schmiedeberg's Arch Pharmacol* **342**:660-665 (1990);
5 Bonci, A., et al., "Increased probability of GABA release during withdrawal from morphine," *J Neurosci* **17**:796-803 (1997).
10

Accordingly, in one embodiment of the invention the additional therapeutic agent administered in combination, concurrently or sequentially with a PDE7 inhibitor is a dopaminergic agent to treat a patient suffering from an addiction or compulsive disorder.
15 In another embodiment of the invention, the PDE7 inhibitor is administered in combination, concurrently or sequentially with a dopamine receptor agonist to treat a patient suffering from an addiction or impulse control disorder. In another embodiment of the invention, the PDE7 inhibitor is administered in combination, concurrently or sequentially with a dopamine D1 receptor agonist (i.e., a dopamine subtype D1 receptor
20 agonist) to treat a patient suffering from an addiction or impulse control disorder.

Exemplary dopaminergic agents suitable for administration in conjunction with PDE7 inhibitors include, for example, levodopa (also referred to as "L-dopa"), carbidopa, and dopamine receptor agonists and precursors such as bromocriptine, pergolide, pramipexole, ropinirole, cabergoline, apomorphine, lisuride, rotigotine and quinagolide, as well as
25 fenoldopam, which is selective for dopamine receptor D1.

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Suitable dosages of D1 receptor agonists for administration in conjunction with a PDE7 inhibitor in accordance with the present invention may be determined by medical practitioners but may be, for example, in the range of 0.1 mg to 1,000 mg per day or biweekly, or 0.25 mg to 100 mg per day or biweekly.

5 C. Methods of Treating and Preventing Relapse

Relapse use, or reinstatement, refers to the process of returning to the use of alcohol or another addictive agent or the practice of an addictive behavior after a period of abstinence from, or limited or reduced use of, an addictive agent or practice of an addictive behavior. In certain situations, relapse use of an addictive agent refers to the
10 return to use of an addictive agent by a subject who has undergone physical withdrawal from the addictive agent. Typically, the subject will have undergone physical withdrawal from the addictive agent during a period of non-use or limited or reduced use of the addictive agent. In one embodiment, relapse use occurs in a subject who has previously undergone a treatment regime with an effective amount of an anti-addiction agent to
15 reduce or eliminate use of an addictive agent, but who is no longer using an effective amount of the anti-addiction agent. Anti-addictive agents include any and all agents used to treat or prevent addiction or withdrawal symptoms.

Alcoholism, like many other addictions, is a chronic relapsing disorder characterized by high recidivism rates. Two major factors triggering relapse behavior are
20 stress and environmental conditioning experiences (O'Brien et al. 1997; Monti et al. 1993; Shaham et al. 1995), which probably facilitate relapse to alcohol-seeking via distinct brain mechanisms. For example, activation of the mesolimbic dopamine system via an opioid-dependent mechanism (or via direct alterations in dopamine transmission in the basolateral nucleus of amygdala) seems to mediate the effect of drug-associated cues
25 (Liu and Wiess 2002; Ciccocioppo et al. 2001), and, extrahypothalamic CRF within the bed nucleus of the stria terminalis and median raphe nucleus is likely to mediate stress-

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induced reinstatement of drug-seeking behavior (Erb et al 1998; Shaham et al. 1995; Lê et al. 2000).

Several lines of evidence suggest that molecular mechanisms underlying relapse to addiction are common to different classes of drugs of abuse. Drug craving and loss of control over drug taking behavior associated to relapse are under the direct influence of stress and environmental conditioning stimuli; the two major factors affecting resumption to drug use.

Chronic drug abuse produces neuroadaptive changes not only within systems implicated in the acute reinforcing effects of ethanol, but also within other motivational systems, notably brain stress-regulatory mechanisms. Stress has an established role in the initiation and maintenance of drug abuse, and is a major determinant of relapse in abstinent individuals. (Brown, et al., *J Studies Alcohol* 56:538 (1995); Marlatt, Relapse prevention: introduction and overview of the model, in *Relapse Prevention: Maintenance Strategies in the Treatment of Addictive Behaviours*, Guilford, London, (1985); McKay, et al., *Drug Alcohol Dep.*, 38, 35, (1995); and Wallace, *J Subst Abuse Treat*, 6:95, (1989)). The significance of stress in drug-seeking behavior has also been amply documented in the animal literature. Physical, social, and emotional stress can facilitate acquisition or increase self-administration of cocaine, heroin, and ethanol in rodents and nonhuman primates. (Goeders and Guerin, *Psychopharmacology*, 114, 63, (1994); Hancu, et al., *Brain Res.*, 698, 46, (1995); Ramsey and Van Rcc, *Brain Res.*, 608, 216, (1993); Ahmed and Koob, *Psychopharmacology*, 132, 289, (1997); Shaham and Stewart, *Psychopharmacology* 119:334 (1995); Nash and Maickel, *Prog Neuropsychopharmacol Biol Psychiatry*, 12, 653, (1988); Mollenauer, et al., *Pharmacol. Biochem. Behav.*, 46, 35, (1993); Blanchard, et al., *Pharmacol. Biochem. Behav.* 28, 437, (1987) and Higley, et al., *Proc. Natl. Acad. Sci. USA*, 88, 7261, (1991)). Stressful stimuli have also been shown to elicit reinstatement of cocaine, heroin, and ethanol-seeking behavior in drug-free animals

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following extinction and these findings provide experimental support for a role of stress in relapse. (Ahmed and Koob (1997); Shaham, *Psychopharmacology*, 111, 477, (1993); and Shaham and Stewart (1995)).

Traditionally, stress-related drug-seeking behavior has been thought to be mediated via activation of the hypothalamic-pituitary-adrenal (HPA) axis. However, growing evidence suggests that the non-neuroendocrine corticotropin-releasing factor (CRF) system in the central nucleus of the amygdala (CeA) may play a significant independent role in the regulation of addictive behavior associated with stress. The CeA is rich in CRF immunoreactive cell bodies, terminals, and receptors, and this neuronal CRF system has been implicated in the mediation of behavioral and emotional responses to stressful stimuli. (Dunn and Berridge, *Brain Res Brain Res Rev*, 15, 71, (1990); and Koob et al., *Semin Neurosci* 6:221 (1994)). For example, immobilization stress elevates extracellular CRF levels in the CeA while intra-CeA injection of the CRF receptor antagonist, α -helical CRF9-41, reduces behavioral signs of anxiety produced by social and environmental stressors (Merali et al., *J. Neurosci.*, 18, 4758, (1998); Merlo Pich et al., *J. Neurosci.*, 15, 5439, (1995); Heinrichs et al., *Brain Res.*, 581, 190 (1992); Swiergiel et al., *Brain Res*, 623, 229 (1993)). Anxiety and stress-like symptoms are central to drug and alcohol withdrawal syndromes. Considering the evidence on a role of CRF neurons in the CeA in the regulation of emotional and anxiogenic effects of stress, it is likely that anxiogenic and stress-like consequences of withdrawal from drugs of abuse may be mediated by the CRF system in the CeA as well.

Changes in the regulation of the activity of the CRF system within the CeA may represent a critical neuroadaptive mechanism responsible for the development of dependence and compulsive drug-seeking behavior.

The data discussed above identify neuroadaptive changes in brain circuitries and perturbations in stress systems as an important element in compulsive drug-seeking

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behavior and dependence. Another important factor in the long-lasting addictive potential of drugs of abuse is the conditioning of their rewarding actions with specific environmental stimuli. Environmental cues repeatedly associated with the subjective effects of drugs of abuse including alcohol can evoke drug craving or elicit automatic behavioral responses (Miller and Gold 1994; Tiffany and Carter 1998) that ultimately may lead to relapse. (Childress et al., *Conditioned craving and arousal in cocaine addiction: A preliminary report*, in *NIDA Research Monograph 81*, (1988) ; Ehrman et al., *Psychopharmacology*, 107, 523, (1992); Monti et al., *J Stud Alcohol* 54:235-45 (1993); Pomerleau et al., *Addict. Behav.*, 8, 1, (1983); Stormark et al., *Addict. Behav.*, 20, 571, (1995); Miller and Gold *Ann. Clin. Psychiatry*, 6, 99, (1994); and Tiffany and Carter, *J Psychopharmacol.* 12, 23, (1998)). Learned responses to drug-related stimuli may, therefore, contribute critically to the high rates of relapse associated with cocaine and other drug addiction.

Data from operant response-reinstatement models developed to investigate drug-seeking behavior associated with exposure to drug-related environmental cues in rats indicate that discriminative stimuli predictive of cocaine, ethanol, or heroin availability reliably elicit strong recovery of extinguished drug-seeking behavior in the absence of further drug availability. (Weiss et al., *Proc. Natl. Acad. Sci. USA*, 97, 4321, (2000); Katner et al., *Neuropsychopharmacology*, 20, 471, (1999); Katner and Weiss, *Alcohol Clin Exp Res.* 23:1751 (1999); and Gracy et al., *Pharmacol. Biochem. Behav.*, 65, 489, (2000)). The response-reinstating effects of these stimuli show remarkable resistance to extinction with repeated exposure and, in the case of cocaine, can still be observed after several months of forced abstinence. Additionally, in the case of ethanol, drug-seeking behavior induced by ethanol-predictive discriminative stimuli was found to be enhanced in genetically alcohol-preferring P rats compared to Alcohol Nonpreferring (NP) and nonselected Wistar rats. (Weiss and Ciccocioppo, *Soc. Neurosci. Abstr.*, 25, 1081,

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(1999)). This observation demonstrates that genetic predisposition toward heightened ethanol intake is reflected also by a greater susceptibility to the motivating effects of ethanol cues (i.e., enhanced drug-seeking under conditions where behavior is not directly reinforced by ethanol itself). Together, these findings strongly support the hypothesis
5 that learned responses to drug-related stimuli are a significant factor in long-lasting vulnerability to relapse.

In humans, relapse risk involves multiple determinants that are likely to interact. For example, exposure to drug cues may augment vulnerability to relapse imparted by protracted withdrawal symptoms resulting from neuroadaptive changes in dependent
10 individuals. Interactive effects exacerbating relapse risk may also exist between the motivating effects of stress and drug-related cues. Recent work addressing these issues has confirmed that additive interactions between the response-reinstating effects of ethanol-associated cues and stress can indeed be demonstrated, and that these effects are enhanced in rats with a history of ethanol dependence. (Liu and Weiss, *Soc. Neurosci.*
15 *Abstr.* 26, 786 (2000)).

In experimental laboratories, reinstatement of drug seeking is obtained with administration of the α -2 adrenoreceptor antagonist yohimbine, which, increasing brain noradrenaline cell firing and release, acts as a pharmacological stressor. Footshock stress and yohimbine-induced reinstatement of drug-seeking behaviors both represent valid
20 experimental models to investigate stress-induced alcohol relapse (Lee et al., *Neuropsychopharmacology* 29:686-93 (2004) and Le et al., *Psychopharmacology* 150:317-24 (2000)).

As shown in the accompanying Examples, PDE7 inhibitors significantly reduce stress-induced relapse use of an addictive agent (Example 1). These data indicate,
25 therefore, that PDE7 inhibitors have anti-relapse properties.

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Interestingly, various reports have shown that the nonselective opiate receptor antagonist naltrexone reduces the urge to drink elicited by presentation of alcohol cues in human alcoholics (Monti et al. 1993, *supra*) and decreases the efficacy of an alcohol cue to reinstate extinguished responding at a previously drug-paired lever in rats (Katner et al. 1999, *supra*). However, naltrexone does not reduce relapse behavior elicited by stress ((Le A.D. Psychopharmacology 1998).

In a related embodiment, the invention includes a method of treating or preventing relapse use of an addictive agent or practice of an addictive or compulsive behavior, comprising administering an effective amount of a PDE7 inhibitor to a subject who previously reduced or eliminated use of an addictive agent or practice of an addictive or compulsive behavior in response to exposure to an effective amount of another anti-addiction treatment, wherein the subject is no longer exposed to an effective amount of the anti-addiction treatment. The anti-addiction treatment may be an anti-addiction drug or may be a non-pharmacologic therapy such as counseling, psychotherapy or hypnosis therapy. The relapse use may be triggered by stress.

In certain embodiments, the subject is no longer exposed to an effective amount of an anti-addiction agent because the subject has become tolerant to the agent, such that the blood plasma concentration of the anti-addiction agent that was previously effective in treating the addiction is no longer effective. In other embodiments, the subject is no longer exposed to an effective amount of an anti-addiction agent because the subject is now exposed to a lower blood plasma concentration of the anti-addiction agent, and this lower blood plasma concentration is not effective.

In certain embodiments of the methods of the present invention, the subject has undergone a period of abstinence from, or limited or reduced use of, the addictive agent or practice of the addictive or compulsive behavior. This period of abstinence or limited or reduced use may be, e.g., at least 24 hours, at least 48 hours, at least 3 days, at least 5

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days, at least one week, at least 2 weeks, at least 1 month, at least 2 months, at least 4 months, at least 6 months, at least 9 months, at least one year, at least 2 years, or at least 5 years.

In another embodiment, the present invention includes a method of treating or preventing relapse use of an addictive agent, comprising providing a PDE7 inhibitor and an opioid antagonist to a subject who has undergone physiological withdrawal from the addictive agent.

In a further embodiment, the present invention includes a method of treating or preventing relapse use of an addictive agent, comprising administering a PDE7 inhibitor and a CB1 antagonist, e.g., disulfiram, topiramate, levetiracetam, SSRIs, or ondansetron, to a subject who has undergone physiological withdrawal from the addictive agent.

In particular embodiments, the relapse use is triggered by stress, an environmental conditioning factor, or both.

While the methods of the present invention may be practiced in subjects addicted to a single addictive agent, they may also be used in subjects addicted to two or more addictive agents. Similarly, while these methods may be used to prevent relapse use of the addictive agent from which the subject has undergone withdrawal, they may also be adapted to prevent relapse use or the commencement of use of an addictive agent different than the one from which the subject has undergone physiological withdrawal.

20

D. Pharmaceutical Compositions, Routes of Administration, Unit Dosage Forms, Kits

The present invention has established the efficacy of using combinations of a PDE7 inhibitor, in combination with one or more additional therapeutic agents, such as opioid antagonists, antidepressants, antiepileptics, antiemetics, and CB1 receptor antagonists. Thus, the present invention further includes compositions comprising one or

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more PDE7 inhibitors and one or more additional therapeutic agents, such as opioid antagonists, mixed opioid antagonists/partial agonist, antidepressants, antiepileptics, antiemetics, CRF1 receptor antagonists and CB1 receptor antagonists.

In particular embodiments, the composition comprises one PDE7 inhibitor and
5 one additional therapeutic agent. In certain embodiments, the additional therapeutic agent is an opioid antagonist or a mixed opioid antagonist/partial agonist. In one embodiment, the opioid antagonist is naltrexone. In another embodiment, the mixed opioid partial agonist/antagonist is buprenorphine. In certain embodiments, the additional therapeutic agent is an antidepressant. In a particular embodiment, the antidepressant is
10 bupropion. In certain embodiments, the additional therapeutic agent is an antiepileptic, an antiemetic, or an opioid antagonist or a mixed opioid partial agonist/antagonist.

The compositions of the present invention may be administered to a subject as a pharmaceutical composition or formulation. In particular embodiments, pharmaceutical compositions of the present invention may be in any form which allows for the
15 composition to be administered to a subject. For example, the composition may be in the form of a solid, liquid or gas (aerosol). Typical routes of administration include, without limitation, oral, topical, parenteral, sublingual, rectal, vaginal, and intranasal. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, epidural, intrasternal injection or infusion techniques.

20 Pharmaceutical compositions used according to the present invention comprise a PDE7 inhibitor, another therapeutic agent, and a pharmaceutically acceptable diluent, excipient, or carrier. "Pharmaceutically acceptable carriers" for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A.R. Gennaro edit. 1985). For example,
25 sterile saline and phosphate buffered saline at physiological pH may be used. Preservatives, stabilizers, dyes and even flavoring agents may be provided in the

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pharmaceutical composition. For example, sodium benzoate, sorbic acid and esters of p hydroxybenzoic acid may be added as preservatives. *Id.* at 1449. In addition, antioxidants and suspending agents may be used. *Id.*

Pharmaceutical compositions of the invention are generally formulated so as to
5 allow the active ingredients contained therein to be bioavailable upon administration of the composition to a subject. Compositions that will be administered to a subject may take the form of one or more dosage units, where for example, a tablet, capsule or cachet may be a single dosage unit, and a container comprising a combination of agents according to the present invention in aerosol form may hold a plurality of dosage units.

10 In particular embodiments, the composition comprising a PDE7 inhibitor and another therapeutic agent is administered in one or more doses of a tablet formulation, typically for oral administration. The tablet formulation may be, e.g., an immediate release formulation, a controlled-release formulation, or an extended-release formulation. In one embodiment, a tablet formulation comprises an effective amount of a composition
15 comprising a PDE7 inhibitor and another therapeutic agent. In particular embodiments, a tablet comprises about 1, 5, 10, 20, 30, 50 100, 150, 200, 250, or 300 mg of a PDE7 inhibitor, and about 1, 5, 10, 20, 30, 50 100, 150, 200, 250, or 300 mg of another therapeutic agent.

The present invention further includes unit-dosage forms of pharmaceutical
20 compositions comprising a PDE7 inhibitor and another therapeutic agent. Each unit-dosage form comprises a therapeutically effective amount of a pharmaceutical composition of the present invention, when used in the recommended amount. For example, a unit-dosage form may include a therapeutically effective amount in a single tablet, or a unit-dosage form may include a therapeutically effective amount in two or
25 more tablets, such that the prescribed amount comprises a therapeutically effective amount.

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In particular embodiments, a PDE7 inhibitor is provided to a subject in an amount in the range of 0.1-1000 mg/day, 1-1000 mg/day, 10-100 mg/day, or 25-50 mg/day. In one embodiment, pioglitazone is provided to a patient at about 30 mg/day.

Certain combinations of PDE7 inhibitors and other therapeutic agents may not be readily adaptable to coformulation. For example, one of the agents may be more amenable to intravenous administration, while another of the agents may be more amenable to oral administration. Or, the serum half-life of the two agents may be such that one must be administered more frequently than the other. Accordingly, the present invention contemplates kits comprising one or more unit dosage forms of a PDE7 inhibitor and one or more unit dosage forms of another therapeutic agent, such that the two unit dosage forms may be provided to a subject in a therapeutically effective manner.

In one embodiment, the present invention includes a kit comprising unit-dosage forms of a PDE7 inhibitor and unit-dosage forms of nicotine. In one embodiment, the unit dosage forms of nicotine comprise a plurality of different unit-dosage forms of nicotine, wherein the different dosage forms of nicotine represent decreasing amount that may be taken one after the other over a period of time, so as to overcome addiction and effectuate withdrawal from the nicotine. The unit-dosage forms of nicotine may be present, e.g., in the form of a transdermal patch, gum, or a lozenge.

20 E. PDE7 Proteins and Inhibitory Agents

Cyclic nucleotide phosphodiesterase type 7 (PDE7) is identified as a unique family based on its primary amino acid sequence and distinct enzymatic activity. The PDE genes identified as PDE7 (PDE7A and PDE7B), code for cAMP-specific PDEs. The biochemical and pharmacological characterization of PDE7 shows a high-affinity cAMP-specific PDE ($K_m=0.2 \mu M$) that is not affected by cGMP nor by selective inhibitors of other PDEs. The PDE7 enzyme selectively decomposes cAMP and is

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characterized as an enzyme that is not inhibited by rolipram, a selective inhibitor of PDE4, which is a distinct, cAMP-specific PDE family. Two sub-types have been identified within the PDE7 family, PDE7A (Michael, T., et al., *J Biol. Chem.* 268(17):12925-12932, 1993; Han, P., et al., *J Biol. Chem.* 272(26):16152-16157, 1997) and PDE7B (U.S. Patent No. 6,146,876; Gardner, C., et al., *Biochem. Biophys. Res. Commun.* 272(1):186-192, 2000; and Saski, T., et al., *Biochem. Biophys. Res. Commun.* 271(3):575-583, 2000). The two gene products exhibit 70% identity in their C-terminal catalytic domains (Hetman J.M., et al., *PNAS* 97(1):472-476 (2000).

PDE7A has three splice variants (PDE7A1, PDE7A2 and PDE7A3); these variants are generated via alternative splicing at both the N- and C-termini (Bloom, T.J., and J.A. Beavo, *Proc. Natl. Acad. Sci. USA.* 93:14188-14192, 1996). The nucleotide sequence of PDE7A, transcript variant 1, is accessible in public databases by the accession number NM_002603. Human PDE7A1 protein (SEQ ID NO:2, encoded by SEQ ID NO:1) has 456 amino acids and migrates at an apparent molecular weight of 53-55 kDa on reduced SDS-PAGE.

The nucleotide sequence of PDE7A, transcript variant 2, is accessible in public databases by the accession number NM_002604. Human PDE7A2 protein (SEQ ID NO:4, encoded by SEQ ID NO:3) has 424 amino acids.

The PDE7A protein has a region of about 270 amino acids at the carboxy terminal end that displays significant similarity (~23% homology) to the analogous regions of other cAMP-hydrolyzing PDEs. This region serves as the catalytic domain. The amino-terminal region of this protein is divergent from that of other PDEs and presumably mediates the distinctive and regulatory properties unique to this enzyme family.

The protein sequence of human PDE7B is accessible in public databases by the accession number NM_018945, provided as SEQ ID NO:6, encoded by SEQ ID NO:5.

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Three splice variants of PDE7B have been reported: PDE7B1, PDE7B2 and PDE7B3. PDE7B is published in WO 01/62904, U.S. Patent No. 6,146,876.

Both PDE7B2 and PDE7B3 possess unique N-terminal sequences. Human PDE7B gene products have an apparent molecular weight of 53-55 kDa on reduced SDS-PAGE (Sasaki, T., Kotera, J., Omori, K., *Biochemical J.* 361:211-220, 2002). As in
5 PDE7A, the PDE7B has a significantly conserved region of about 270 amino acids common to all PDEs at the carboxy terminal, which serves as the catalytic domain. Similar to the PDE7A protein, the amino-terminal region of PDE7B protein is divergent and presumably accounts for the distinctive and regulatory properties unique to the
10 individual PDE families. The PDE7B protein shows homology to other cAMP-dependent PDEs (23%) within the catalytic domain. The PDE7B polypeptide is 61% homologous to PDE7A, according to WO 2004/044196.

PDE7 is also uniquely localized in mammalian subjects relative to other PDE families. PDE7A expression has been detected in the majority of tissues analyzed,
15 including the brain, heart, kidney, skeletal muscle, spleen and uterus (Bloom, et al., *PNAS* 93:14188, 1996). Within the brain, PDE7A is widely distributed in both neuronal and non-neuronal cell populations (Miro, et al., *Synapse* 40:201, 2001). PDE7A's wide expression in the brain, including the basal ganglia and substantia nigra, provides a theoretical basis for a role for PDE7A in brain functions.

20 In the practice of the methods of the invention, representative PDE7 inhibitory agents that inhibit the phosphodiesterase activity of PDE7 include: molecules that bind to PDE7 and inhibit the enzyme activity of PDE7 (such as small molecule inhibitors or blocking peptides that bind to PDE7 and reduce enzymatic activity), and molecules that decrease the expression of PDE7 at the transcriptional and/or translational level (such as
25 PDE7 antisense nucleic acid molecules, PDE7 specific RNAi molecules and PDE7 ribozymes), thereby preventing PDE7 from cleaving cAMP. The PDE7 inhibitory agents

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can be used alone as a primary therapy or in combination with other therapeutics (such as dopamine receptor agonists) as an adjuvant therapy to enhance the therapeutic benefits, as discussed *supra*.

5 The inhibition of PDE7 is characterized by at least one of the following changes that occur as a result of administration of a PDE7 inhibitory agent in accordance with the methods of the invention: the inhibition of PDE7-dependent enzymatic cleavage of the 3'-phosphodiester bond in cAMP to form 5'-adenosine monophosphate (5'-AMP), a reduction in the gene or protein expression level of PDE7, measured, for example, by gene expression analysis (e.g., RT-PCR analysis) or protein analysis (e.g., Western blot).

10 In some embodiments, a PDE7 inhibitory agent is a molecule or composition that inhibits the expression of PDE7A, PDE7B, or both PDE7A and PDE7B, such as an antisense or small inhibitory nucleotide (e.g., siRNA) that specifically hybridizes with the cellular mRNA and/or genomic DNA corresponding to the gene(s) of the target PDE7 so as to inhibit their transcription and/or translation, or a ribozyme that specifically cleaves
15 the mRNA of a target PDE7.

Potency of PDE7 Inhibitory Agents

In one embodiment, a PDE7 inhibitory agent useful in the methods of the invention is a compound that is sufficiently potent to inhibit the enzymatic activity of PDE7 (PDE7A, PDE7B, or PDE7A and PDE7B) at an $IC_{50} \leq 1 \mu M$, preferably less than
20 or about $0.1 \mu M$. In one embodiment, the PDE7 inhibitory agent is sufficiently potent to inhibit the enzymatic activity of PDE7 (PDE7A, PDE7B, or PDE7A and PDE7B) at an IC_{50} of from about 0.1 to about 500 nM. In one embodiment, the PDE7 inhibitory agent is potent to inhibit the enzymatic activity of PDE7 (PDE7A, PDE7B, or PDE7A and PDE7B) at an IC_{50} of from about 1 to about 100 nM.

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Representative methods for determining the IC_{50} for a PDE7 (PDE7A or PDE7B) inhibitory agent are well known in the art, such as the Scintillation Proximity Assay (SPA) disclosed in Bardelle et al., *Anal Biochem* 15:275(2):148-55 (1999).

PDE7A or PDE7B Selective Inhibitory Agents

5 In one embodiment, the PDE7 inhibitor useful in the method of the invention is a PDE7A inhibitory agent. In one embodiment, the PDE7A inhibitory agent is potent to inhibit the enzymatic activity of PDE7A at an IC_{50} of from about 0.1 to about 500 nM. In one embodiment, the PDE7A inhibitor has an IC_{50} of from about 1 to about 100 nM. A suitable assay for determining the IC_{50} for a PDE7A inhibitor uses recombinant human
10 PDE7A2 enzymes expressed in a baculoviral system. This assay method is a modification of the SPA assay reported by Bardelle et al. supra.

In some embodiments, the PDE7 inhibitory agent exhibits isozyme-selective activity against PDE7A. A PDE7A selective inhibitory agent reduces PDE7A activity at least two-fold more than PDE7B activity, more preferably at least 10-fold, at least 20-
15 fold, at least 50-fold, or at least 100-fold. In some embodiments, the PDE7A inhibitory agent is an inhibitory agent that is at least 10-fold (such as at least 20-fold, or at least 50-fold or at least 100-fold) more selective for inhibiting PDE 7A activity than for the enzyme activity of any other PDE (PDE1-6, 7B, and 8-11).

In one embodiment, the PDE7B inhibitor has an IC_{50} of from about 0.1 to about
20 500 nM. In one embodiment, the PDE7B inhibitory agent is sufficiently potent to inhibit the enzymatic activity of PDE7B at an IC_{50} of from about 0.1 to about 500 nM. In one embodiment, the PDE7B inhibitor has an IC_{50} of from about 1 to about 100 nM. Methods for determining the IC_{50} for a PDE7B inhibitor are well known in the art, such as the assays disclosed in Bardelle et al., supra.

25 In some embodiments, the PDE7 inhibitor exhibits isozyme-selective activity against PDE7B. A PDE7B selective inhibitory agent reduces PDE7B activity at least

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two-fold more than PDE7A activity, more preferably at least 10-fold, at least 20-fold, at least 50-fold, or at least 100-fold. In some embodiments, the PDE7B inhibitory agent is an inhibitory agent that is at least 10-fold (such as at least 20-fold, or at least 50-fold or at least 100-fold) more selective for inhibiting PDE7B activity than for the enzyme activity
5 of any other PDE (PDE1-6, 7A, and 8-11).

PDE7 Selectivity as Compared to Other PDEs

In some embodiments, the PDE7 inhibitory agent has an IC_{50} for inhibiting PDE1B activity of greater than 5 times (such as at least 10-fold, at least 20-fold, or at least 50-fold or at least 100-fold) the lesser of the IC_{50} for inhibiting PDE7A activity and
10 the IC_{50} for inhibiting PDE7B activity. Stated differently, the PDE7 inhibitor is more potent (by 5 times, 10 times, 20 times, 50 times or 100 times) at inhibiting the activity of PDE7A or PDE7B (whichever PDE7A or PDE7B isozyme upon which the PDE7 inhibitor has the most effect), than it is at inhibiting the activity of PDE1B. For purposes of the present specification, by way of example, this property may be still more simply
15 stated as the PDE7 inhibitor is more potent (by 5 times, 10 times, 20 times, 50 times or 100 times) at inhibiting the activity of PDE7 than it is at inhibiting the activity of PDE1B.

Dual inhibition of both PDE7 and PDE1B may confer additional benefit in the treatment of movement disorders based on a report that deletion of the gene for PDE1B in mice stimulated the metabolism of dopamine and sensitized the animals to the effects of
20 dopaminergic agonists (Siuciak, et al., *Neuropharmacology* 53(1): 113-23 (2007)).

In some embodiments, the PDE7 inhibitory agent has an IC_{50} for inhibiting PDE10 activity of greater than 5 times (such as at least 10-fold, or at least 20-fold, or at least 50-fold or at least 100-fold) the lesser of the IC_{50} for inhibiting PDE7A activity and the IC_{50} for inhibiting PDE7B activity. Dual inhibition of both PDE7 and PDE10 may
25 confer additional benefit in the treatment of movement disorders based on a report that

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selective inhibitors of PDE10 cause an increase in cAMP levels in the striatum (Siuciak J.A. et al., *Neuropharmacology* 51(2):386-96 (2006)).

In some embodiments, the PDE7 inhibitory agent has an IC_{50} for inhibiting PDE3 activity of greater than 10 times (such as at least 20-fold, at least 50-fold or at least 100-fold) the lesser of the IC_{50} for inhibiting PDE7A activity and the IC_{50} for inhibiting PDE7B activity. This is because the administration of selective inhibitors of PDE3 to patients in heart failure was shown to increase their rate of mortality (Packer M. et al., *N Engl J Med.* 325(21):1468-75 (1991)).

In some embodiments, the PDE7 inhibitory agent has an IC_{50} for inhibiting PDE4 activity of greater than 10 times (such as at least 20-fold, at least 50-fold or at least 100-fold) the lesser of the IC_{50} for inhibiting PDE7A activity and the IC_{50} for inhibiting PDE7B activity. This is because deletion of one of the PDE4 genes in mice has been shown to lead to cardiac myopathy (Lehnart S.E. et al., *Cell* 123(1):25-35 (2005)).

In some embodiments, the PDE7 inhibitory agent has a half maximally effective dose ("ED₅₀") in an in vivo assay of PDE4 inhibition (for example, sedation or inhibition of TNF alpha levels after endotoxin treatment) of greater than 10 times (such as at least 20-fold, at least 50-fold or at least 100-fold) the lesser of the ED₅₀ in an in vivo assay of PDE7A and PDE7B inhibition (for example, prevention of relapse to cocaine or other psychostimulant addiction). In accordance with such embodiments, it has been determined that some compounds having dual PDE4/PDE7 inhibitory activity possess greater selectivity against PDE7 than PDE4 *in vivo*, as compared to the PDE4/PDE7 selectivity of the compound as determined in an *in vitro* assay.

In some embodiments, the PDE7 inhibitory agent has an IC_{50} for inhibiting PDE3 activity and PDE4 activity of greater than 10 times (such as at least 20-fold, at least 50-fold or at least 100-fold) the lesser of the IC_{50} for inhibiting PDE7A activity and the IC_{50} for inhibiting PDE7B activity.

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In some embodiments, the PDE7 inhibitory agent has an IC_{50} for inhibiting PDE8 activity of greater than 10 times (such as at least 20-fold, at least 50-fold or at least 100-fold) the lesser of the IC_{50} for inhibiting PDE7A activity and the IC_{50} for inhibiting PDE7B activity.

5 In some embodiments, the PDE7 inhibitory agent has an IC_{50} for inhibiting PDE4 activity and PDE8 activity of greater than 10 times (such as at least 20-fold, at least 50-fold or at least 100-fold) the lesser of the IC_{50} for inhibiting PDE7A activity and the IC_{50} for inhibiting PDE7B activity. In accordance with this embodiment, it is known that the PDE families that specifically/preferentially hydrolyze cAMP include PDE4, PDE7, and
10 PDE8.

In some embodiments, the PDE7 inhibitory agent has an IC_{50} for inhibiting the activity of PDE1, PDE2, PDE3, PDE4, and PDE8, PDE10, and PDE11 of greater than 10 times the lesser of the IC_{50} for inhibiting PDE7A activity and the IC_{50} for inhibiting PDE7B activity. In accordance with this embodiment, it is known that the PDE families
15 that specifically/preferentially hydrolyze cAMP include PDE4, PDE7, and PDE8 and the PDE1, PDE2, PDE3, PDE10, and PDE11 families show substantial activity against both cAMP and cGMP.

In some embodiments, the PDE inhibitory agent is a selective PDE7 inhibitor for which the lesser of the IC_{50} for inhibiting PDE7A activity and the IC_{50} for inhibiting
20 PDE7B activity is less than one-tenth (such as one-twentieth, one-fiftieth, or one-hundredth) the IC_{50} that the agent has for inhibiting any other PDE enzyme from the PDE1-6 and PDE8-11 enzyme families.

A selective PDE7 inhibitor can be identified, for example, by comparing the ability of an agent to inhibit PDE7 (PDE7A, PDE7B or PDE7A and PDE7B) enzyme
25 activity to its ability to inhibit PDE enzymes from the other PDE families. For example, an agent may be assayed for its ability to inhibit PDE7 activity as well as PDE1, PDE2,

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PDE3, PDE4, PDE5, PDE6, PDE8, PDE9, PDE10, and PDE11. The ratio of the IC₅₀ inhibition for each of the PDE(1-6 and 8-11) isozymes to the IC₅₀ inhibition of PDE7 (i.e., the more sensitive of PDE7A or PDE7B) may be determined by a standard *in vitro*, *in vivo*, or *ex vivo* assay, such as those described herein.

5 In some embodiments, a PDE7 inhibitor is selective for PDE7 and substantially inactive against other PDEs (e.g., PDE1, PDE2, PDE3, PDE4, and PDE8, PDE10, and PDE11) due to targeting of the PDE7 inhibitor to one or more target tissues, such as the brain and/or skeletal muscle. As described herein, PDE7 is uniquely localized in mammalian subjects relative to other PDE families. Within the brain, PDE7A is widely
10 distributed in both neuronal and non-neuronal cell populations, including the basal ganglia and substantia nigra (Miro et al., Synapse 40:201, 2001). PDE7B is expressed in the brain in the striatum (Reycs-Irisarri et al., Neuroscience 132:1173, 2005).

Types of PDE7 Inhibitory Agents

The PDE7 inhibitory agent can be any type of agent including, but not limited to,
15 a chemical compound, a protein or polypeptide, a peptidomimetic, a nucleic acid molecule, or ribozyme. In some embodiments, PDE7 inhibitory agents are small molecule inhibitors including natural and synthetic substances that have a low molecular weight (i.e., less than about 450 g/mole), such as, for example, peptides, peptidomimetics and nonpeptide inhibitors such as chemical compounds.

20

Chemical Compounds:

The PDE7 inhibitors useful in the methods of the invention include agents that are administered by a conventional route (e.g., oral, intramuscular, subcutaneous, transdermal, transbucal, intravenous, etc.) into the bloodstream and are ultimately
25 transported through the vascular system across the blood brain barrier to inhibit PDE7 in the brain. Accordingly, for these methods of administration, the PDE7 inhibitors have the ability to cross the blood brain barrier. Those PDE inhibitors described below that have

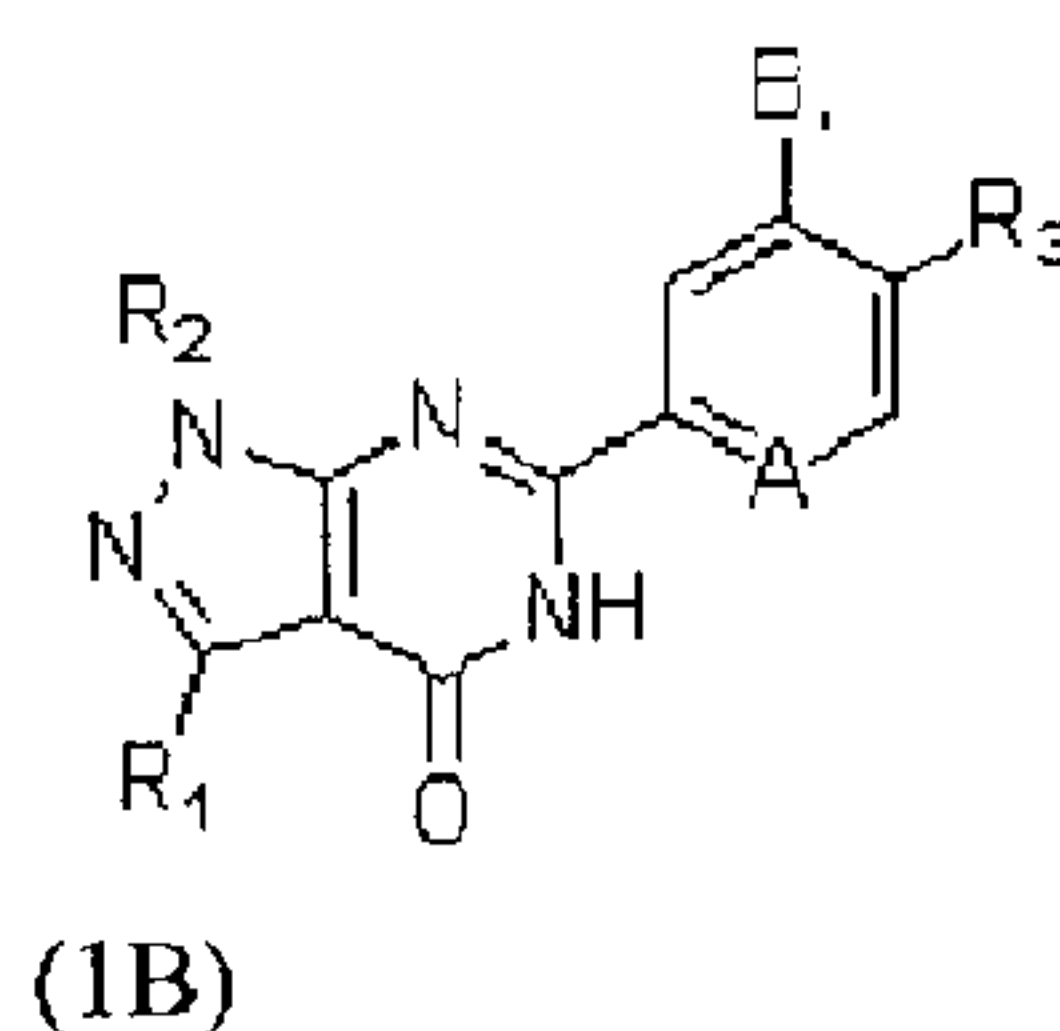
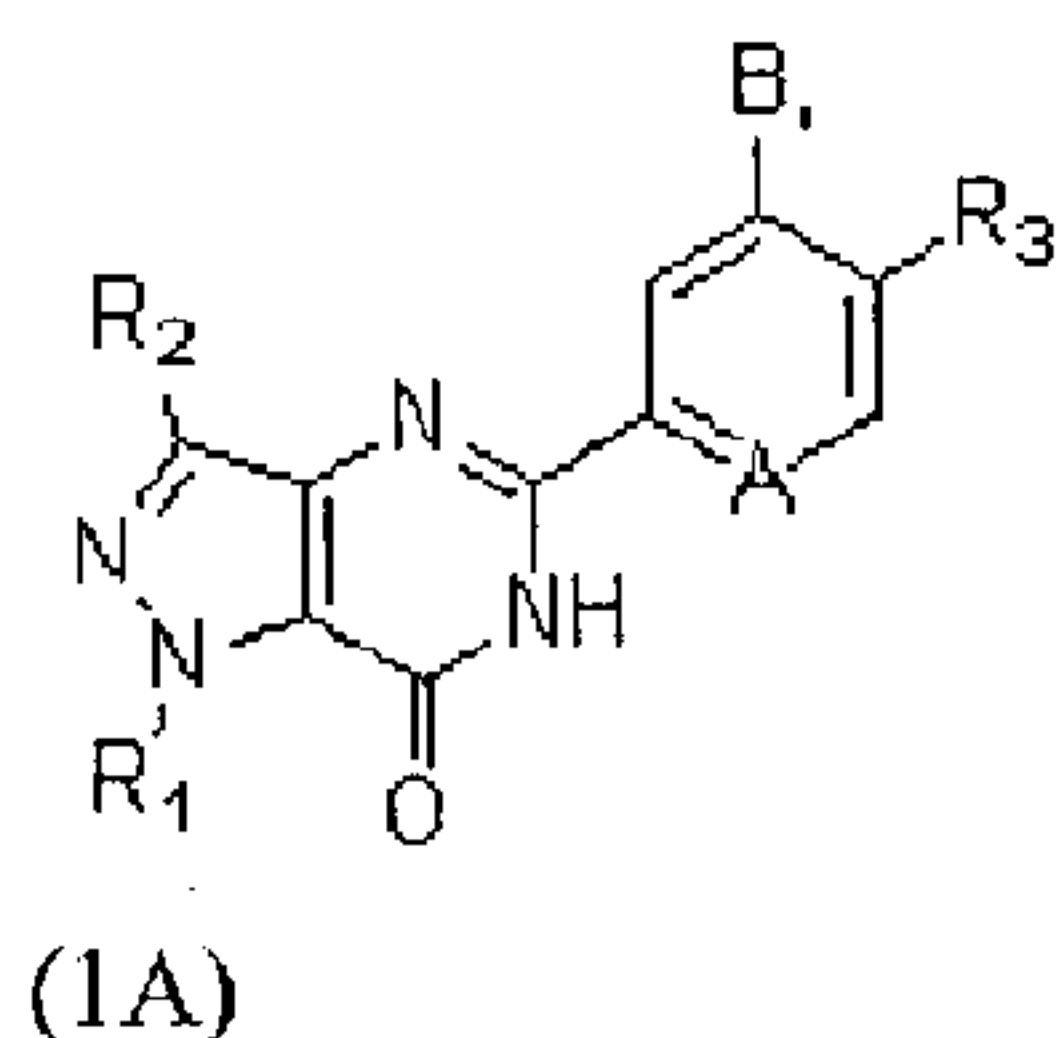
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the ability to cross the blood brain barrier (e.g., those having a molecular weight less than about 450 g/mole and that are sufficiently lipophilic) are useful in the methods of the invention when the inhibitors are administered by a route that ultimately transports the inhibitors to the brain in the bloodstream.

5 The following is a description of exemplary PDE7 inhibitors useful in the methods of the invention.

In one embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in EP 1 454 897, WO 2003/053975, and US 20050148604 .

10 In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formulas:



15

The substituents for the above compounds are defined as follows:

A represents N or CR₄,

B represents a hydrogen atom or a halogen atom,

20

R₁ represents optionally substituted C₃₋₇ cycloalkyl or tert-butyl,

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R₂ represents hydrogen, methyl, or ethyl,

R₃ represents a hydrogen, nitro, cyano or halogen atom, NR₅R₆, C(=X)R₇, SO₂NR₅R₆, OR₈, NR₈CONR₅R₆, NR₈SO₂R₉, NR₈CO₂R₉, a heteroaryl group, optionally substituted C₁₋₃ alkyl, optionally substituted C₁₋₆ alkenyl, or optionally substituted saturated or unsaturated heterocycloalkyl,

R₄ represents hydrogen, or C₁₋₃ alkoxy substituted, if desired, by one or more fluorine atoms,

R₅ and R₆ are the same or different, and represent a hydrogen atom, optionally substituted C₁₋₆ alkyl, optionally substituted heterocycloalkyl, or optionally substituted acyl or, together with the nitrogen atom which they are bound to, form azetidiny, pyrrolidiny, piperidiny, morpholino, thiomorpholino, piperaziny, or homopiperaziny, each of these groups being optionally substituted by optionally substituted C₁₋₄ alkyl, OH, C₁₋₃ alkoxy, CO₂H, NR₅R₆, an oxo group, NR₉COR₇, or C(=O)R₇,

R₇ represents optionally substituted C₁₋₆ alkyl, OH, OR₈, or NR₅R₆,

R₈ represents hydrogen, an optionally substituted C₁₋₆ alkyl group, or optionally substituted heterocycloalkyl,

R₉ represents an optionally substituted C₁₋₆ alkyl group, and

X represents O, S, or NH.

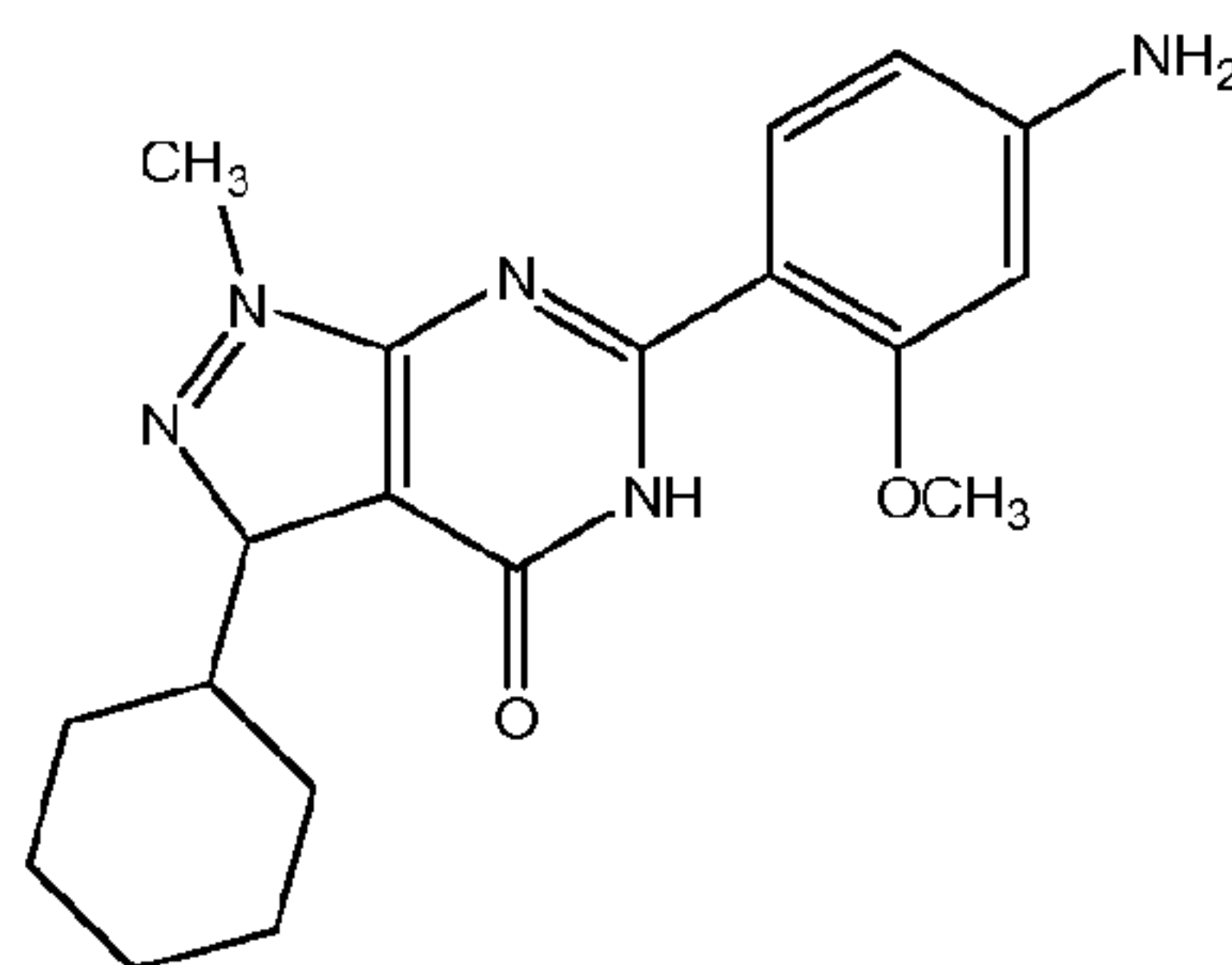
In regard to the above compounds, "optionally substituted" refers to optionally substituted linear, branched or cyclic alkyl group such as methyl, ethyl, propyl or cyclohexyl; a hydroxyl group; a cyano group; an alkoxy group such as methoxy or ethoxy; an optionally substituted amino group such as amino, methylamino or dimethylamino; an optionally substituted acyl group such as acetyl or propionyl; a carboxyl group; an optionally substituted aryl group such as phenyl or naphthyl; an optionally substituted heteroaryl group such as pyridinyl, thiazolyl, imidazolyl or pyrazyl; an optionally substituted saturated or unsaturated heterocycloalkyl group such as

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piperazinyl or morphonyl; an optionally substituted carbamoyl group; an optionally substituted amido group; a halogen atom such as chlorine, fluorine or bromine; a nitro group; an optionally substituted sulfone group; an optionally substituted sulfonylamido group; an oxo group; a urca group; and an optionally substituted linear, branched or
 5 cyclic alkenyl group such as ethenyl, propenyl or cyclohexenyl.

Examples of the heteroaryl group as R^3 include a 5- to 7-membered monocyclic heteroaryl group having 2 to 8 carbon atoms and containing 1 to 4 hetero atoms consisting of oxygen atoms, nitrogen atoms or sulfur atoms, and a polycyclic heteroaryl group comprising two or more such identical or different monocyclic compounds fused
 10 together, examples of the monocyclic and polycyclic heteroaryl groups being pyrrole, furyl, thienyl, imidazolyl, thiazolyl, pyridyl, pyrazyl, indolyl, quinolyl, isoquinolyl, and tetrazolyl.

In one embodiment, a PDE7 inhibitor useful in the invention has the formula:



Compound 1.

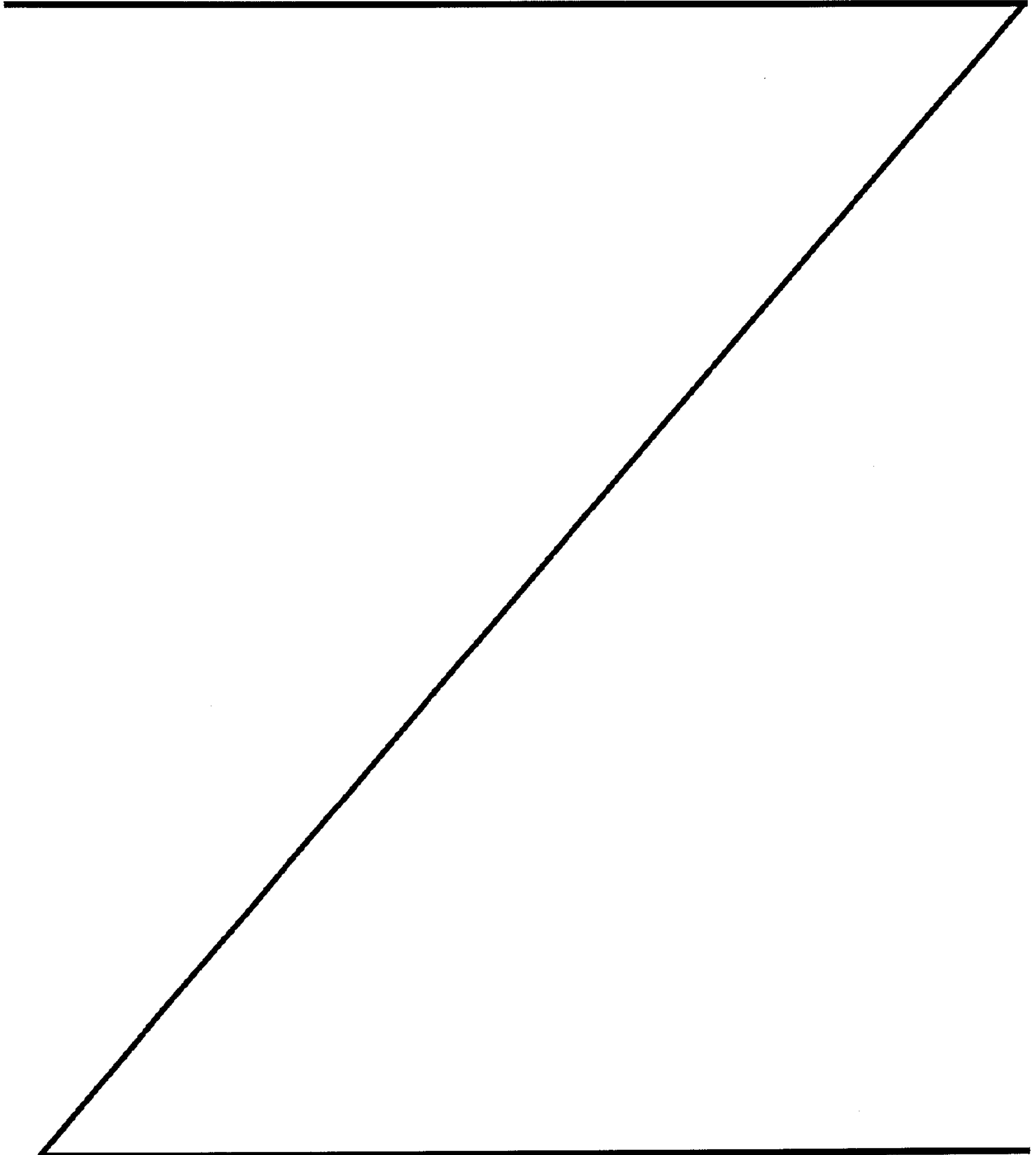
In others embodiments, PDE7 inhibitors useful in the methods of the invention have the formulas:

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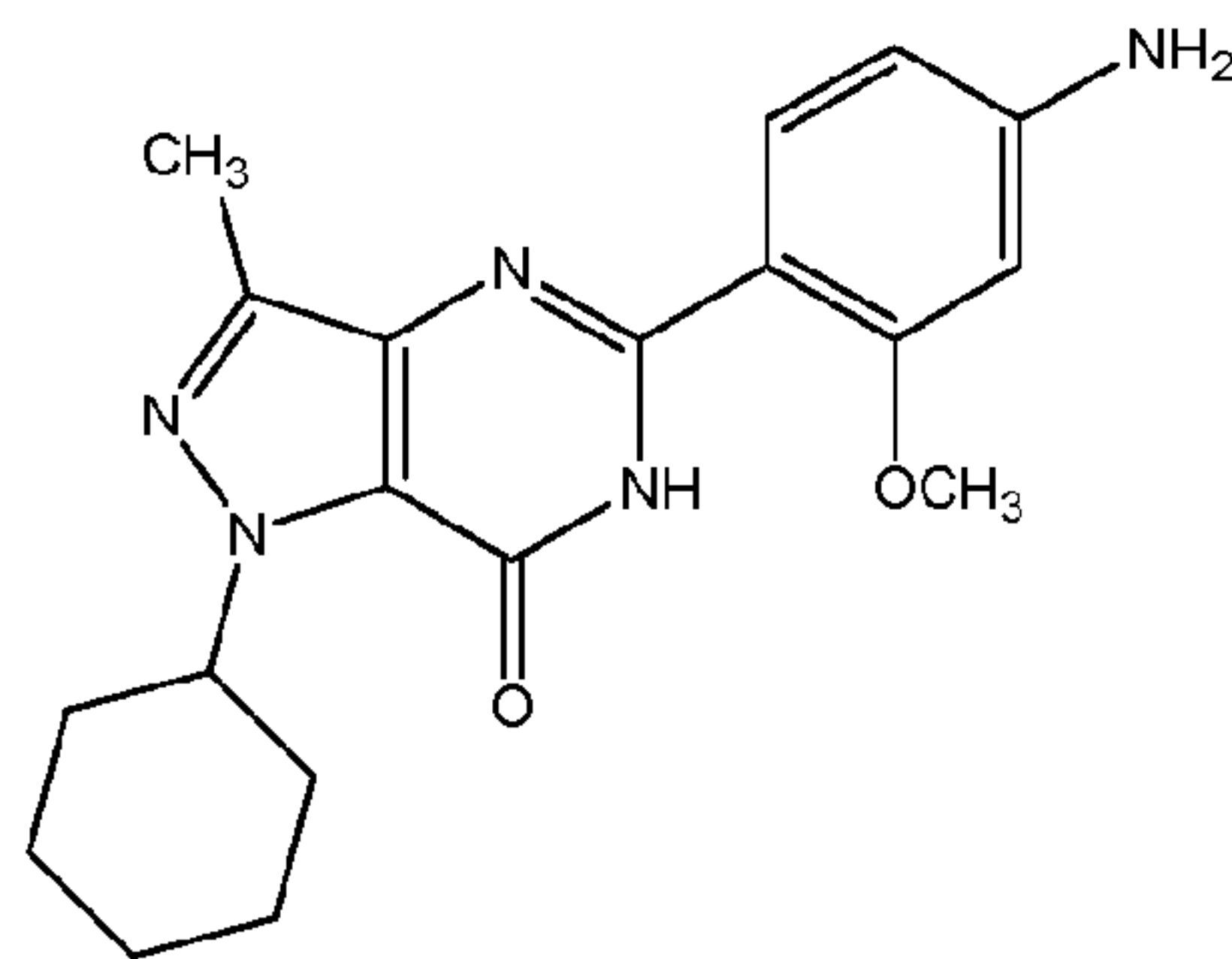
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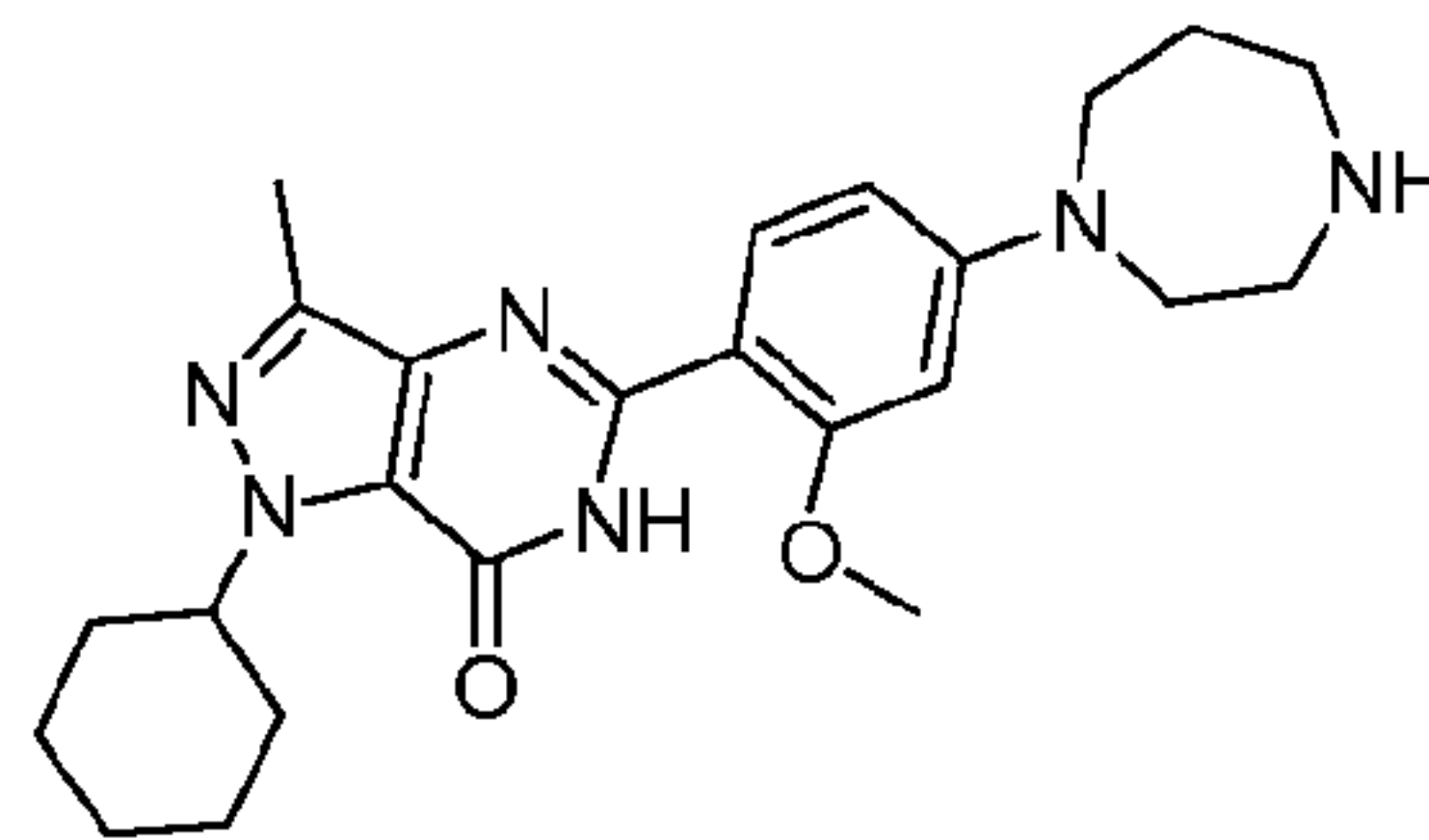
In another embodiment, a PDE7 inhibitor useful in the methods of the invention has the formula:



5

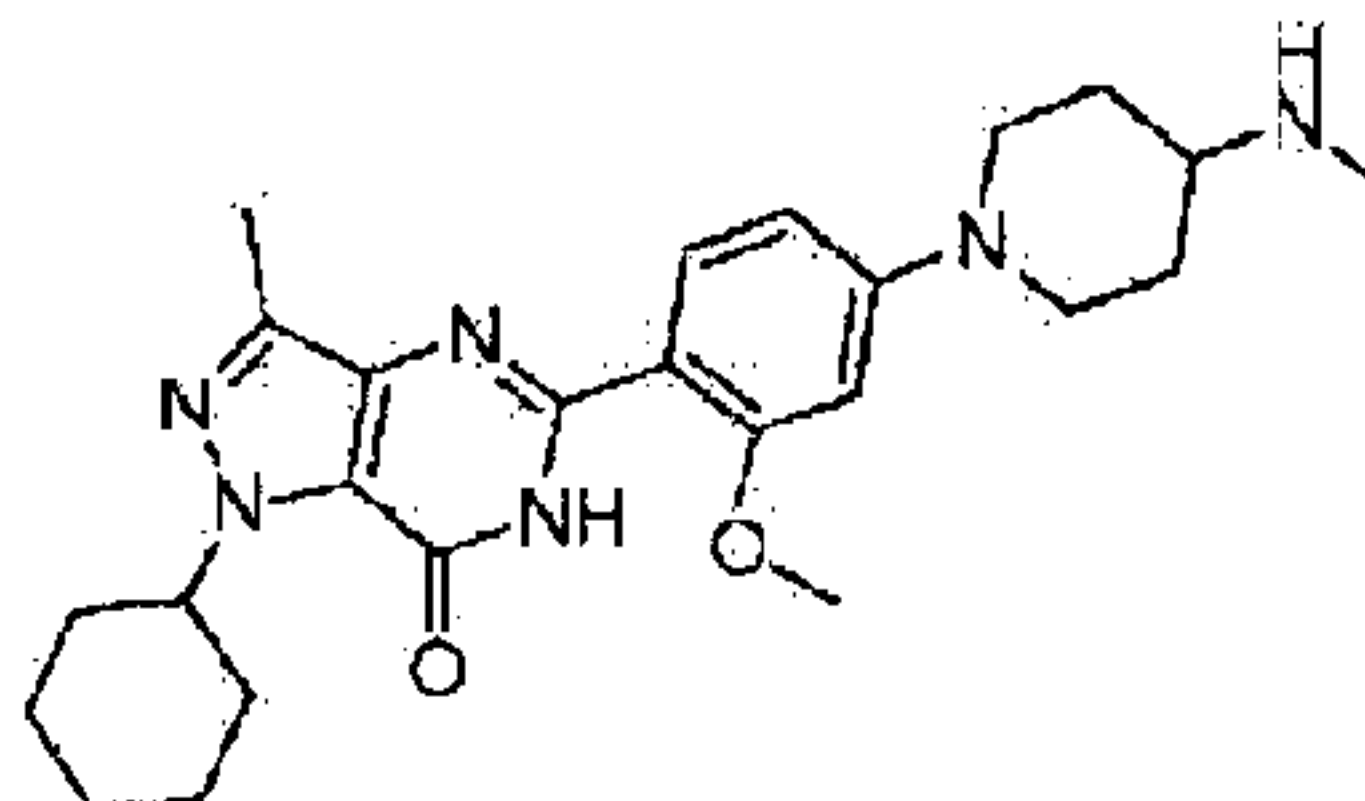
Compound 2.

In other embodiments, PDE7 inhibitors useful in the methods of the invention have the formulas:



10

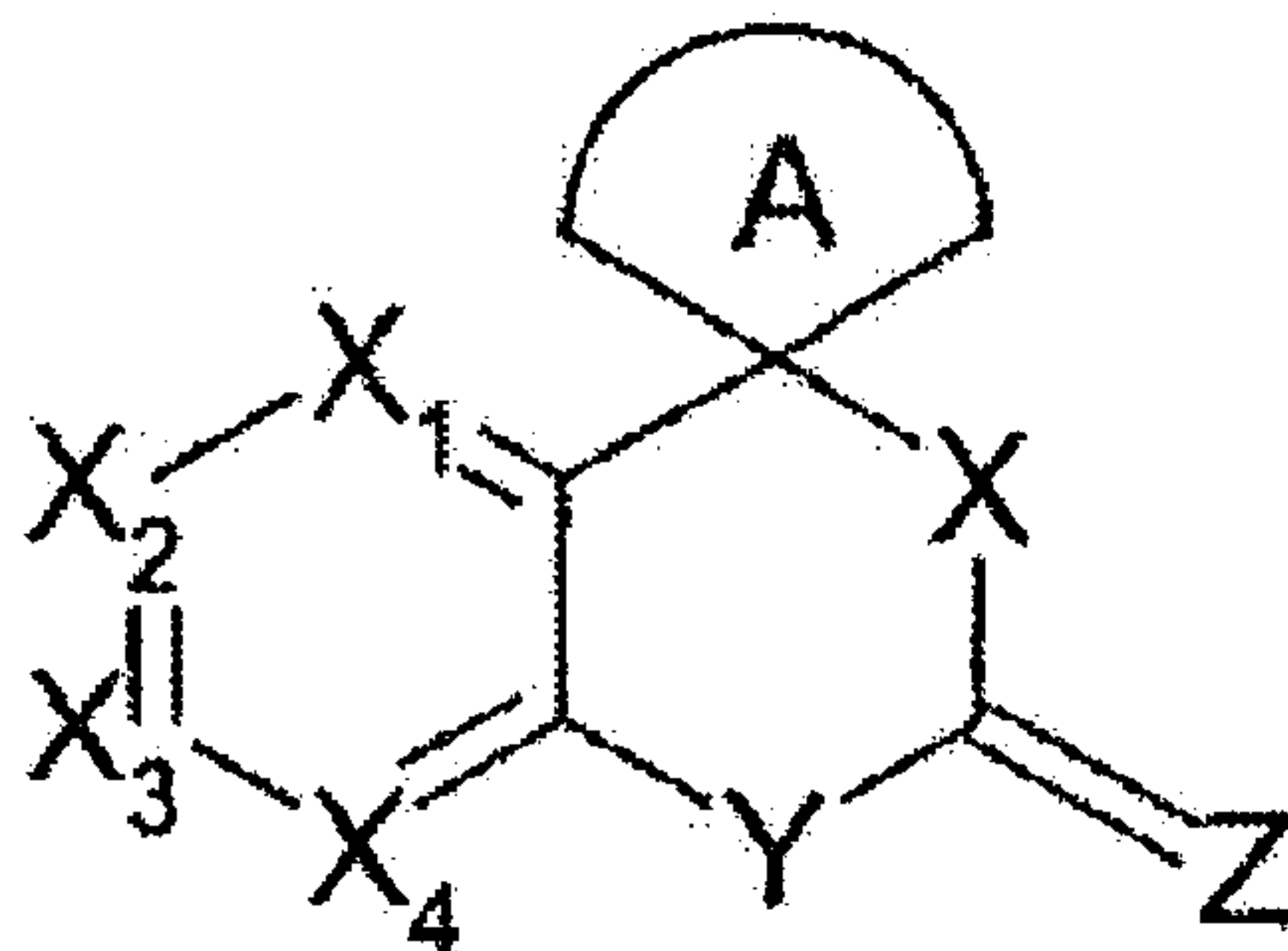
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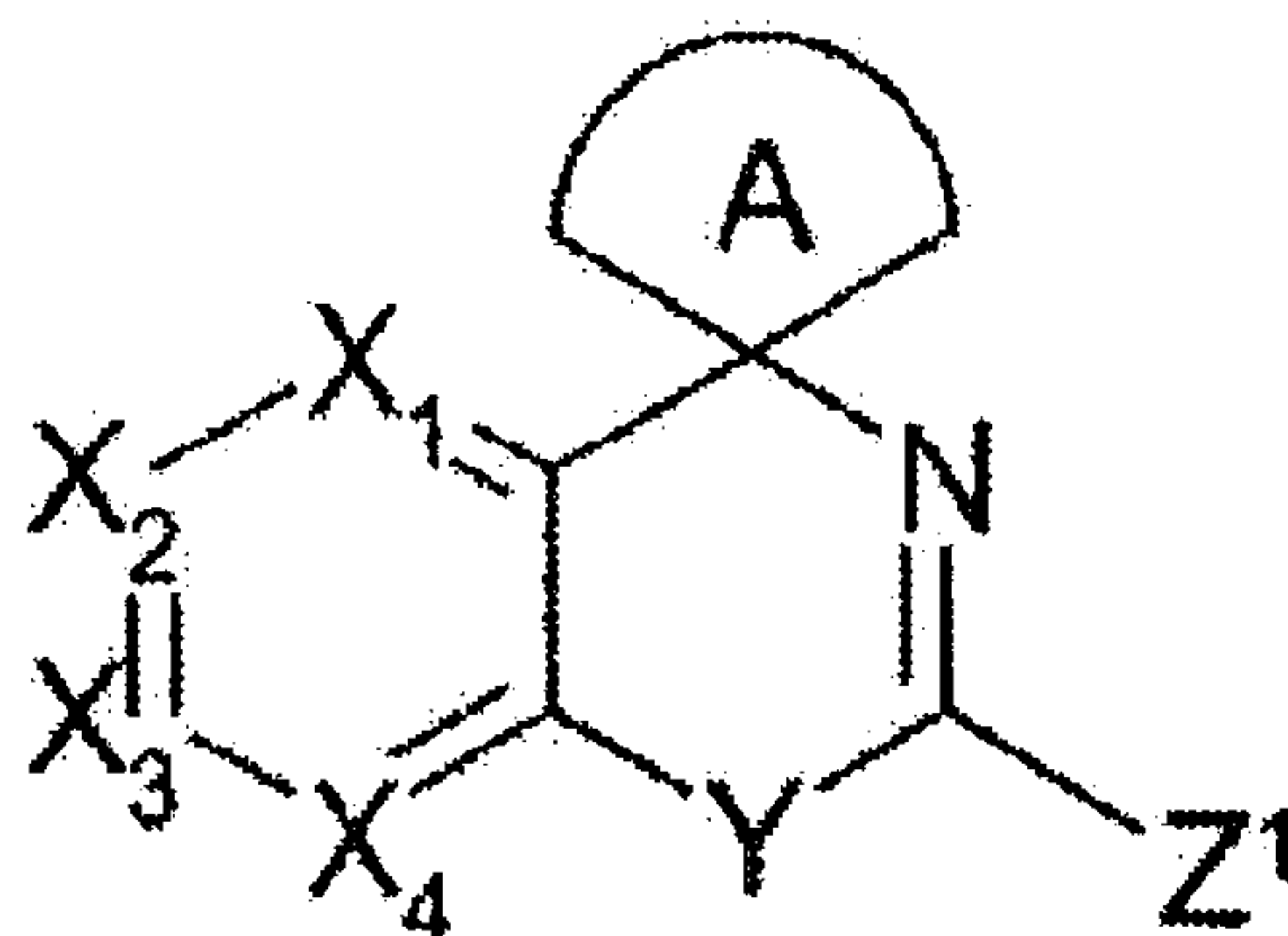
The preparation of the above compounds is described in EP 1 454 897, WO 2003/053975, and US 20050148604.

In another embodiment, PDE7 inhibitors useful in the methods of the invention
 5 are selected from those compounds generally or specifically disclosed in US 2002/0198198, WO 2002/076953, WO 2002/074754, WO 2006/092691, *Bioorganic & Medicinal Chemistry Letters* 14 (2004) 4623-4626, and *Bioorganic & Medicinal Chemistry Letters* 14 (2004) 4627-4631.

In one embodiment, PDE7 inhibitors useful in the methods of the
 10 invention have the formulas:

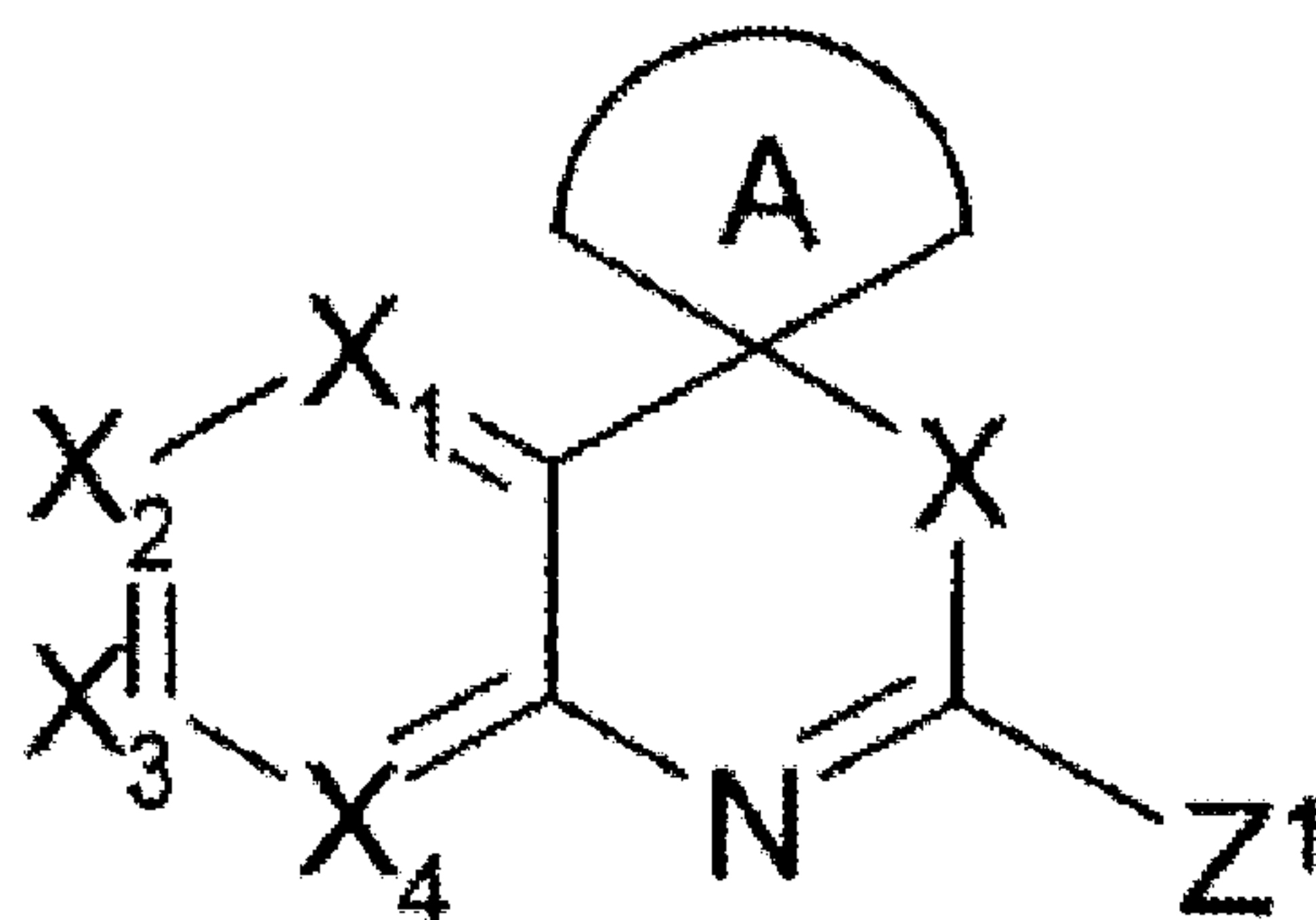


(2A)



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(2B)



(2C).

5 The substituents for the above compounds are defined as follows:

(a) X₁, X₂, X₃, and X₄ are the same or different and are selected from:

N, provided that not more than two of the groups X₁, X₂, X₃, and X₄ simultaneously represent a nitrogen atom, or,

C-R₁, in which R₁ is selected from:

10 Q₁, or

lower alkyl, lower alkenyl, or lower alkynyl, these groups being unsubstituted or substituted with one or several groups Q₂;

the group X₅-R₅ in which,

X₅ is selected from:

15 a single bond,

lower alkylene, lower alkenylene, or lower alkynylene; optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO₂, or N, the carbon atoms of these groups being unsubstituted or substituted with one or several groups, identical or different, selected from SR₆, OR₆, NR₆R₇, =O, =S, or =NR₆ in which R₆ and R₇ are the same or different and are selected from hydrogen or lower alkyl, and,

20 R₅ is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO₂, or

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N, cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO₂ or N, or a bicyclic group, these groups being unsubstituted or substituted with one or several groups selected from Q₃, heteroaryl, or lower alkyl optionally substituted with Q₃;

5 in which Q₁, Q₂, and Q₃ are the same or different and are selected from:

hydrogen, halogen, CN, NO₂, SO₃H, P(=O)(OH)₂, OR₂, OC(=O)R₂, C(=O)OR₂, SR₂, S(=O)R₂, NR₃R₄, Q-R₂, Q-NR₃R₄, NR₂-Q-NR₃R₄, or NR₃-Q-R₂ in which Q is selected from C(=NR), C(=O), C(=S), or SO₂, R is selected from
 10 hydrogen, or lower alkyl, and R₂, R₃, and R₄ are the same or different and are selected from:

hydrogen, lower alkyl optionally interrupted with C(=O), (CH₂)_n-aryl, (CH₂)_n-heteroaryl, (CH₂)_n-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO₂, or N, in which n is an integer selected from
 15 0, 1, 2, 3 or 4;

these groups being unsubstituted or substituted with one or several groups selected from lower alkyl, halogen, CN, CH₃, SO₃H, SO₂CH₃, CF₃, C(=O)NHSO₂CH₃, OR₆, COOR₆, C(=O)R₆, NR₆R₇, C(=O)NR₆R₇, or SO₂NR₆R₇, in which R₆ and R₇ are the same or different and are selected from hydrogen or lower alkyl
 20 optionally substituted with one or two groups selected from OR, COOR or NRR₈ in which R and R₈ are hydrogen or lower alkyl, and,

R₆ and R₇, and/or, R₃ and R₄, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O), SO₂, or N, and which may be
 25 substituted with,

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a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, or N, and which may be substituted with a lower alkyl, or,

a lower alkyl optionally substituted with OR', NR'R'', C(=O)NR'R'' or COOR' in which R' and R'' are the same or different and are selected from H, lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl, and R' and R'' together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, or N; or,

(b) X is O, S, or NR₉, in which R₉ is selected from hydrogen, CN, OH, NH₂, lower alkyl, lower alkenyl, or lower alkynyl, these groups being unsubstituted or substituted with cycloalkyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO₂, or N, cycloalkenyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO₂, or N, aryl, heteroaryl, OR₁₀, or NR₁₀R₁₁ in which R₁₀ and R₁₁ are the same or different and are selected from hydrogen or lower alkyl;

(c) Y is selected from O, S, or N-R₁₂, in which R₁₂ is selected from hydrogen, CN, OH, NH₂, lower alkyl, lower alkenyl, or lower alkynyl, these groups being unsubstituted or substituted with cycloalkyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO₂, or N, cycloalkenyl optionally interrupted with 1 or 2 heteroatoms chosen from O, S, S(=O), SO₂, or N, aryl, heteroaryl, OR₁₀, or NR₁₀R₁₁ in which R₁₀ and R₁₁ are the same or different and are selected from hydrogen or lower alkyl;

(d) Z is chosen from CH-NO₂, O, S, or NR₁₃ in which R₁₃ is selected from hydrogen, CN, OH, NH₂, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO₂, or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO₂, or N,

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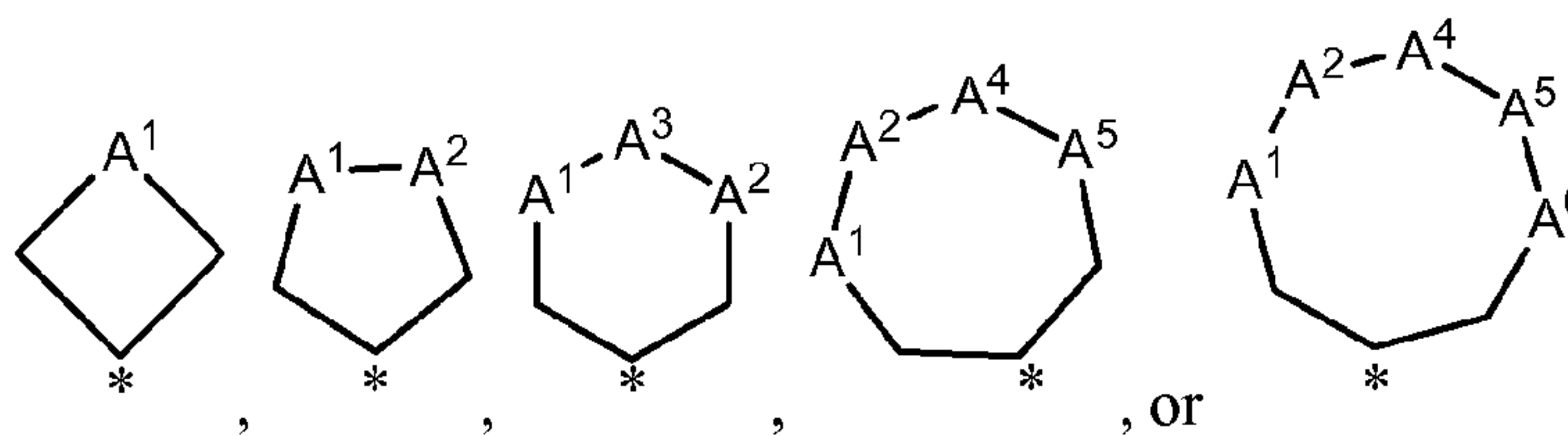
$C(=O)R_{14}$, $C(=O)NR_{14}R_{15}$, OR_{14} , or, lower alkyl, unsubstituted or substituted with one or several groups which are the same or different and which are selected OR_{14} or $NR_{14}R_{15}$;

R_{14} and R_{15} being independently selected from hydrogen or lower alkyl, or, R_{14} and R_{15} , together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms chosen from O, S, or N, and which may be substituted with a lower alkyl;

(e) Z_1 is chosen from H, CH_3 , or $NR_{16}R_{17}$ in which R_{16} and R_{17} are the same or different and are selected from hydrogen, CN, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, $S(=O)$, SO_2 , or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, $S(=O)$, SO_2 , or N, $C(=O)R_{14}$, $C(=O)NR_{14}R_{15}$, OR_{14} , or, lower alkyl unsubstituted or substituted with one or several groups selected from OR_{14} or $NR_{14}R_{15}$,

R_{14} and R_{15} being chosen from hydrogen or lower alkyl, and, R_{14} and R_{15} , and/or, R_{16} and R_{17} , together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms chosen from O, S, or N, and which may be substituted with a lower alkyl;

(f) A is a cycle selected from:



20 in which

A_1 , A_2 , A_3 , A_4 , A_5 , and A_6 are the same or different and are selected from O, S, C, $C(=O)$, SO, SO_2 , or NR_{18} in which R_{18} is selected from hydrogen, aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, $S(=O)$, SO_2 , or N, cycloalkenyl optionally interrupted with one or several heteroatoms

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chosen from O, S, S(=O), SO₂, or N, lower alkyl unsubstituted or substituted with aryl, heteroaryl, cycloalkyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO₂, or N, cycloalkenyl optionally interrupted with one or several heteroatoms chosen from O, S, S(=O), SO₂, or N, CN, NR₁₉R₂₀, C(=O)NR₁₉R₂₀, OR₁₉,
5 C(=O)R₁₉ or C(=O)OR₁₉ in which R₁₉ and R₂₀ are identical or different and are selected from hydrogen or lower alkyl;

* represents the carbon atom which is shared between the cycle A and the backbone cycle containing X and/or Y;

each carbon atom of the cycle A is unsubstituted or substituted with 1 or 2 groups,
10 identical or different, selected from lower alkyl optionally substituted with OR₂₁, NR₂₁R₂₂, COOR₂₁, or CONR₂₁R₂₂, lower haloalkyl, CN, F, =O, SO₂NR₁₉R₂₀, OR₁₉, SR₁₉, C(=O)OR₁₉, C(=O)NR₁₉R₂₀, or NR₁₉R₂₀ in which R₁₉ and R₂₀ are identical or different and are selected from hydrogen or lower alkyl optionally substituted with OR₂₁, NR₂₁R₂₂, COOR₂₁, or CONR₂₁R₂₂, in which R₂₁ and R₂₂ are identical or different and are selected
15 from hydrogen or lower alkyl, and, R₁₉ and R₂₀, and/or, R₂₁ and R₂₂, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;

two atoms of the cycle A, which are not adjacent, may be linked by a 2, 3 or 4 carbon atom chain which may be interrupted with 1 heteroatom chosen from O, S or N; provided that not more than two of the groups A₁, A₂, A₃, A₄, A₅, and A₆ simultaneously
20 represent a heteroatom; and

their tautomeric forms, their racemic forms, their isomers, and their pharmaceutically acceptable derivatives.

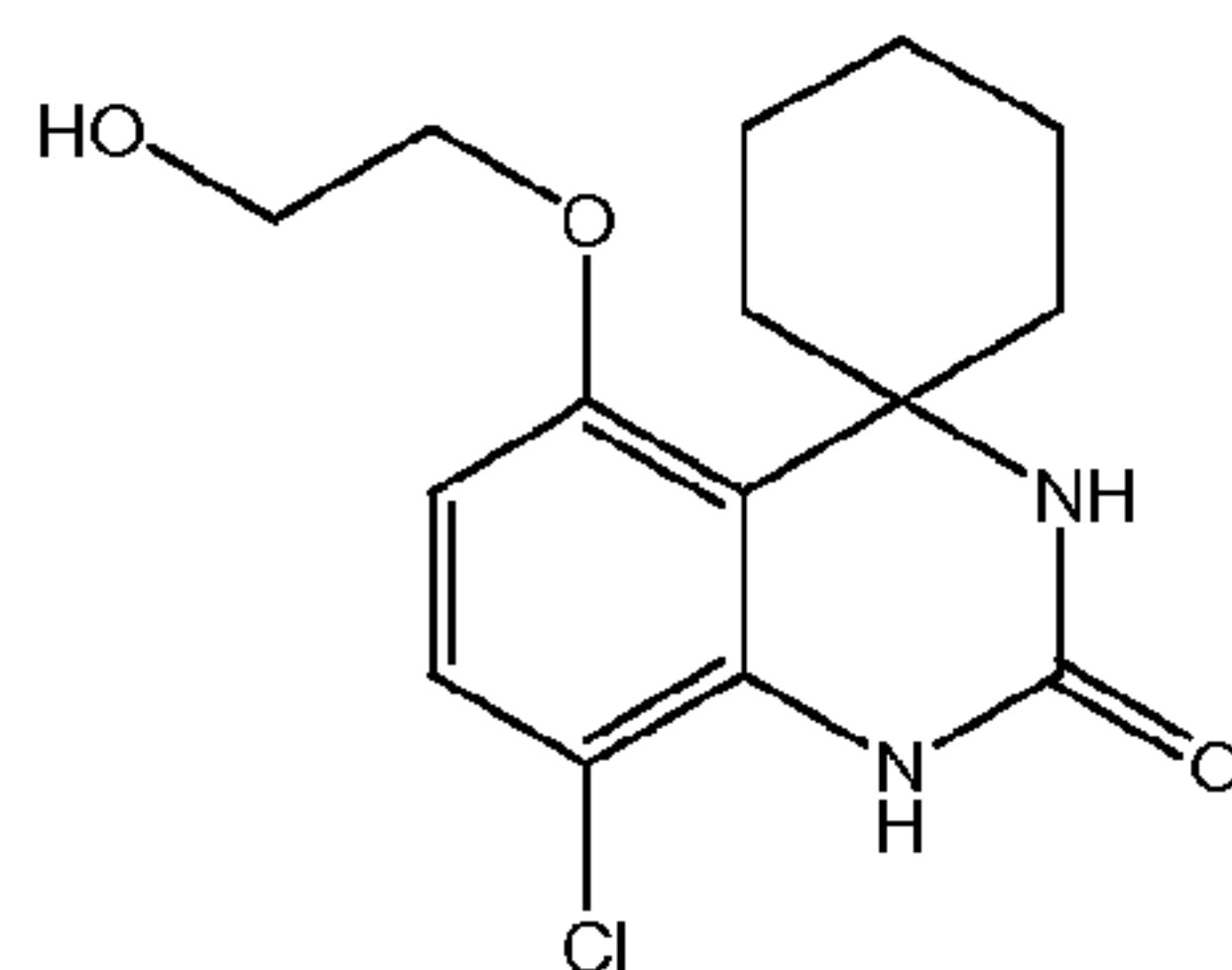
In regard to the above compounds, halogen includes fluoro, chloro, bromo, and iodo. Preferred halogens are F and Cl. Lower alkyl includes straight and branched
25 carbon chains having from 1 to 6 carbon atoms. Examples of such alkyl groups include methyl, ethyl, isopropyl, and tert-butyl. Lower alkenyl includes straight and branched

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hydrocarbon radicals having from 2 to 6 carbon atoms and at least one double bond. Examples of such alkenyl groups are ethenyl, 3-buten-1-yl, 2-ethenylbutyl, and 3-hexen-1-yl. Lower alkynyl includes straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and at least one triple bond. Examples of such alkynyl groups are ethynyl, 3-butyn-1-yl, propynyl, 2-butyn-1-yl, and 3-pentyn-1-yl. Lower haloalkyl includes a lower alkyl as defined above, substituted with one or several halogens. An example of haloalkyl is trifluoromethyl. Aryl is understood to refer to an aromatic carbocycle containing between 6 and 10 carbon atoms. An example of an aryl group is phenyl. Heteroaryl includes aromatic cycles which have from 5 to 10 ring atoms, from 1 to 4 of which are independently selected from the group consisting of O, S, and N. Representative heteroaryl groups have 1, 2, 3 or 4 heteroatoms in a 5- or 6-membered aromatic ring. Examples of such groups are tetrazole, pyridyl, and thienyl. Representative cycloalkyl contain from 3 to 8 carbon atoms. Examples of such groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. The term "interrupted" means that in a backbone chain, a carbon atom is replaced by an heteroatom or a group as defined herein. For example, in "cycloalkyl or cycloalkenyl optionally interrupted with C(=O) or with 1 heteroatom chosen from O, S, S(=O), SO₂ or N", the term "interrupted" means that C(=O) or a heteroatom can replace a carbon atom of the ring. Example of such groups are morpholine or piperazine. Cycloalkenyl includes 3- to 10- membered cycloalkyl containing at least one double bond. Heterocyclic rings include heteroaryl as defined above and cycloalkyl or cycloalkenyl, as defined above, interrupted with 1, 2 or 3 heteroatoms chosen from O, S, S(=O), SO₂, or N. Bicyclic substituents refer to two cycles, which are the same or different and which are chosen from aryl, heterocyclic ring, cycloalkyl or cycloalkenyl, fused together to form said bicyclic substituents. An example of a bicyclic substituent is indolyl.

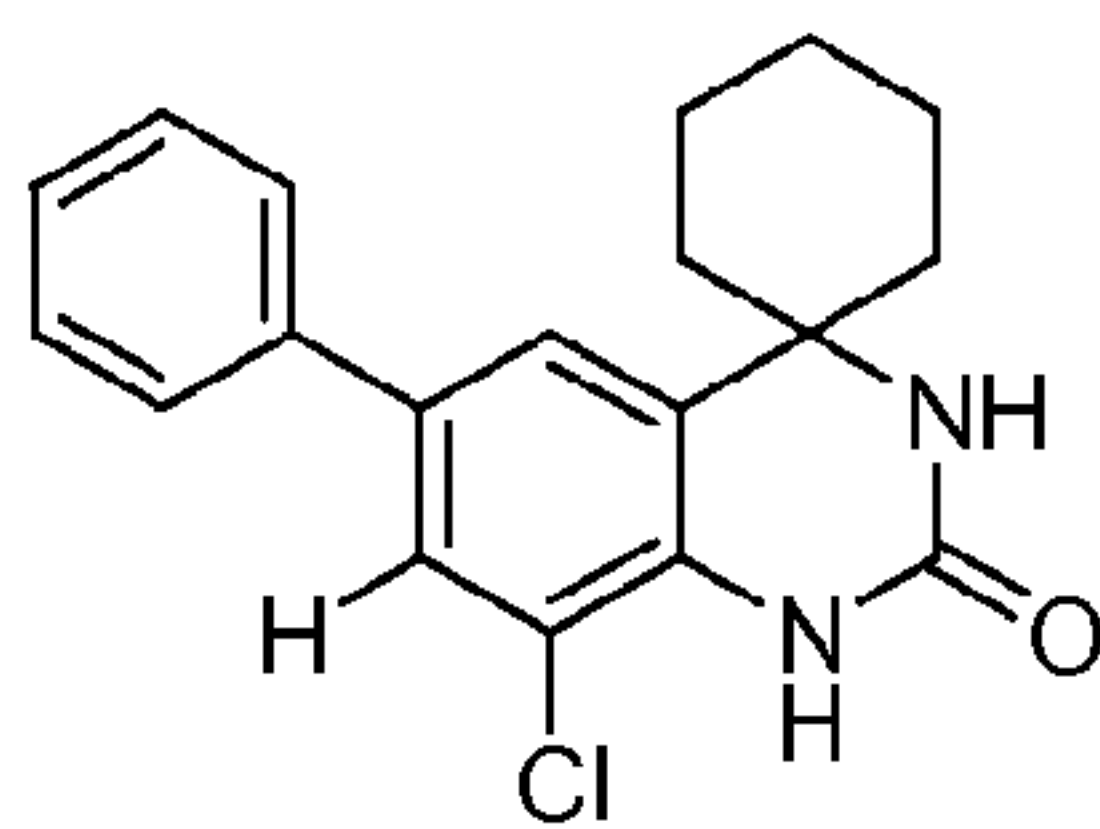
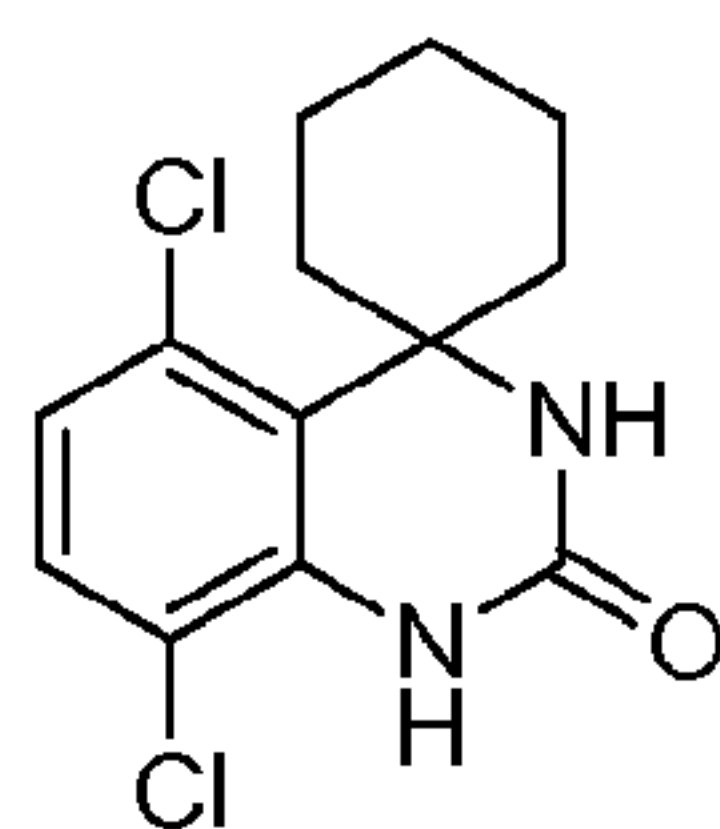
-83-

In one embodiment, a PDE7 inhibitor useful in the methods of the invention has the formula:



Compound 3.

In other embodiments, PDE7 inhibitors useful in the methods of the invention
5 have the formulas:

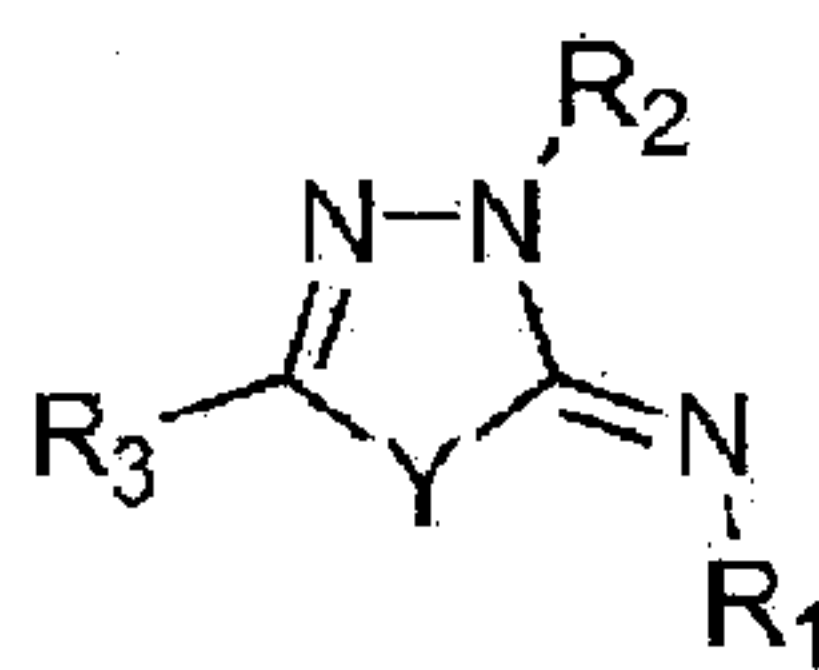


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The preparation of the above compounds is described in US 2002/0198198, WO 2002/076953, WO 2002/074754, WO 2006/092691, *Bioorganic & Medicinal Chemistry Letters* 14 (2004) 4623-4626, and *Bioorganic & Medicinal Chemistry Letters* 14 (2004) 4627-4631.

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In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in EP 1 193 261, WO 2002/28847, US 20030045557, U.S. Patent No. 7,122,565, *Bioorganic & Medicinal Chemistry Letters* 14 (2004) 4607-4613, and *Bioorganic & Medicinal Chemistry Letters* 14 (2004) 4615-4621. In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



(3)

10 The substituents for the above compounds are defined as follows:

Y is S or O;

R₁ is C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, cycloalkyl, cycloalkenyl, heterocycle, aryl, or a polycyclic group; each optionally substituted with one or several groups X₁-R₄, identical or different, in which X₁ is a single bond, lower alkylene, C₂-C₆ alkenylene, cycloalkylene, arylene, or divalent heterocycle, and R₄ is:

- (1) H, =O, NO₂, CN, halogen, lower haloalkyl, lower alkyl, carboxylic acid bioisostere;
- (2) COOR₅, C(=O)R₅, C(=S)R₅, SO₂R₅, SOR₅, SO₃R₅, SR₅, OR₅;
- (3) C(=O)NR₇R₈, C(=S)NR₇R₈, C(=CH-NO₂)NR₇R₈, C(=N-CN)NR₇R₈, C(=N-SO₂NH₂)NR₇R₈, C(=NR₇)NHR₈, C(=NR₇)R₈, C(=NR₉)NHR₈, C(=NR₉)R₈, SO₂NR₇R₈, or NR₇R₈, wherein R₇ and R₈ are the same or different and are selected from OH, R₅, R₆, C(=O)NR₅R₆, C(=O)R₅, SO₂R₅, C(=NR₉)NHR₁₀, C(=NR₉)R₁₀, C(=CH-NO₂)NR₉R₁₀, C(=N-SO₂NH₂)NR₉R₁₀, C(=N-CN)NR₉R₁₀, or C(=S)NR₉R₁₀;

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R_2 is lower alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, cycloalkyl, cycloalkenyl, heterocycle, aryl; each optionally substituted with one or several groups which are the same or different and which are selected from:

- (1) H, carboxylic acid bioisostere, lower haloalkyl, halogen,
- 5 (2) $COOR_5$, OR_5 , SO_2R_5 ,
- (3) $SO_2NR_{11}R_{12}$, $C(=O)NR_{11}R_{12}$, $NR_{11}R_{12}$, wherein R_{11} and R_{12} are the same or different and are selected from OH, R_5 , R_6 , $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5 , $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, or $C(=NR_9)R_{10}$;

- 10 R_3 is $X_2-R'_3$, wherein X_2 is a single bond or, a group selected from C_1 - C_4 alkylene, C_2 - C_6 alkenylene, C_2 - C_6 alkynylene, each optionally substituted with one or several groups which are the same or different and which are selected from:

- (1) H, C_1 - C_3 alkyl, C_3 - C_4 cycloalkyl, aryl, heterocycle, $=O$, CN,
- (2) OR_5 , $=NR_5$; or
- 15 (3) $NR_{13}R_{14}$, wherein R_{13} and R_{14} are the same or different and are selected from R_5 , R_6 , $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5 , $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$, or $C(=NR_9)R_{10}$;

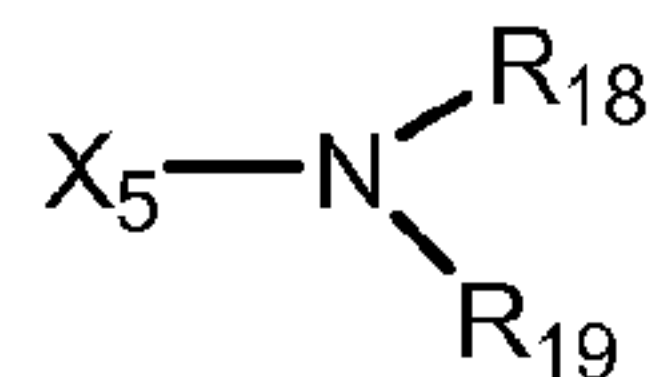
- R'_3 is cycloalkyl, cycloalkenyl, aryl, heterocycle, or a polycyclic group; each optionally substituted with one or several groups X_3 - R_{17} wherein X_3 is a single bond,
- 20 lower alkylenc, C_2 - C_6 alkenylenc, C_2 - C_6 alkynylenc, cycloalkylenc, arylenc, divalent heterocycle or a divalent polycyclic group, and, R_{17} is:

- (1) H, $=O$, NO_2 , CN, lower haloalkyl, halogen, carboxylic acid bioisostere, cycloalkyl,
- (2) $COOR_5$, $C(=O)R_5$, $C(=S)R_5$, SO_2R_5 , SOR_5 , SO_3R_5 , SR_5 , OR_5 ;
- 25 (3) $C(=O)NR_{15}R_{16}$, $C(=S)NR_{15}R_{16}$, $C(=N-CN)NR_{15}R_{16}$, $C(=N-SO_2NH_2)NR_{15}R_{16}$, $C(=CH-NO_2)NR_{15}R_{16}$, $SO_2NR_{15}R_{16}$, $C(=NR_{15})NHR_{16}$, $C(=NR_{15})R_{16}$,

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$C(=NR_9)NHR_{16}$, $C(=NR_9)R_{16}$, or $NR_{15}R_{16}$ wherein R_{15} and R_{16} are the same or different and are selected from OH, R_5 , R_6 , $C(=O)NR_5R_6$, $C(=O)R_5$, SO_2R_5 , $C(=S)NR_9R_{10}$, $C(=CH-NO_2)NR_9R_{10}$, $C(=N-CN)NR_9R_{10}$, $C(=N-SO_2NH_2)NR_9R_{10}$, $C(=NR_9)NHR_{10}$ or $C(=NR_9)R_{10}$,

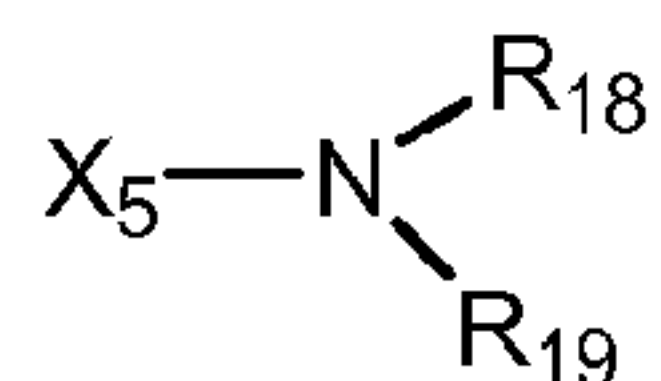
- 5 (4) heterocycle optionally substituted with one or several groups R_5 ;
 wherein R_5 and R_6 are the same or different and are selected from H, lower alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, X_4 -cycloalkyl, X_4 -cycloalkenyl, X_4 -aryl, X_4 -heterocycle or X_4 -polycyclic group, wherein X_4 is a single bond, lower alkylene, or C_2-C_6 alkenylene; each optionally substituted with one or several groups that are the same or different and
 10 selected from halogen, =O, $COOR_{20}$, CN, OR_{20} , O-lower alkyl optionally substituted with OR_{20} , $C(=O)$ -lower alkyl, lower haloalkyl,



- 15 in which X_5 is a single bond or lower alkylene and R_{18} , R_{19} , and R_{20} , are the same or different and are selected from H or lower alkyl;

- X_6 -heterocycle, X_6 -aryl, X_6 -cycloalkyl, X_6 -cycloalkenyl, or X_6 -polycyclic group, wherein X_6 is a single bond or lower alkylene, these groups being optionally substituted with one or several groups, identical or different, selected from halogens, $COOR_{21}$, OR_{21} ,
 20 or $(CH_2)_nNR_{21}R_{22}$ in which n is 0, 1, or 2 and R_{21} and R_{22} are the same or different and are selected from H or lower alkyl;

R_9 is selected from H, CN, OH, lower alkyl, O-lower alkyl, aryl, heterocycle, SO_2NH_2 , or



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in which X_5 is a single bond or lower alkylene and R_{18} and R_{19} are the same or different and are selected from H or lower alkyl;

R_{10} is selected from hydrogen, lower alkyl, cyclopropyl, or heterocycle;

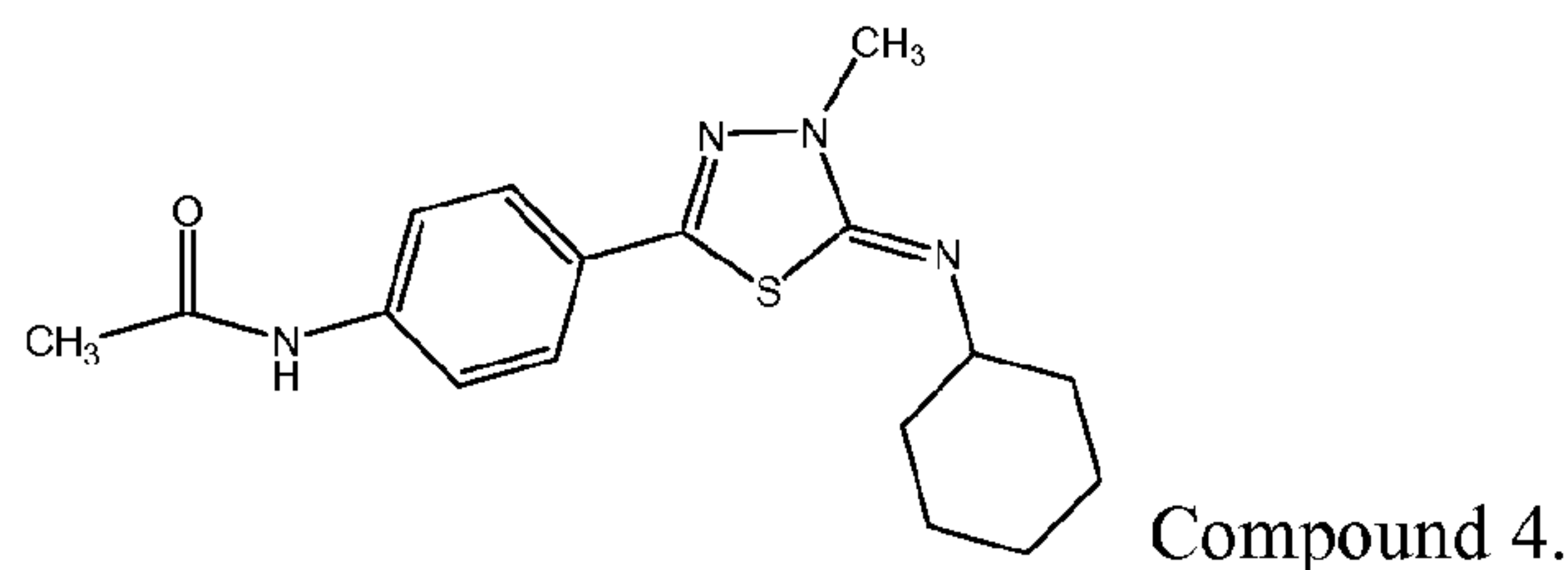
5 or their pharmaceutically acceptable derivatives.

In regard to the above compounds, aryl refers to an unsaturated carbocycle, exclusively comprising carbon atoms in the cyclic structure, the number of which is between 5 and 10, including phenyl, naphthyl, or tetrahydronaphthyl. Heterocycle refers to a nonsaturated or saturated monocycle containing between 1 and 7 carbon atoms in the
10 cyclic structure and at least one heteroatom in the cyclic structure, such as nitrogen, oxygen, or sulfur, preferably from 1 to 4 heteroatoms, identical or different, selected from nitrogen, sulfur and oxygen atoms. Suitable heterocycles include morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, pyrimidinyl, 2- and 3-furanyl, 2- and 3-thienyl, 2-pyridyl, 2- and 3-pyranyl, hydroxypyridyl, pyrazolyl, isoxazolyl, tetrazole, imidazole, triazole, and the like. Polycyclic groups include at least two cycles, identical or different,
15 selected from aryl, heterocycle, cycloalkyl, cycloalkenyl groups fused together to form said polycyclic group such as 2- and 3-benzothienyl, 2- and 3-benzofuranyl, 2-indolyl, 2- and 3-quinolinyl, acridinyl, quinazolinyl, indolyl benzo[1,3]dioxolyl, and 9-thioxantanyl. Bicyclic groups refer to two cycles, which are the same or different and which are chosen
20 from aryl, heterocycle, cycloalkyl or cycloalkenyl, fused together to form said bicyclic groups. Halogen refers to fluorine, chlorine, bromine, or iodine. Lower alkyl refers to an alkyl is linear or branched and contains 1 to 6 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, butyl, isopropyl, tert-butyl, isobutyl, n-butyl, pentyl, hexyl and the like. Alkenyl refers to a linear or branched unsaturated carbon atom chain,
25 comprising one or several double bonds, preferably one or two double bonds. Alkynyl refers to a linear or branched unsaturated carbon atom chain, comprising one or several triple bonds, preferably one or two triple bonds. Lower haloalkyl refers to a lower alkyl

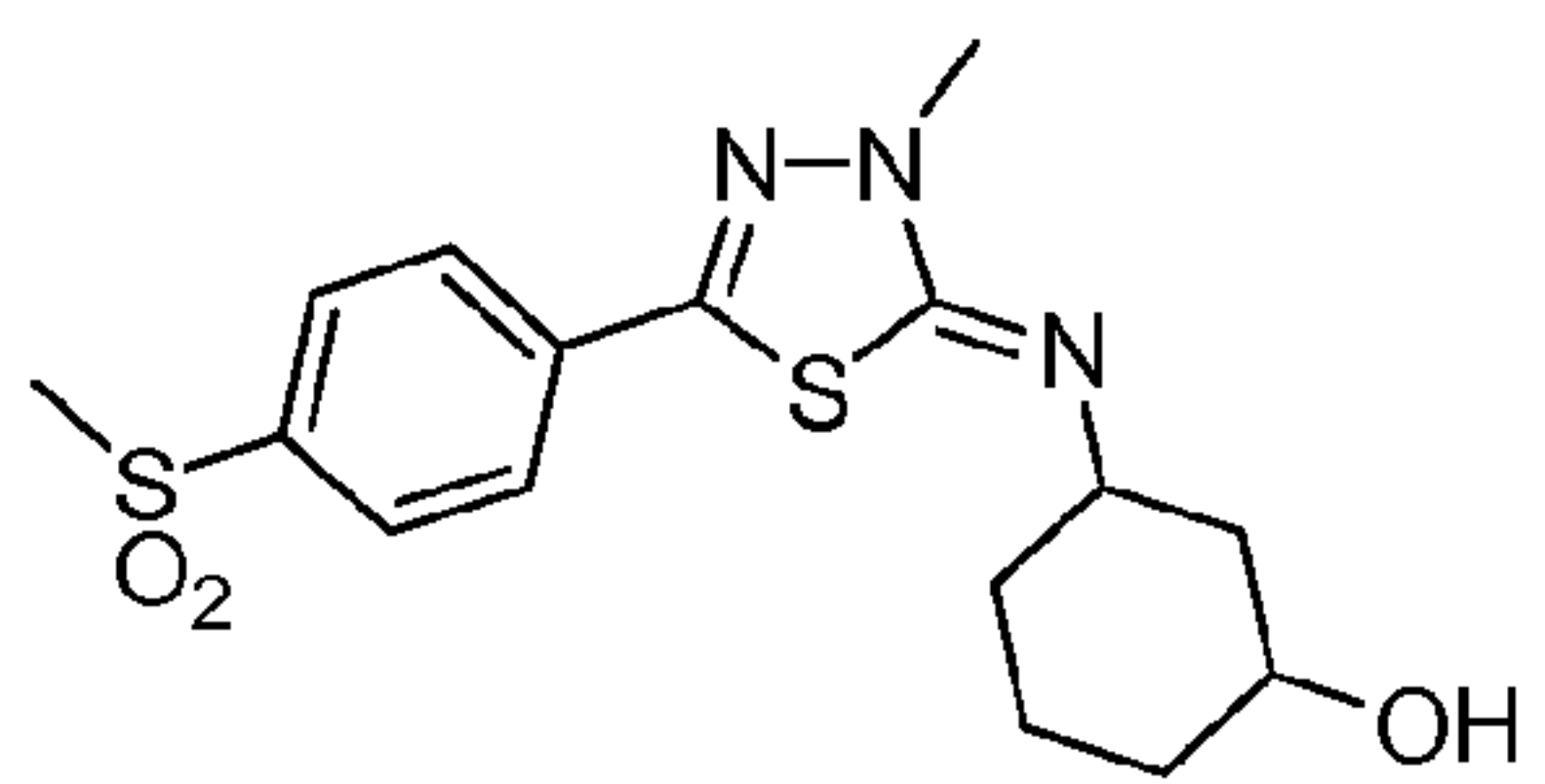
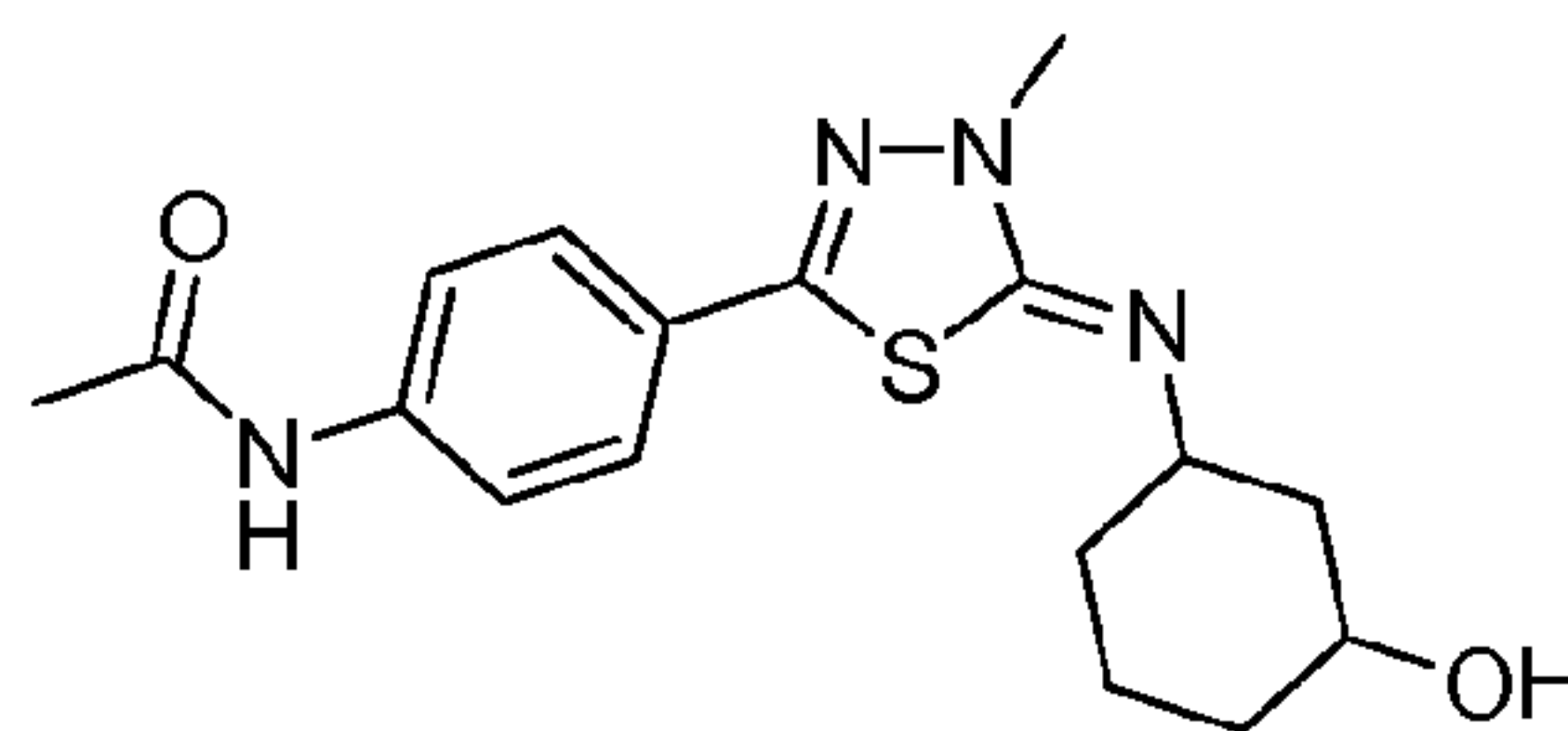
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substituted with one or several halogens; preferred lower haloalkyl groups include perhaloalkyl groups such as CF_3 . Cycloalkyl refers to saturated monocarbocycle containing from 3 to 10 carbon atoms; including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. Cycloalkenyl refers to unsaturated monocarbocycle containing from 3 to 10 carbon atoms. Examples of suitable cycloalkenyl are 3-cyclohexene, and 3-cycloheptene. Carboxylic acid bioisostere has the classical meaning; common carboxylic acid bioisostere are tetrazole-5-yl, $\text{C}(=\text{O})\text{N}(\text{H})\text{OH}$, isoxazol-3-yl, hydroxythiadiazolyl, sulfonamido, sulfonylcarboxamido, phosphonic acid, phosphonamido, phosphinic acid, sulfonic acids, acyl sulfonamido, mercaptoazole, acyl cyanamides.

In one embodiment, a PDE7 inhibitor useful in the methods of the invention has the formula:



In other embodiments, PDE7 inhibitors useful in the methods of the invention have the formulas:



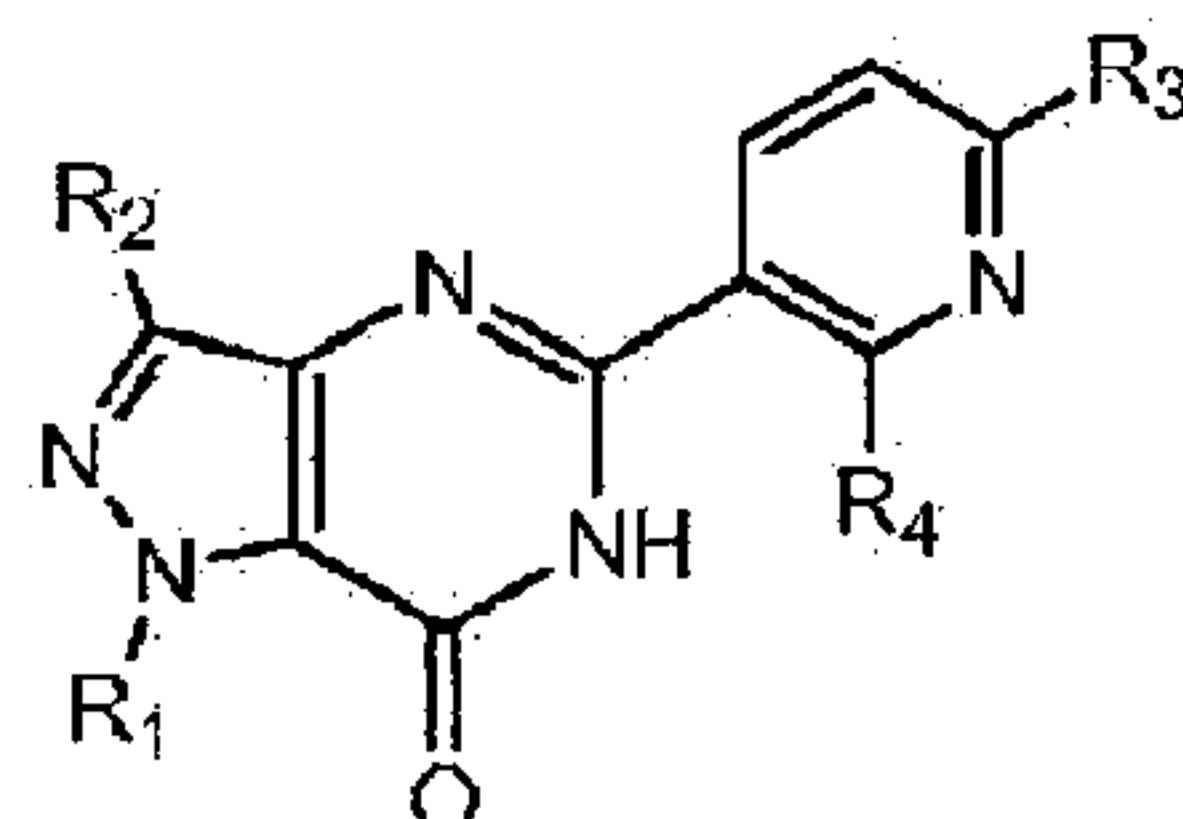
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The preparation of the above compounds is described in EP 1 193 261, WO 02/28847, US 20030045557, U.S. Patent No. 7,122,565, *Bioorganic & Medicinal Chemistry Letters* 14 (2004) 4607-4613, and *Bioorganic & Medicinal Chemistry Letters* 14 (2004) 4615-4621.

5 In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in WO 2004/111054, US 20060128728, and US 20070270419.

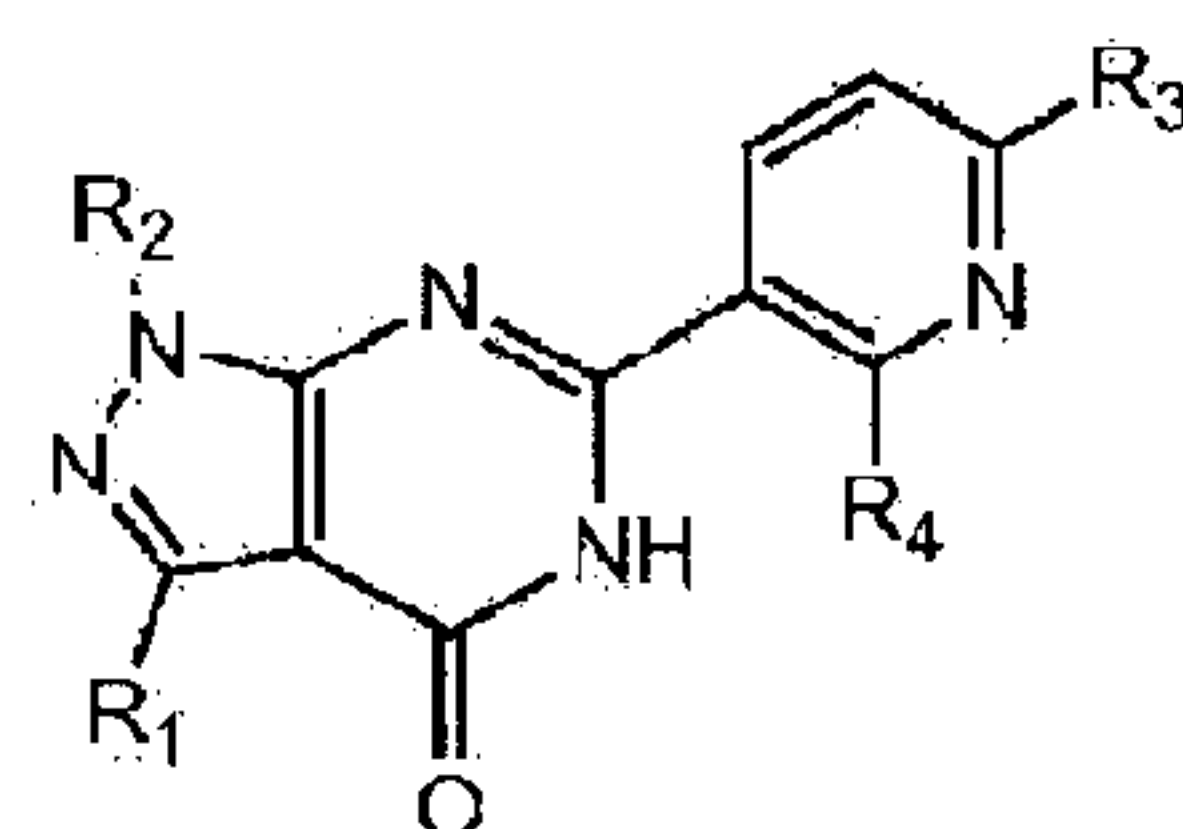
In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formulas:

10



(4A)

and



(4B)

15

The substituents for the above compounds are defined as follows:

R₁ is a substituted or unsubstituted C₃₋₈ cycloalkyl group or tert-butyl group;

R₂ is a hydrogen atom or C₁₋₃ alkyl group;

R₃ is a group: NR₅R₆, C(=O)R₇, or S(O)₀₋₂R₈;

20 R₄ is a hydrogen atom or C₁₋₃ alkoxy group which is unsubstituted or substituted by one or more fluorine atom(s);

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R₅ and R₆ are, same or different from each other, a hydrogen atom, substituted or unsubstituted C₁₋₆ alkyl group, substituted or unsubstituted acyl group, substituted or unsubstituted heterocycloalkyl group, and substituted or unsubstituted heterocycloalkyl ring formed with a nitrogen atom which is binding R₅ and R₆;

5 R₇ is a group: OR₉ or NR₅R₆;

R₈ is a hydrogen atom, a halogen atom, a group: NR₅R₆, substituted or unsubstituted C₁₋₆ alkyl group, or substituted or unsubstituted aryl group;

R₉ is a hydrogen atom or substituted or unsubstituted C₁₋₆ alkyl group;

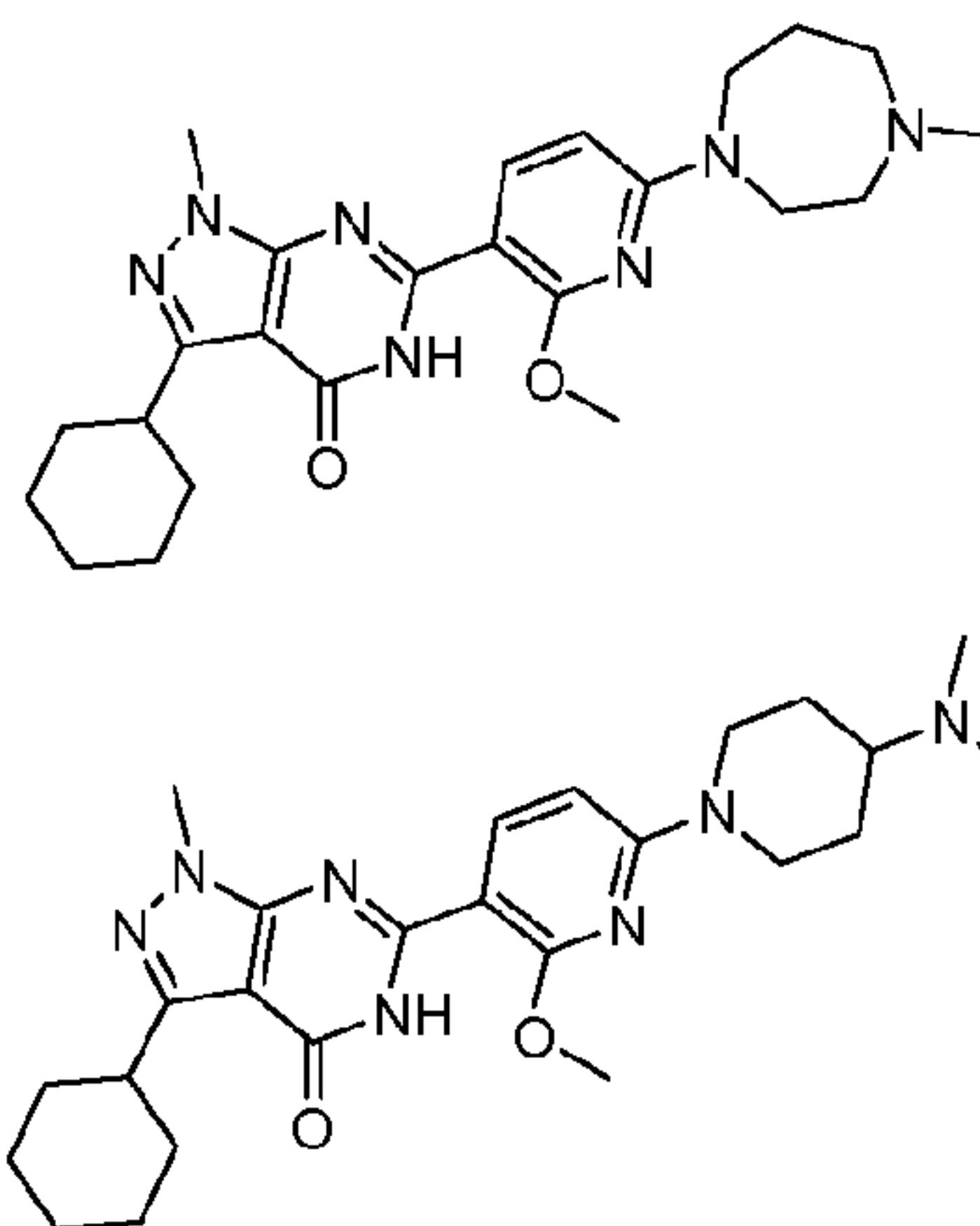
or pharmaceutically acceptable salts or solvates thereof.

10 In regard to the above compounds, the term "C₁-C₃ alkyl group" includes a straight or branched-chained alkyl group having 1 to 3 carbon atoms. The term "C₃-C₈ cycloalkyl group" includes a cycloalkyl group having 3 to 8 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cyclooctyl. The term "heterocycloalkyl group" is 3 to 7 membered heterocyclic group containing the same or
15 different 1 to 4 hetero atom(s) such as oxygen, nitrogen or sulfur atom(s), and examples may include pyrrolidinyl, piperidinyl, piperazinyl, homopiperazinyl, tetrahydrofuryl, tetrahydrophyranyl, morpholinyl and azetidiny. The term "C₁-C₃ alkoxy group" means alkoxy group having 1 to 3 carbon atoms. The term "acyl group" means acyl group having 1 to 8 carbon atoms. The term "aryl group" is phenyl, naphthyl, biphenyl group,
20 having 6 to 12 carbon atoms, and the term "heteroaryl group" is 5 to 7 membered monocyclic or polycyclic group thereof containing 2 to 8 carbon atoms and the same or different 1 to 4 hetero atom(s) such as oxygen, nitrogen, sulfur atom(s). The examples include pyrrole, furyl, thienyl, imidazolyl, thiazolyl, pyrazinyl, indolyl, quinolinyl, isoquinolinyl, tetrazolyl, pyridinyl, pyrazolyl pyridazinyl and pyrimidinyl. Examples of
25 suitable substituent of "substituted or unsubstituted C₁-C₆ alkyl group" include hydroxyl group and halogen atom, and examples of suitable substituent of "substituted or

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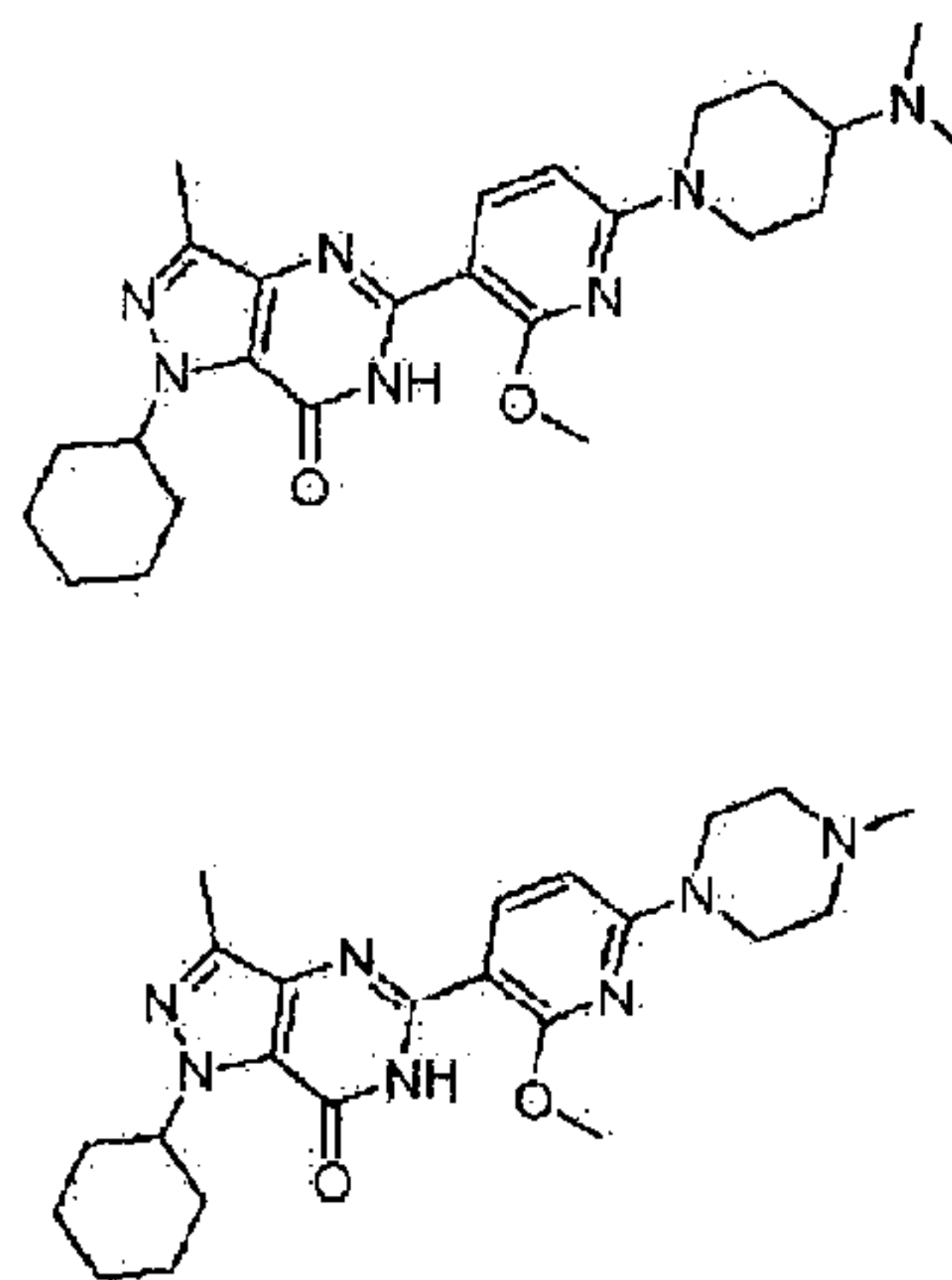
unsubstituted acyl group" include halogen atom and nitro group. Further, examples of suitable substituent of "substituted or unsubstituted aryl group" include C₁-C₃ alkyl, halogen atom, amino group, acyl group, amide group, hydroxyl group, acylamino group, carboxyl group and sulfonyl group. Examples of suitable substituent of "substituted or unsubstituted C₃-C₈ cycloalkyl group" is C₁-C₃ alkyl, hydroxyl group and oxo group, and examples of suitable substituent of "substituted or unsubstituted heterocycloalkyl group" may include carboxy group, acyl group, alkoxy group, amino group, alkylamino group, acylamino group, hydroxyl group, oxo group, ethylenedioxy group, methyl group, ethyl group and hydroxyethyl group.

10 In other embodiments, PDE7 inhibitors useful in the methods of the invention have the formulas:



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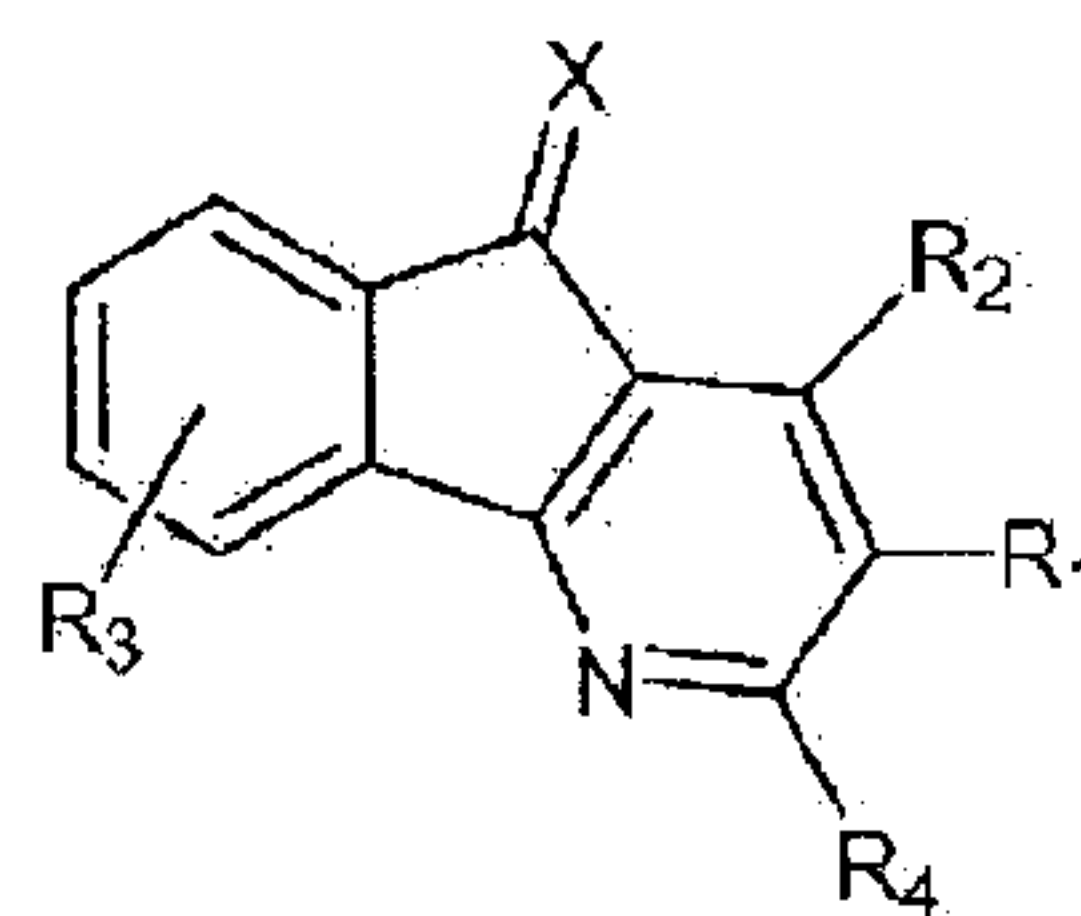
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The preparation of the above compounds is described in WO 2004/111054, US 20060128728, and US 20070270419.

In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in U.S. Patent No. 6,903,109, US 20040082578, WO 2003/088963, and US 20060154949 .

10

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



(5)

15

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The substituents for the above compounds are defined as follows:

(a) R_1 is selected from the group consisting of:

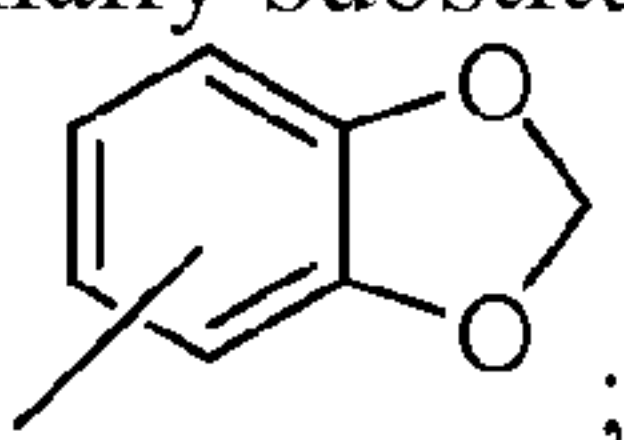
- (i) COR_5 , wherein R_5 is selected from H, optionally substituted C_{1-8} straight or branched chain alkyl, optionally substituted aryl and optionally substituted arylalkyl; wherein the substituents on the alkyl, aryl and arylalkyl group are selected from C_{1-8} alkoxy, phenylacetyloxy, hydroxy, halogen, p-tosyloxy, mesyloxy, amino, cyano, carboalkoxy, or $NR_{20}R_{21}$ wherein R_{20} and R_{21} are independently selected from the group consisting of hydrogen, C_{1-8} straight or branched chain alkyl, C_{3-7} cycloalkyl, benzyl, or aryl;
- (ii) $COOR_6$, wherein R_6 is selected from H, optionally substituted C_{1-8} straight or branched chain alkyl, optionally substituted aryl and optionally substituted arylalkyl; wherein the substituents on the alkyl, aryl and arylalkyl group are selected from C_{1-8} alkoxy, phenylacetyloxy, hydroxy, halogen, p-tosyloxy, mesyloxy, amino, cyano, carboalkoxy, or $NR_{20}R_{21}$ wherein R_{20} and R_{21} are independently selected from the group consisting of hydrogen, C_{1-8} straight or branched chain alkyl, C_{3-7} cycloalkyl, benzyl, or aryl;
- (iii) cyano;
- (iv) a lactone or lactam formed with R_4 ;
- (v) $CONR_7R_8$ wherein R_7 and R_8 are independently selected from H, C_{1-8} straight or branched chain alkyl, C_{3-7} cycloalkyl, trifluoromethyl, hydroxy, alkoxy, acyl, alkylcarbonyl, carboxyl, arylalkyl, aryl, heteroaryl, and heterocyclyl; wherein the alkyl, cycloalkyl, alkoxy, acyl, alkylcarbonyl, carboxyl, arylalkyl, aryl, heteroaryl, and heterocyclyl groups may be substituted with carboxyl, alkyl, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, substituted heteroaryl, hydroxamic acid, sulfonamide, sulfonyl, hydroxy, thiol, alkoxy, or arylalkyl;

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or R₇ and R₈ taken together with the nitrogen to which they are attached form a heterocyclyl or heteroaryl group;

(vi) a carboxylic ester or carboxylic acid bioisostere including optionally substituted heteroaryl groups;

- 5 (b) R₂ is selected from the group consisting of optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C₃₋₇ cycloalkyl, optionally substituted heterocyclyl, wherein the heterocyclyl is 1,3-dioxolane

or furan, or R₂ is  ;

- (c) R₃ is from one to four groups independently selected from the group
10 consisting of:

- (i) hydrogen, halo, C₁₋₈ straight or branched chain alkyl, arylalkyl, C₃₋₇ cycloalkyl, C₁₋₈ alkoxy, cyano, C₁₋₄ carboalkoxy, trifluoromethyl, C₁₋₈ alkylsulfonyl, halogen, nitro, hydroxy, trifluoromethoxy, C₁₋₈ carboxylate, aryl, heteroaryl, and heterocyclyl;
- 15 (ii) NR₁₀R₁₁ wherein R₁₀ and R₁₁ are independently selected from H, C₁₋₈ straight or branched chain alkyl, arylalkyl, C₃₋₇ cycloalkyl, carboxyalkyl, aryl, heteroaryl, or heterocyclyl, or R₁₀ and R₁₁ taken together with the nitrogen to which they are attached form a heterocyclyl or heteroaryl group;

- (iii) NR₁₂COR₁₃ wherein R₁₂ is selected from hydrogen or alkyl and R₁₃
20 is selected from hydrogen, alkyl, substituted alkyl, C₁₋₃ alkoxyl, carboxyalkyl, R₃₀R₃₁N(CH₂)_p, R₃₀R₃₁NCO(CH₂)_p, aryl, arylalkyl, heteroaryl, or heterocyclyl, or R₁₂ and R₁₃ taken together with the carbonyl group form a carbonyl containing heterocyclyl group, wherein R₃₀ and R₃₁ are independently selected from H, OH, alkyl, and alkoxy, and p is an integer from 1-6, wherein the alkyl group may be substituted with carboxyl,

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alkyl, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, substituted heteroaryl, hydroxamic acid, sulfonamide, sulfonyl, hydroxy, thiol, alkoxy, or arylalkyl;

(d) R_4 is selected from the group consisting of (i) hydrogen, (ii) C_{1-3} straight or branched chain alkyl, (iii) benzyl, and (iv) $NR_{13}R_{14}$, wherein R_{13} and R_{14} are
 5 independently selected from hydrogen and C_{1-6} alkyl; wherein the C_{1-3} alkyl and benzyl groups are optionally substituted with one or more groups selected from C_{3-7} cycloalkyl, C_{1-8} alkoxy, cyano, C_{1-4} carboalkoxy, trifluoromethyl, C_{1-8} alkylsulfonyl, halogen, nitro, hydroxy, trifluoromethoxy, C_{1-8} carboxylate, amino, $NR_{13}R_{14}$, aryl, and heteroaryl; and

(e) X is selected from S and O;
 10 and the pharmaceutically acceptable salts, esters and pro-drug forms thereof.

In an alternative embodiment, R_1 , R_3 , and R_4 are as above and R_2 is $NR_{15}R_{16}$, where R_{15} and R_{16} are independently selected from hydrogen, C_{1-8} straight or branched chain alkyl, arylalkyl, C_{3-7} cycloalkyl, aryl, heteroaryl, and heterocyclyl, or R_{15} and R_{16} taken together with the nitrogen to which they are attached form a heterocyclyl or
 15 heteroaryl group.

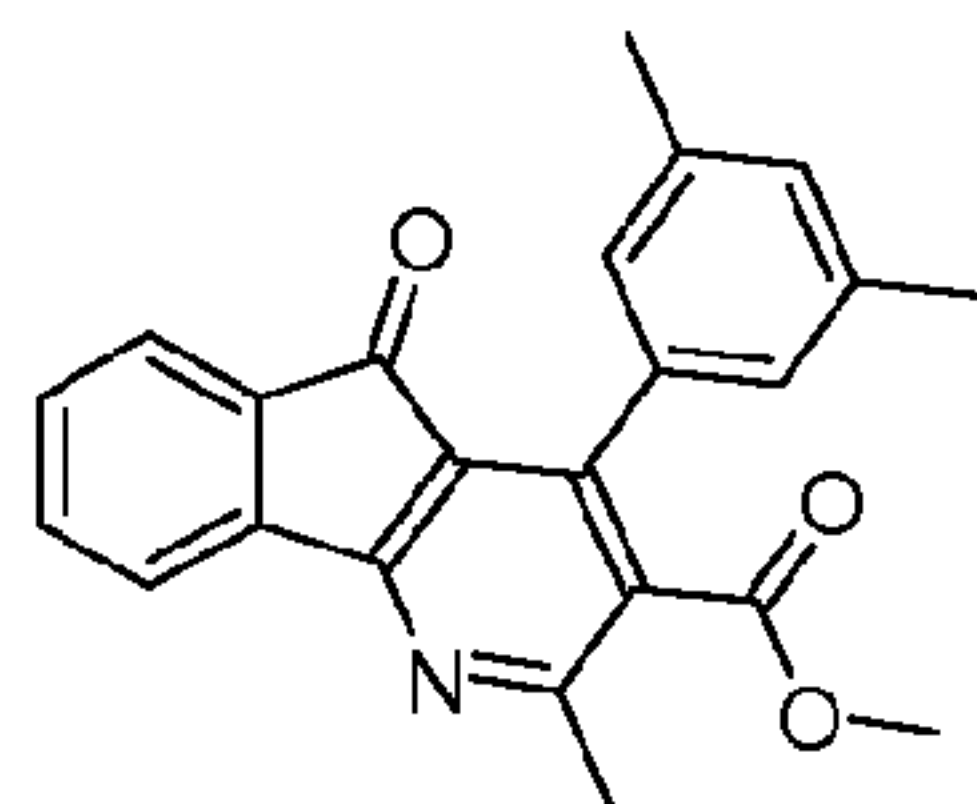
In regard to the above compounds, "alkyl" refers to straight, cyclic and branched-chain alkyl. The alkyl group may be optionally substituted with one or more groups such as halogen, OH, CN, mercapto, nitro, amino, C_1 - C_8 -alkyl, C_1 - C_8 -alkoxyl, C_1 - C_8 -alkylthio, C_1 - C_8 -alkyl-amino, di(C_1 - C_8 -alkyl)amino, (mono-, di-, tri-, and per-) halo-
 20 alkyl, formyl, carboxy, alkoxycarbonyl, C_1 - C_8 -alkyl-CO—O—, C_1 - C_8 -alkyl-CO—NH—, carboxamide, hydroxamic acid, sulfonamide, sulfonyl, thiol, aryl, aryl(c_1 - c_8)alkyl, heterocyclyl, and heteroaryl. The term "bioisostere" is defined as "groups or molecules which have chemical and physical properties producing broadly similar biological properties." (Burger's Medicinal Chemistry and Drug Discovery, M. E. Wolff, ed. Fifth
 25 Edition, Vol. 1, 1995, Pg. 785). The term "acyl" as used herein, whether used alone or as part of a substituent group, means an organic radical having 2 to 6 carbon atoms

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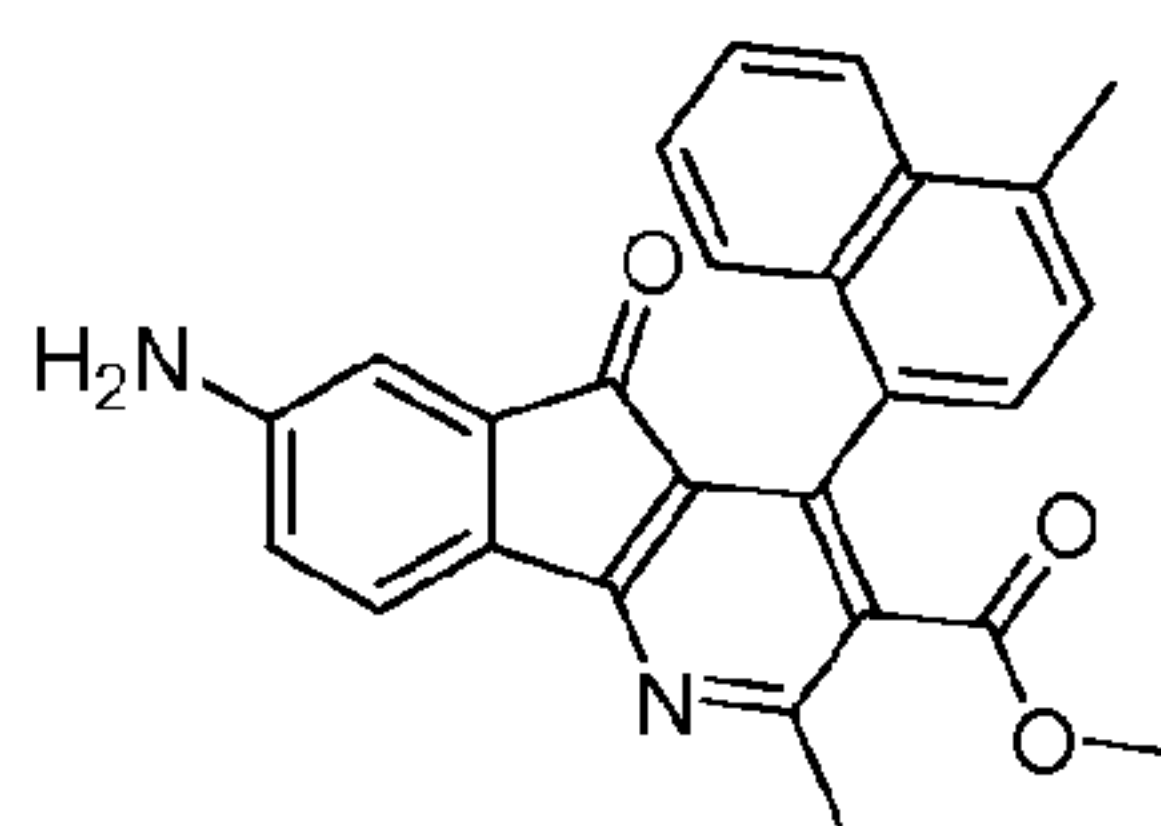
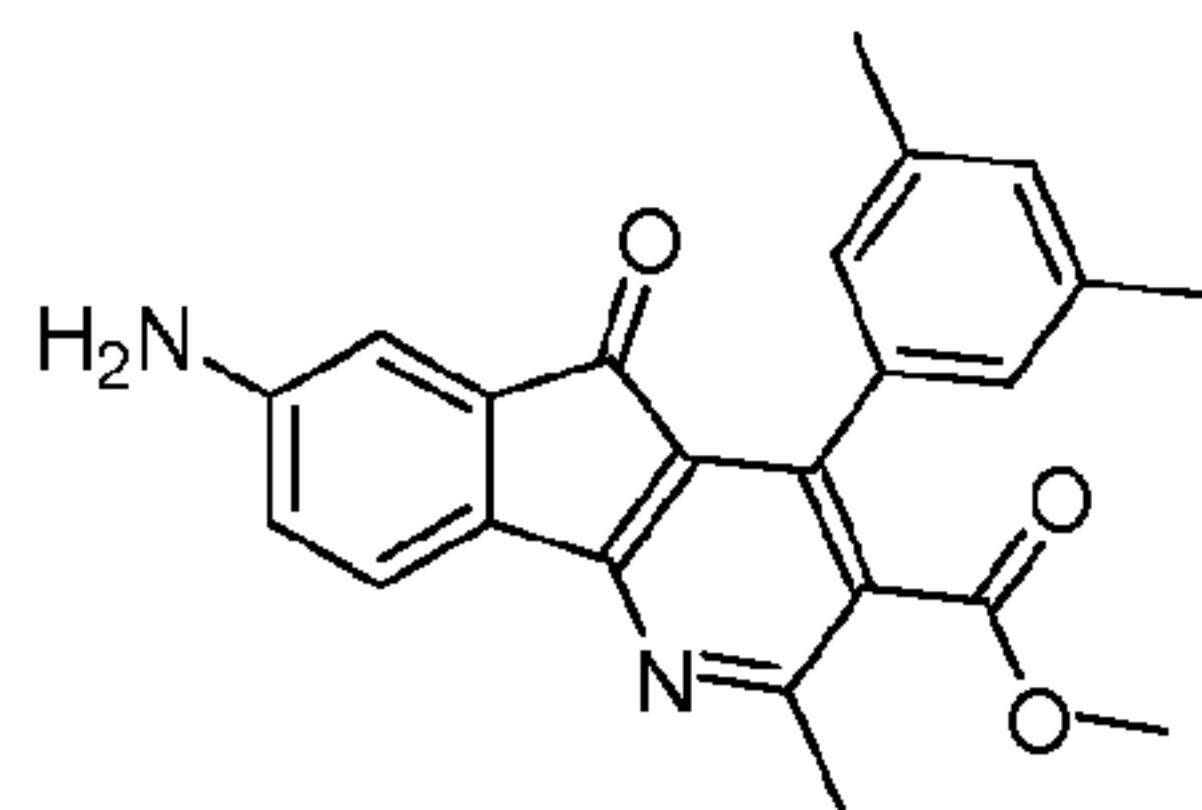
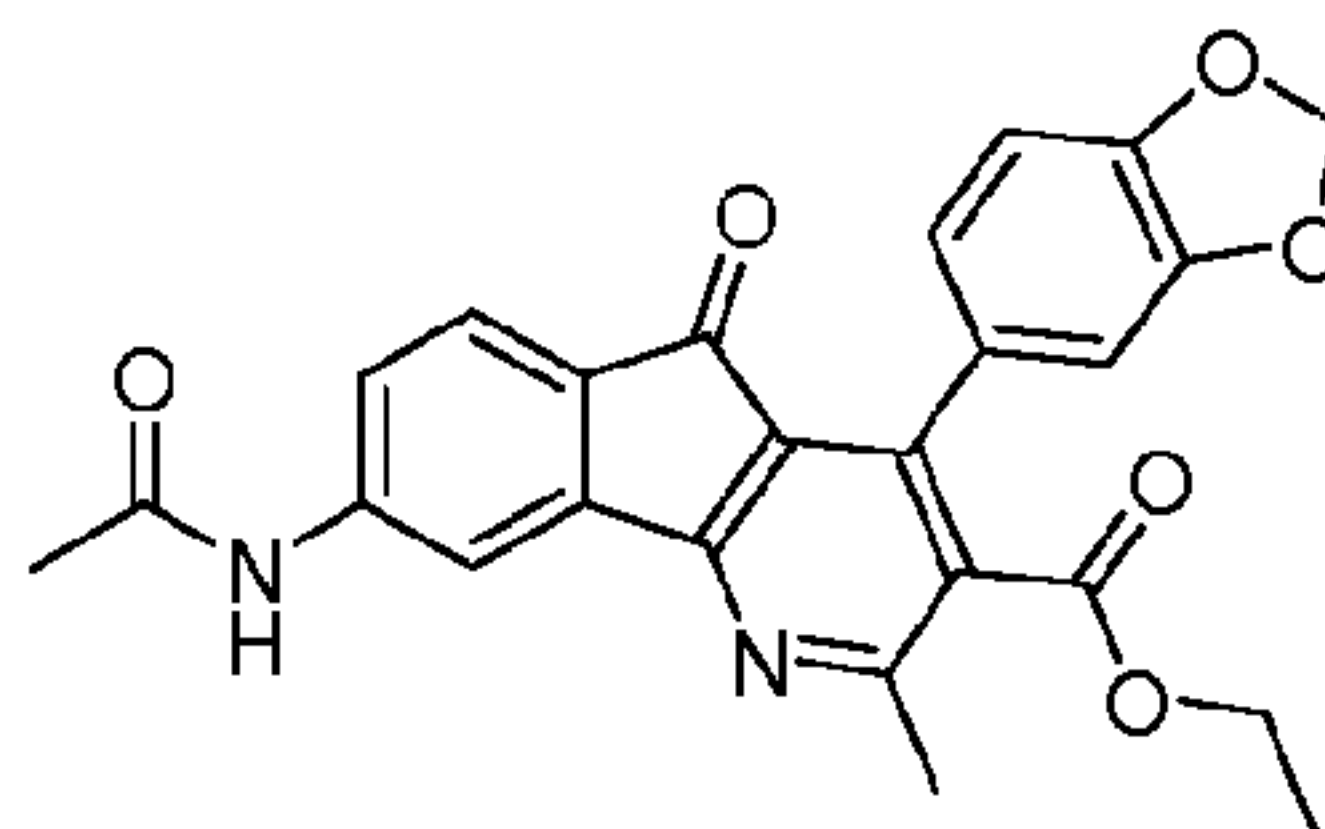
(branched or straight chain) derived from an organic acid by removal of the hydroxyl group. "Aryl" or "Ar," whether used alone or as part of a substituent group, is a carbocyclic aromatic radical including, but not limited to, phenyl, 1- or 2-naphthyl and the like. The carbocyclic aromatic radical may be substituted by independent replacement of 1 to 5 of the hydrogen atoms thereon with halogen, OH, CN, mercapto, nitro, amino, C₁-C₈-alkyl, C₁-C₈-alkoxyl, C₁-C₈-alkylthio, C₁-C₈-alkyl-amino, di(C₁-C₈-alkyl)amino, (mono-, di-, tri-, and per-) halo-alkyl, formyl, carboxy, alkoxycarbonyl, C₁-C₈-alkyl-CO—O—, C₁-C₈-alkyl-CO—NH—, or carboxamide. Illustrative aryl radicals include, for example, phenyl, naphthyl, biphenyl, fluorophenyl, difluorophenyl, benzyl, benzoyloxyphenyl, carboethoxyphenyl, acetylphenyl, ethoxyphenyl, phenoxyphenyl, hydroxyphenyl, carboxyphenyl, trifluoromethylphenyl, methoxyethylphenyl, acetamidophenyl, tolyl, xylyl, dimethylcarbamyphenyl and the like. The term "heteroaryl" refers to a cyclic, fully unsaturated radical having from five to ten ring atoms of which one ring atom is selected from S, O, and N; 0–2 ring atoms are additional heteroatoms independently selected from S, O, and N; and the remaining ring atoms are carbon. The radical may be joined to the rest of the molecule via any of the ring atoms. The terms "heterocycle," "heterocyclic," and "heterocycle" refer to an optionally substituted, fully or partially saturated cyclic group which is, for example, a 4- to 7-membered monocyclic, 7- to 11-membered bicyclic, or 10- to 15-membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, or 3 heteroatoms selected from nitrogen atoms, oxygen atoms, and sulfur atoms, where the nitrogen and sulfur heteroatoms may also optionally be oxidized. The nitrogen atoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom.

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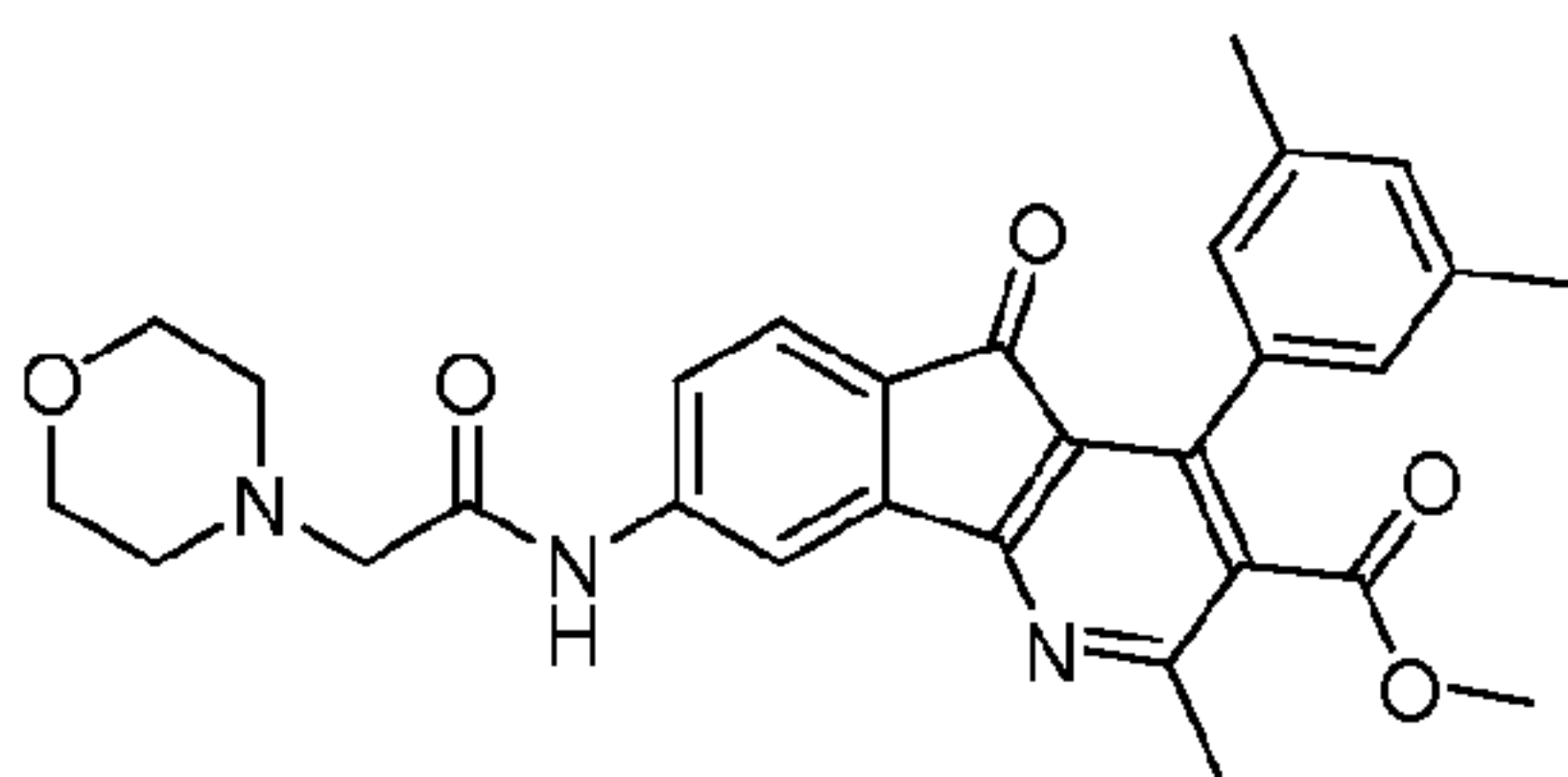
In other embodiments, PDE7 inhibitors useful in the methods of the invention have the formulas:



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The preparation of the above compounds is described in U.S. Patent No. 6,903,109, US 20040082578, WO 2003/088963, and US 20060154949.

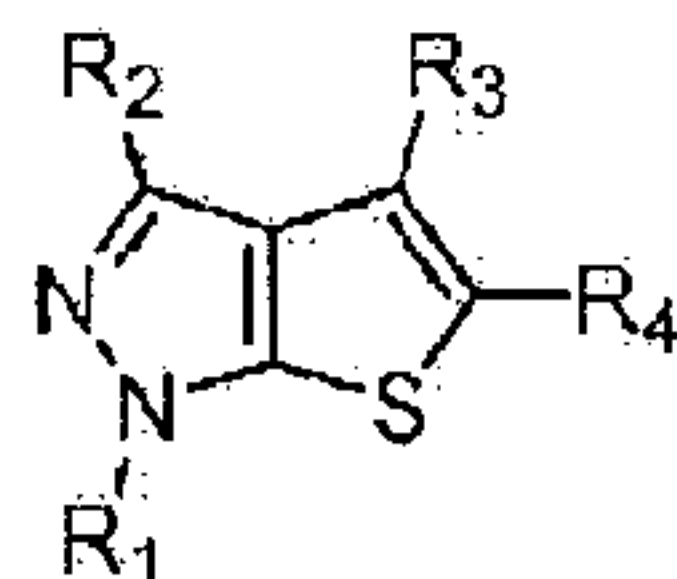
-98-

In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in U.S. Patent No. 6,958,328, WO 2002/085894, and US 20030212089.

These PDE7 inhibitors have the same formula as those
 5 described above (e.g., U.S. Patent No. 6,903,109), except that R₁ is not a carboxylic ester or carboxylic acid bioisostere. The preparation of these compounds is described in U.S. Patent No. 6,958,328, US 20030212089, and WO 2002/085894.

In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in WO
 10 2006/004040 and EP 1 775 298.

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



(6)

The substituents for the above compounds are defined as follows:

R₁ is substituted or unsubstituted C₃₋₈ alkyl group, substituted or unsubstituted cycloalkyl group, or substituted or unsubstituted heterocycloalkyl group (e.g., cyclohexyl, cycloheptyl, or tetrahydropyranyl);

20 R₂ is a hydrogen atom or substituted or unsubstituted C₁₋₃ alkyl group (e.g., methyl);

R₃ is a hydrogen atom, substituted or unsubstituted C₁₋₃ alkyl group, or a halogen atom; and

R₄ is substituted or unsubstituted aryl group, substituted or unsubstituted
 25 heteroaryl group, or a group CONR₅R₆, or CO₂R₇,

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wherein R₅ and R₆ are, same or different from each other, a hydrogen atom; C₁₋₆ alkyl group which may be substituted by a halogen atom, substituted or unsubstituted aryl group, substituted or unsubstituted heteroaryl group, substituted or unsubstituted heterocycloalkyl group, substituted or unsubstituted cycloalkyl group, a group
5 NR₇COR₈, COR₈, NR₉R₁₀; substituted or unsubstituted cycloalkyl group; substituted or unsubstituted heterocycloalkyl group; substituted or unsubstituted aryl group; substituted or unsubstituted heteroaryl group; or substituted or unsubstituted heterocycloalkyl group in which the ring is formed together with the nitrogen atom binding R₅ and R₆;

wherein R₇ is a hydrogen atom or substituted or unsubstituted C₁₋₃ alkyl group;
10 wherein R₈ is substituted or unsubstituted heterocycloalkyl group, or a group OH, OR₇, or NR₉R₁₀;

wherein R₉ and R₁₀ are, same or different from each other, a hydrogen atom; substituted or unsubstituted C₁₋₃ alkyl group, substituted or unsubstituted heterocycloalkyl group; substituted or unsubstituted acyl; a group SO₂R₇, or substituted or unsubstituted
15 heterocycloalkyl group in which the ring is formed together with the nitrogen atom binding R₅ and R₆;

or pharmaceutically acceptable salts or solvates thereof.

In regard to the above compounds, the term "cycloalkyl group" means cycloalkyl group having 3 to 8 carbon atoms. The term "heterocycloalkyl group" may be 3 to
20 7 membered monocyclic or polycyclic heterocyclic group containing the same or different 1 to 4 hetero atom(s) such as oxygen, nitrogen or sulfur atom(s), and examples may include piperidinyl, pyrrolidinyl, piperazinyl, tetrahydrofuryl, tetrahydropyranyl, morpholinyl, azetidiny, imidazolidinyl, oxazolidinyl, hexahydropyrrolidinyl, octahydroindolidinyl, octahydroquinolidinyl, octahydroindolyl, and oxo-derivatives
25 thereof. The term "aryl group" may be aromatic hydrocarbon group, which consists of mono-benzene ring, or binding or condensed benzene ring, such as phenyl, naphthyl,

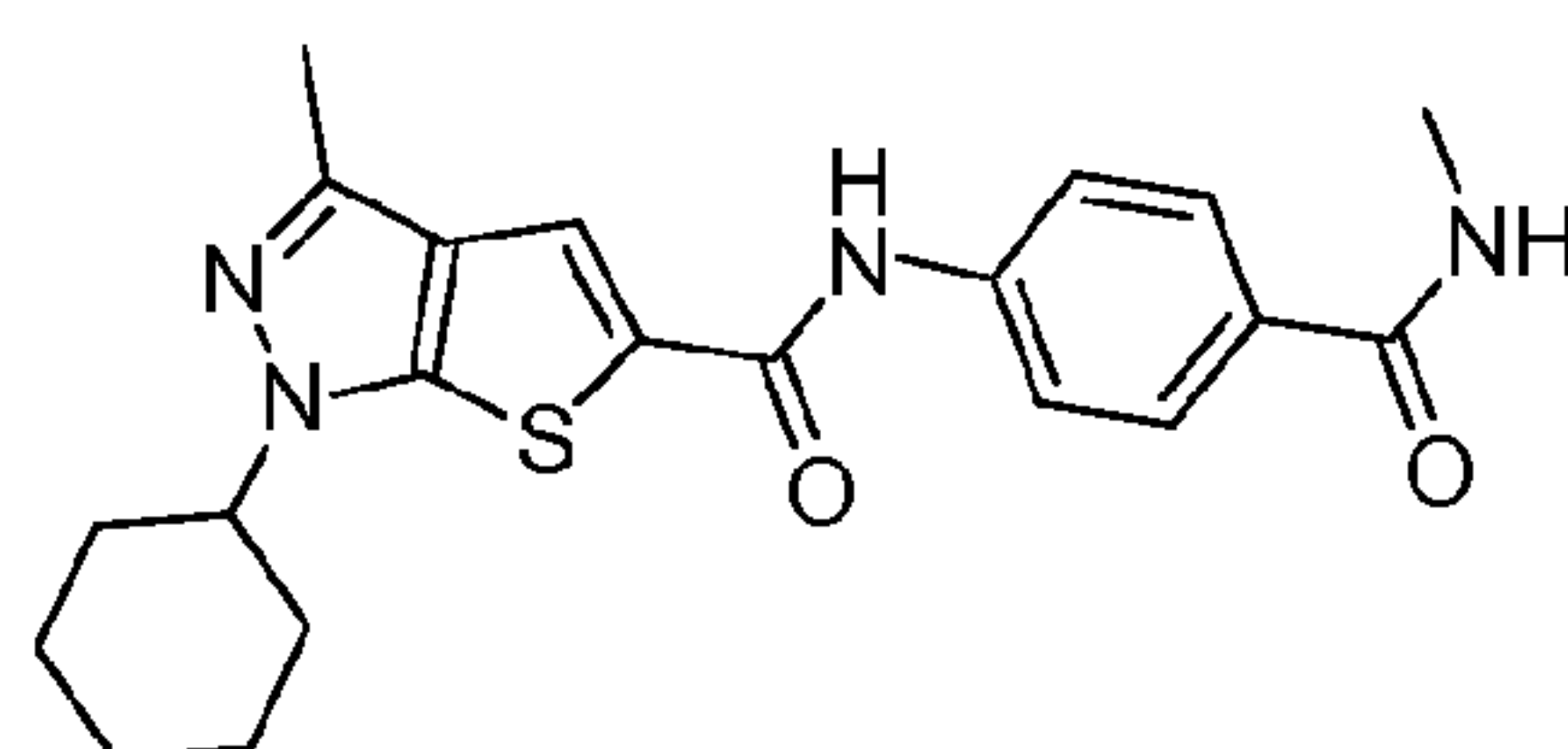
-100-

biphenyl and the like; and dicyclic or tricyclic group, which consists of benzene ring condensed with cycloalkyl or heterocyclic ring, such as 1,2,3,4-tetrahydronaphthalene, 2,3-dihydroindene, indoline, coumarone and the like. The term "heteroaryl group" may be 5 to 7 membered monocyclic heteroaryl group or polycyclic heteroaryl group, and having 2 to 8 carbon atoms with 1 to 4 hetero atom(s) such as oxygen, nitrogen, sulfur atom(s), in which the polycyclic heteroaryl group has condensed ring system by the same or different monocyclic heteroaryl or benzene ring each other; or polycyclic group which is consisted of heteroaryl group condensed with cycloalkyl or heterocycloalkyl ring. Examples of suitable substituent of the present invention may include straight, branched-chained or 10 cyclic C₁-C₈ alkyl group, which may be substituted by one or more methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, cyclohexyl, cycloheptyl, methoxymethyl, hydroxymethyl, trifluoromethyl, C₁-C₃ alkoxy group, halogen atom, and hydroxyl group; hydroxyl group; cyano group; substituted or unsubstituted alkoxy group such as methoxy, ethoxy group; amino group which may be substituted by C₁-C₆ alkyl group or acyl group such as 15 amino, methylamino, ethylamino, dimethylamino, acylamino and the like; carboxylic group; substituted or unsubstituted ester group; phosphate group; sulfonic group; substituted or unsubstituted aryl group; substituted or unsubstituted heteroaryl group; saturated or unsaturated heterocycloalkyl group which may be substituted; substituted or unsubstituted carbamoyl group; substituted or unsubstituted amide group; substituted or 20 unsubstituted thioamide group; halogen atom; nitro group; substituted or unsubstituted sulfone group; substituted or unsubstituted sulfonylamide group; oxo group; substituted or unsubstituted urea group; straight, branched-chained or cyclic alkenyl group such as ethenyl, propenyl, cyclohexenyl and the like.

In other embodiments, PDE7 inhibitors useful in the methods of the invention 25 have the formulas:

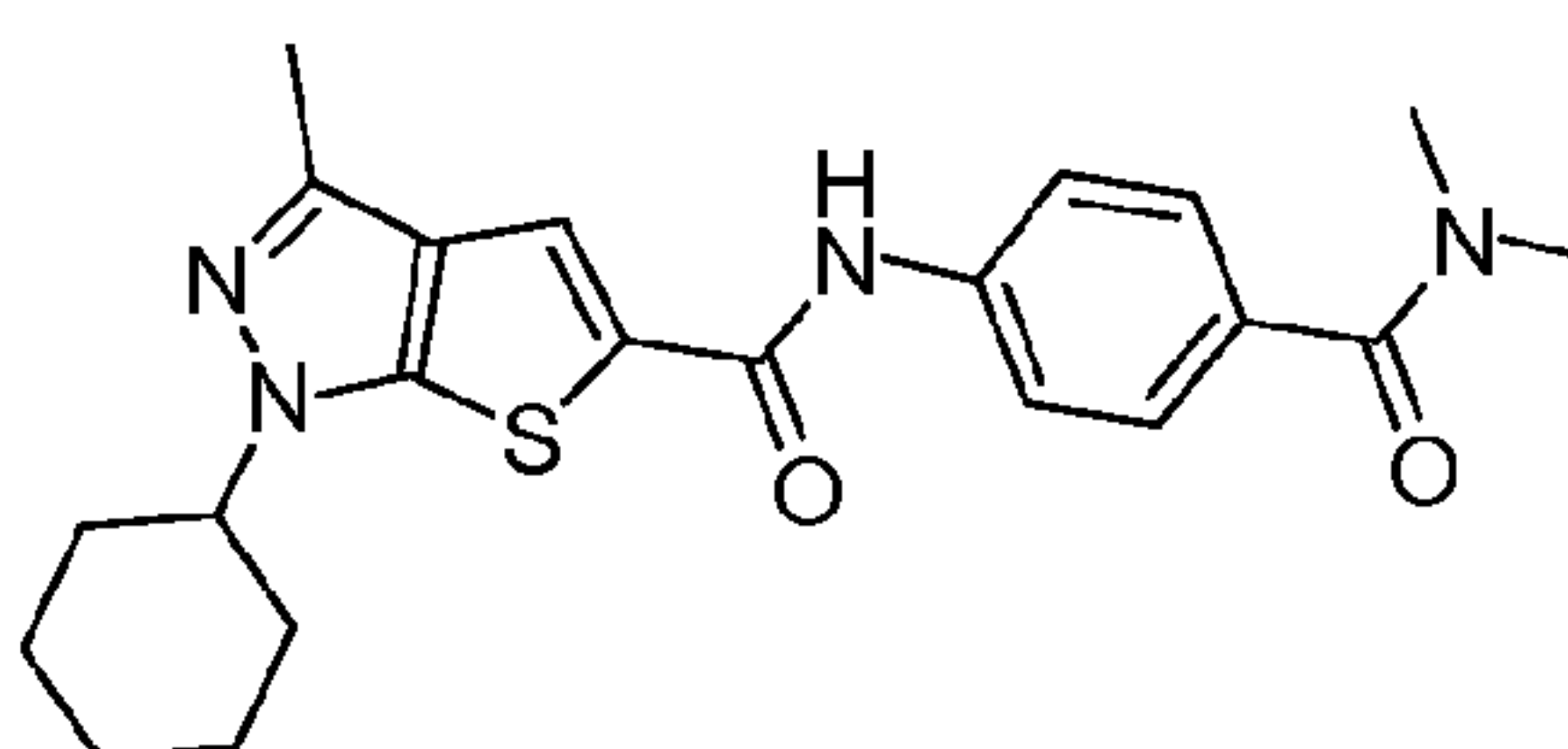
-101-

(6A)



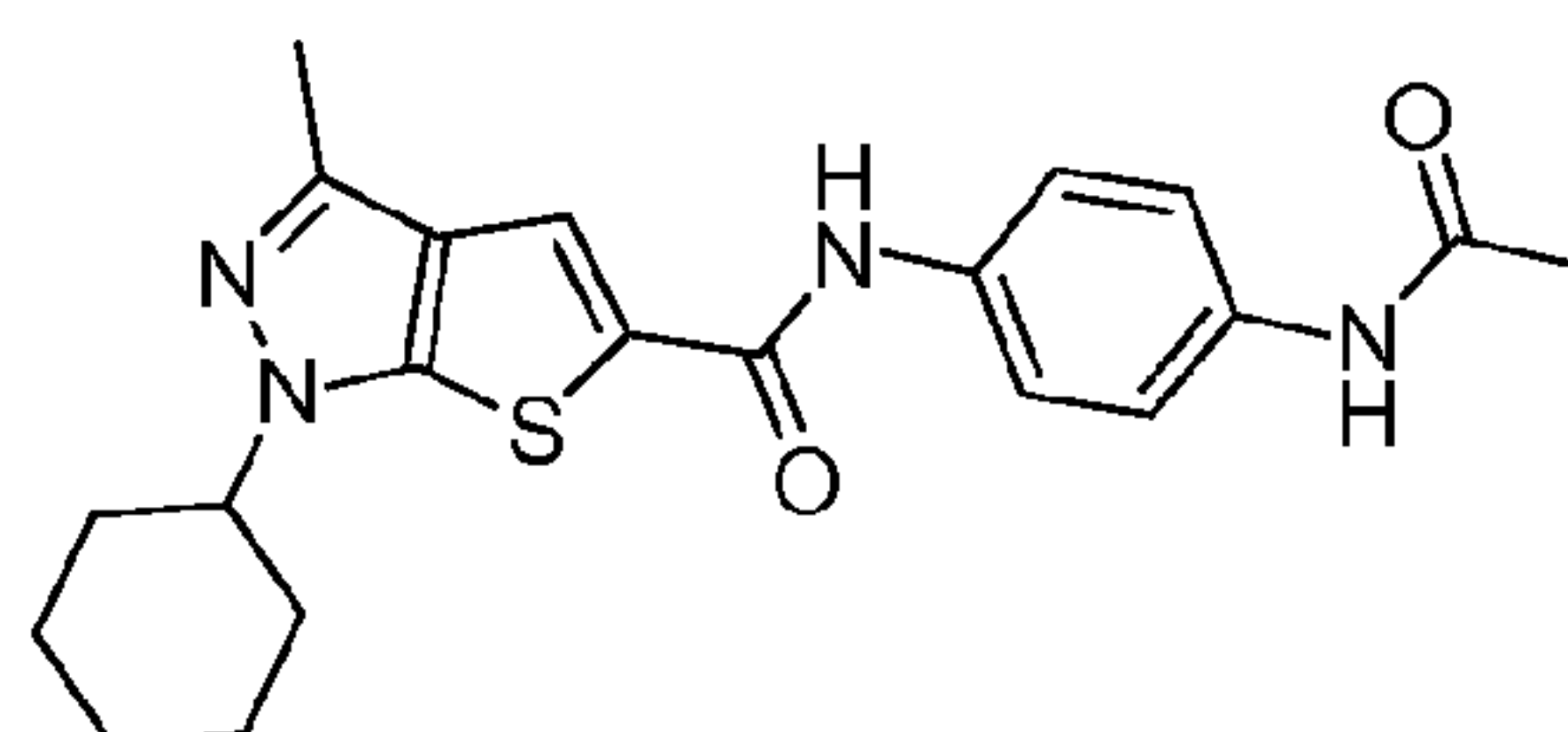
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(6B)

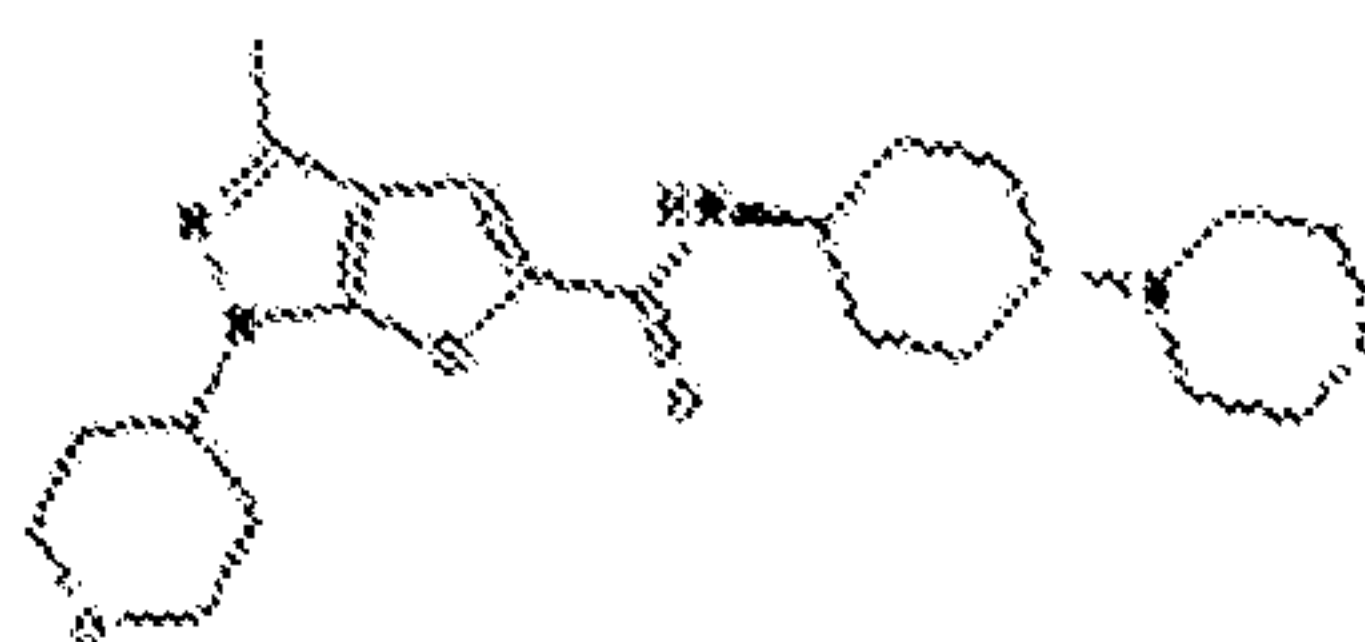


(6C)

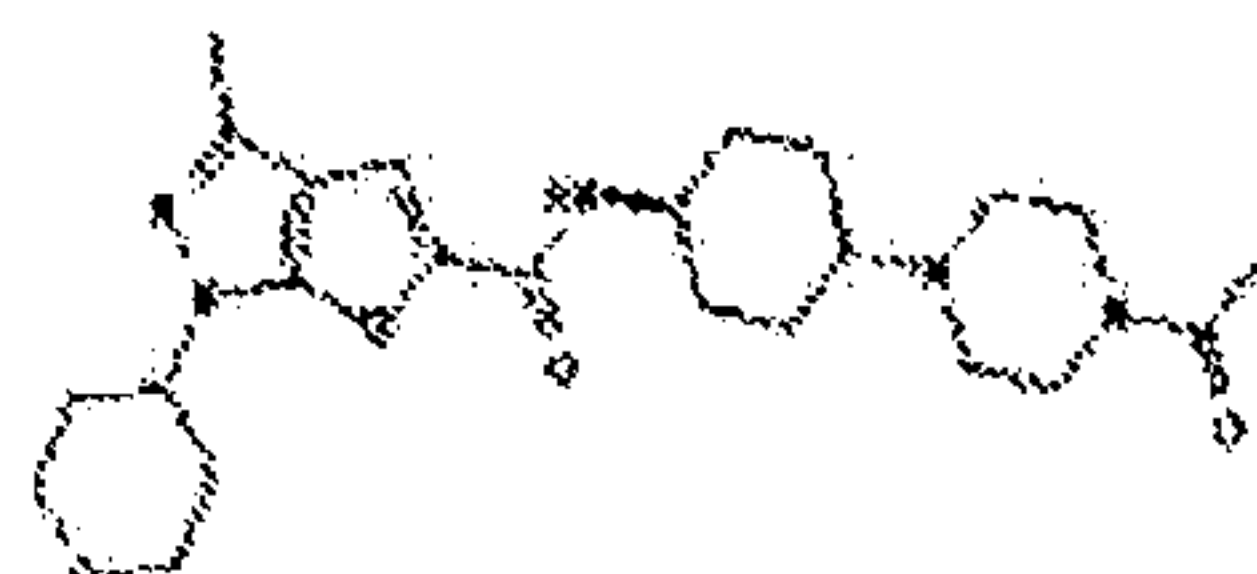
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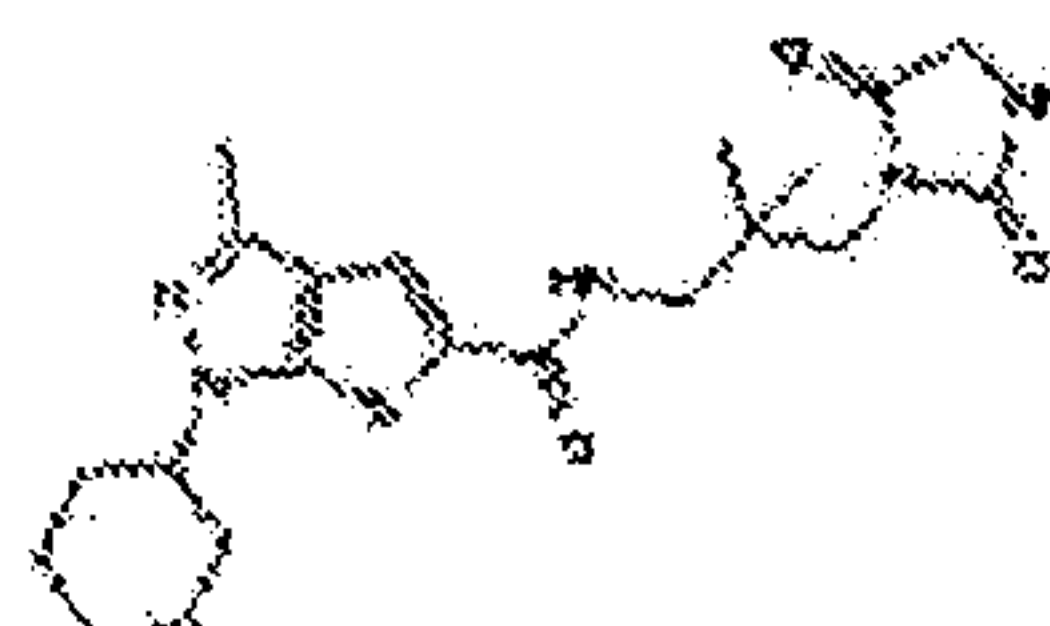
(6D)



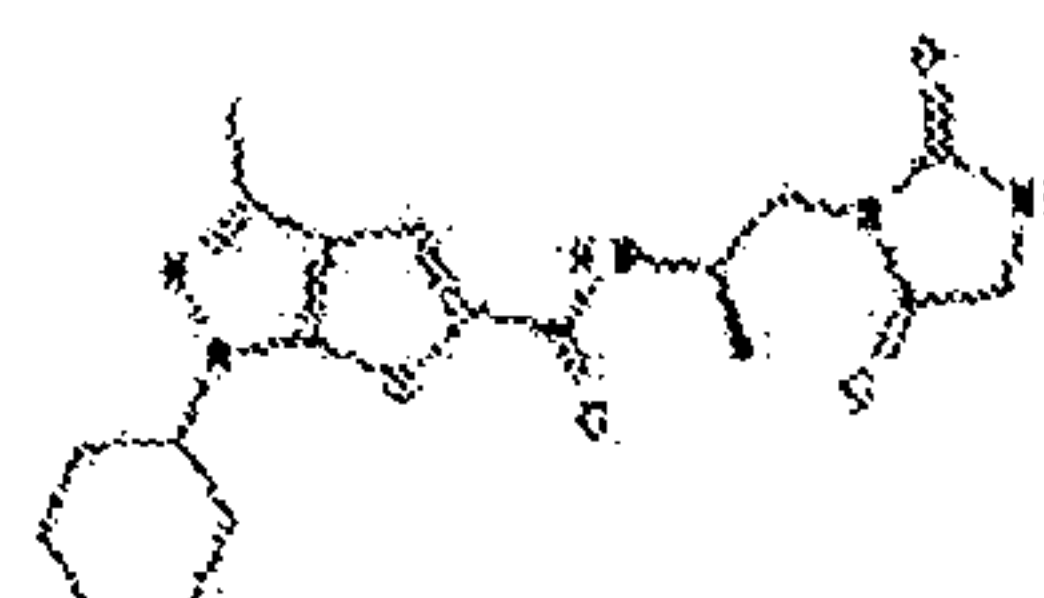
(6E)



(6F)



(6G)

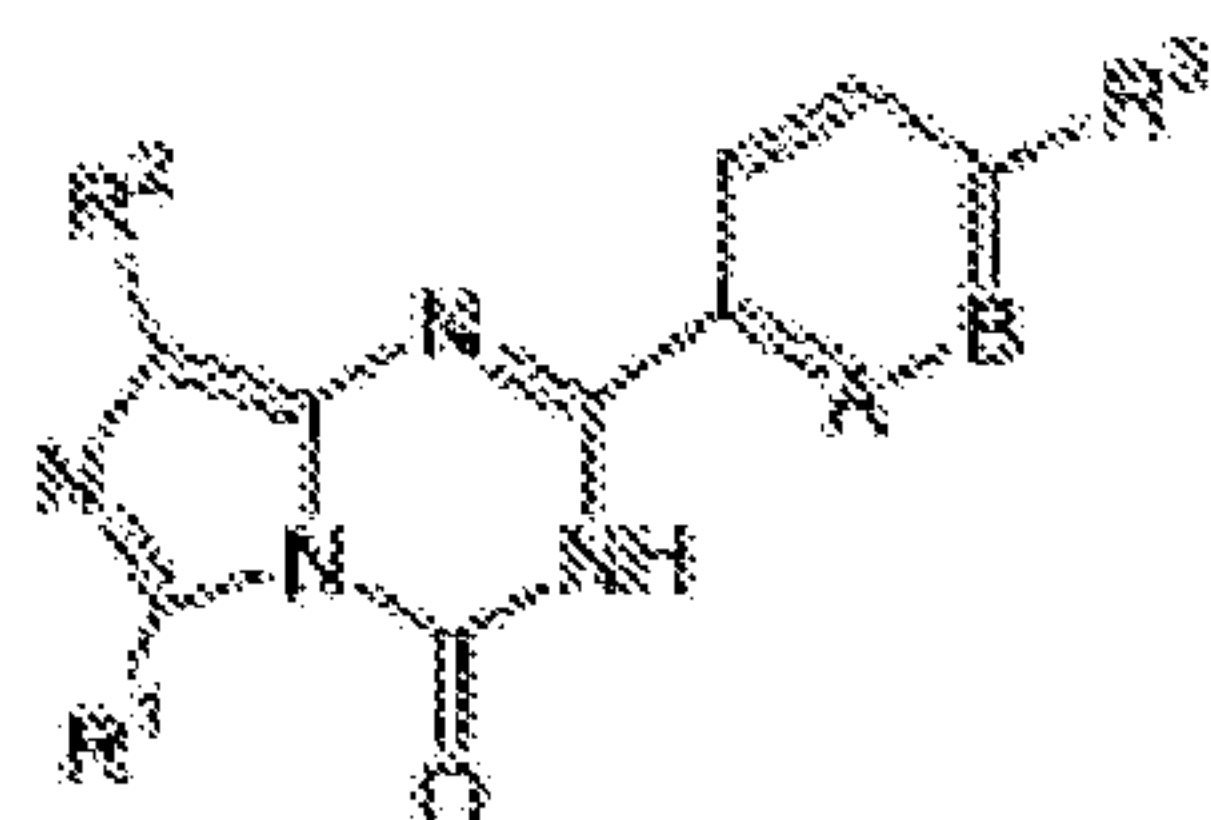


(6H).

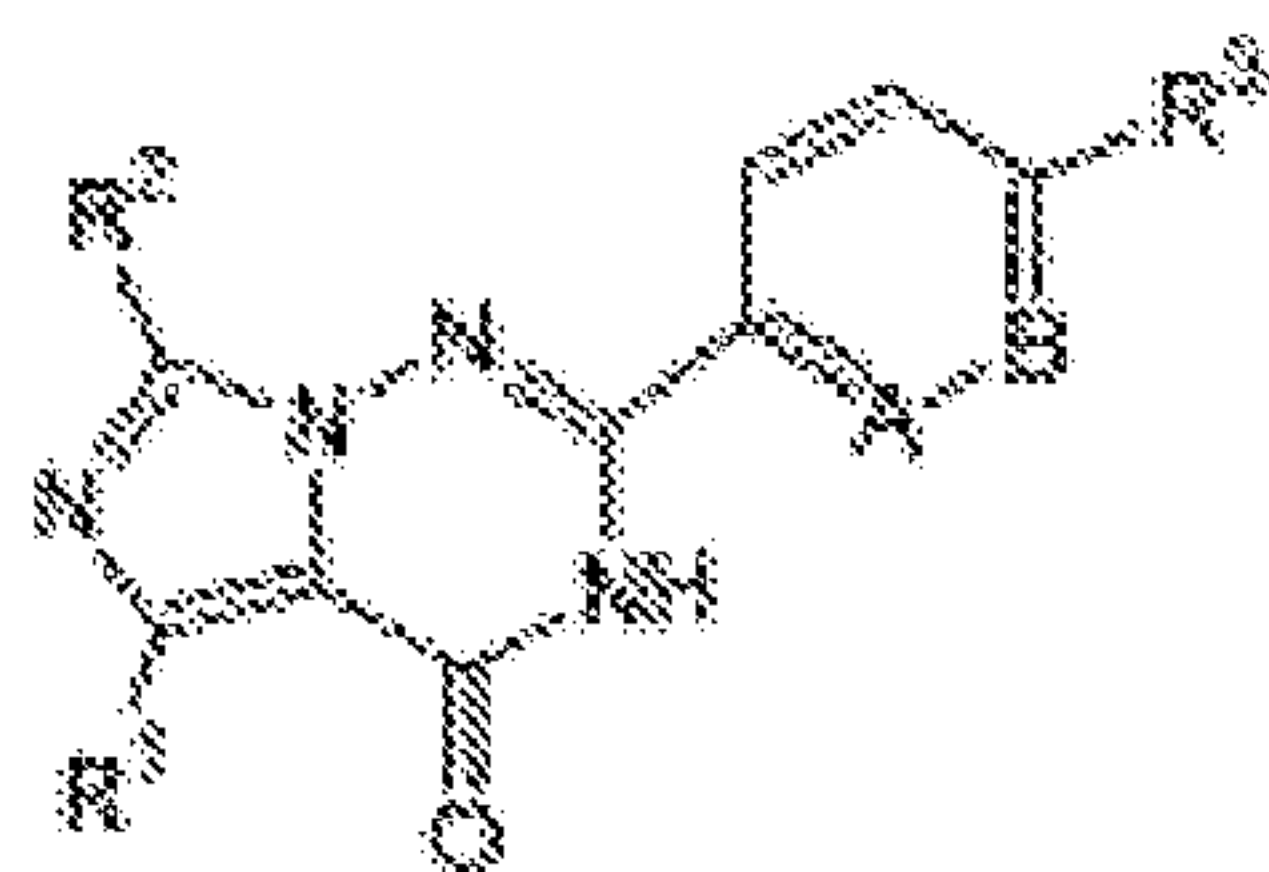
15 In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in WO 2004/111053 and US 20060128707.

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formulas:

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(7A)



(7B)

5

The substituents for the above compounds are defined as follows:

A is N or CR₄;

B is N or CH;

10 R₁ is substituted or unsubstituted C₃₋₈ cycloalkyl group or tert-butyl group;

R₂ is a hydrogen atom or C₁₋₆ alkyl group;

R₃ is a hydrogen atom; nitro group; cyano group; a halogen atom; heteroaryl group; substituted or unsubstituted C₁₋₆ alkyl group; substituted or unsubstituted C₂₋₆ alkenyl group; saturated or unsaturated heterocycloalkyl group which is substituted or
 15 unsubstituted; a group: NR₅R₆, C(O)R₇, SO₂R₇, OR₈, NR₈COR₇, NR₈SO₂R₇;

R₄ is a hydrogen atom or C₁₋₃ alkoxy group which is unsubstituted or substituted by one or more fluorine atom(s);

R₅ and R₆ are, same or different from each other, a hydrogen atom; substituted or unsubstituted C₁₋₆ alkyl group; substituted or unsubstituted acyl group; or substituted or
 20 unsubstituted heterocycloalkyl group;

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R₇ is a hydrogen atom; substituted or unsubstituted C₁₋₆ alkyl group; substituted or unsubstituted heterocycloalkyl group; OH; OR₈ or NR₅R₆;

R₈ is a hydrogen atom, substituted or unsubstituted C₁₋₆ alkyl group; or substituted or unsubstituted heterocycloalkyl group;

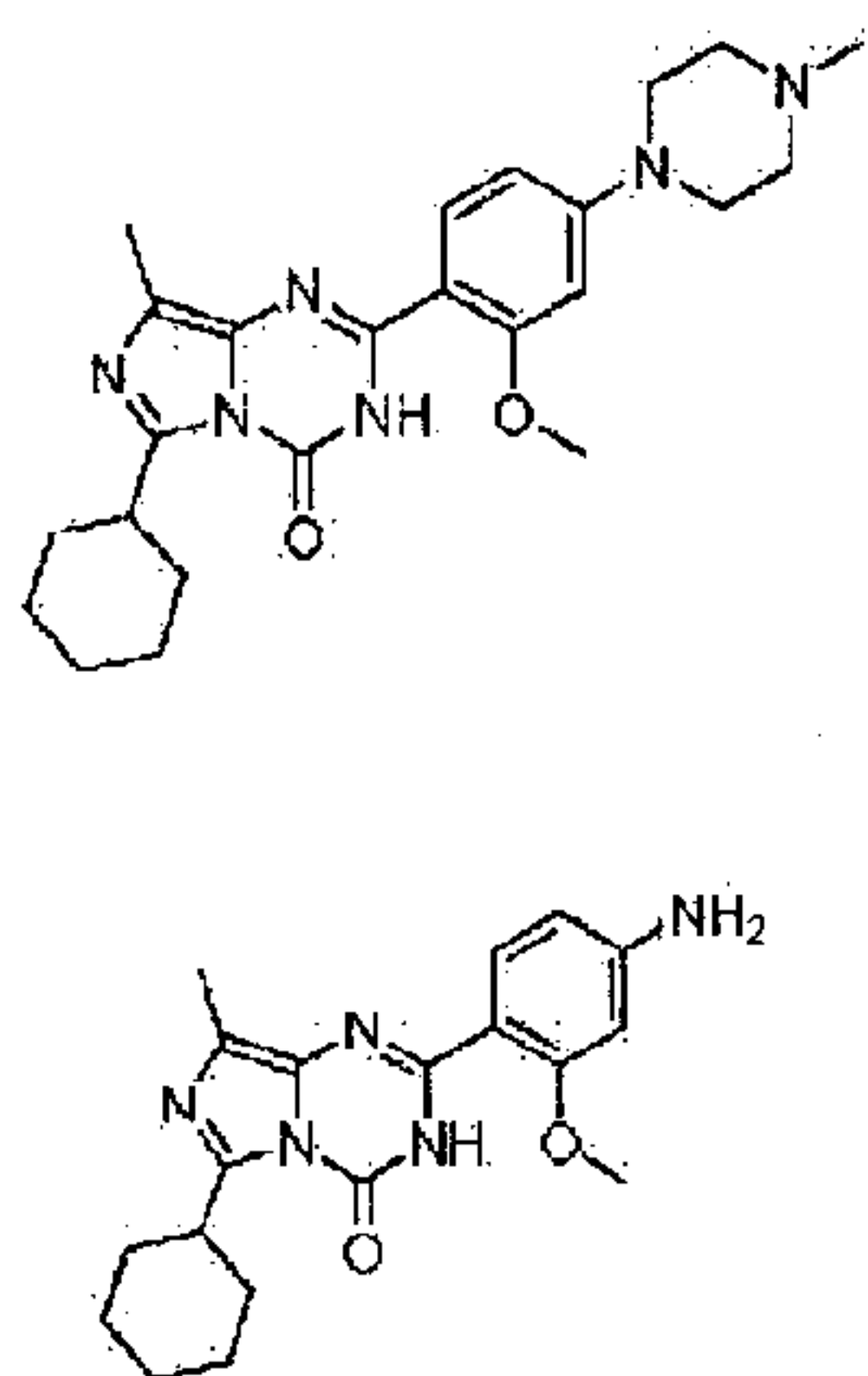
5 or pharmaceutically acceptable salts or solvates thereof.

In regard to the above compounds, the term "C₁-C₆ alkyl group" refers to a straight or branched-chained alkyl group having 1 to 6 carbon atoms, and the term "C₂-C₆ alkenyl group" refers to a straight or branched-chained alkenyl group having 2 to 6 carbon atoms. The term "cycloalkyl group" refers to a cycloalkyl group having 3 to 8 carbon
10 atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The term "heterocycloalkyl group" is 3 to 7 membered heterocyclic group containing the same or different 1 to 4 hetero atom(s) such as oxygen, nitrogen or sulfur atom(s), and examples may include piperidinyl, pyrrolidinyl, piperazinyl, tetrahydrofuryl, tetrahydropyranyl, morpholinyl, azetidiny, and homopiperazinyl. The term "heteroaryl
15 group" is 5 to 7 membered monocyclic or polycyclic group thereof containing 2 to 8 carbon atoms and the same or different 1 to 4 hetero atom(s) such as oxygen, nitrogen or sulfur atom(s). The examples include pyrrole, furyl, thienyl, imidazolyl, thiazolyl, pyrazinyl, indolyl, quinolinyl, isoquinolinyl, tetrazolyl, pyridinyl, pyrazolyl, pyridazinyl, and pyrimidinyl. The "halogen atom" includes fluorine, chlorine, bromine and iodine.
20 Examples of the suitable substituent of "substituted or unsubstituted C₁-C₆ alkyl group", "substituted or unsubstituted C₃-C₈ cycloalkyl group", "substituted or unsubstituted alkenyl group", "substituted or unsubstituted heterocycloalkyl group" and "substituted or unsubstituted acyl group" include a straight or branched-chained, or substituted or unsubstituted alkyl group such as methyl, ethyl, propyl, isopropyl, n-butyl, tert-butyl,
25 substituted or unsubstituted cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl; hydroxyl group; cyano group; alkoxy group

-105-

such as methoxy and ethoxy; substituted or unsubstituted amino group such as amino, methylamino, ethylamino, and dimethylamino; substituted or unsubstituted acyl group such as acetyl, and propionyl; substituted or unsubstituted aryl group; substituted or unsubstituted heteroaryl group; saturated or unsaturated heterocycloalkyl group which is substituted or unsubstituted; substituted or unsubstituted carbamoyl group; substituted or unsubstituted amide group; halogen atom; nitro group; substituted or unsubstituted sulfone group; oxo group; urea group; a straight or branched-chained, or cyclic alkenyl group which is substituted or unsubstituted such as ethenyl, propenyl, and cyclohexenyl.

In other embodiments, PDE7 inhibitors useful in the methods of the invention have the formulas:

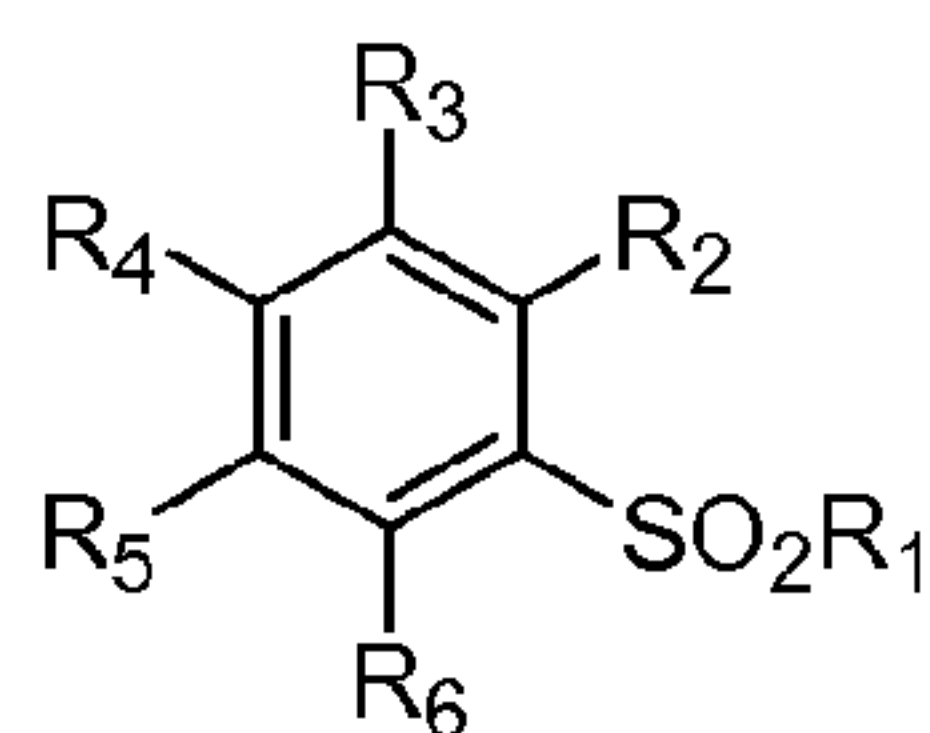


The preparation of the above compounds is described in US 2006/0128707 and WO 2004/111053.

In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in U.S. Patent No. 6,617,357, US 2002/0156064, and *Molecular Pharmacology*, 66:1679-1689, 2004.

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:

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(8)

The substituents for the above compounds are defined as follows:

R_1 is NR_aR_b where R_a and R_b are independently H or C_{1-6} alkyl, or represents a 5 to 7 member ring comprised of carbon or carbon and one or more additional heteroatoms selected from O, N, or S;

R_2 is H, C_{1-8} alkyl, C_{1-3} alkyl-Ar, C_{1-3} alkyl- C_{3-6} cycloalkyl, C_{2-8} alkenyl, C_{2-4} alkenyl-Ar, or C_{2-4} alkenyl- C_{3-6} cycloalkyl, wherein Ar is substituted or unsubstituted phenyl;

R_3 is NO_2 , halo, CN, $C(O)OR_7$, COR_1 , or NR_aR_b where R_a and R_b are independently H or C_{1-6} alkyl;

R_4 is H, OC_{1-6} alkyl, halo, $C(O)NR_aR_b$, $C(O)OR_7$, C_{1-8} alkyl, $OCHF_2$, CH_2OR_8 , OC_{1-3} alkyl-Ar, or $CH_2NHC(O)CH_3$;

R_5 is H, halo, or alkyl;

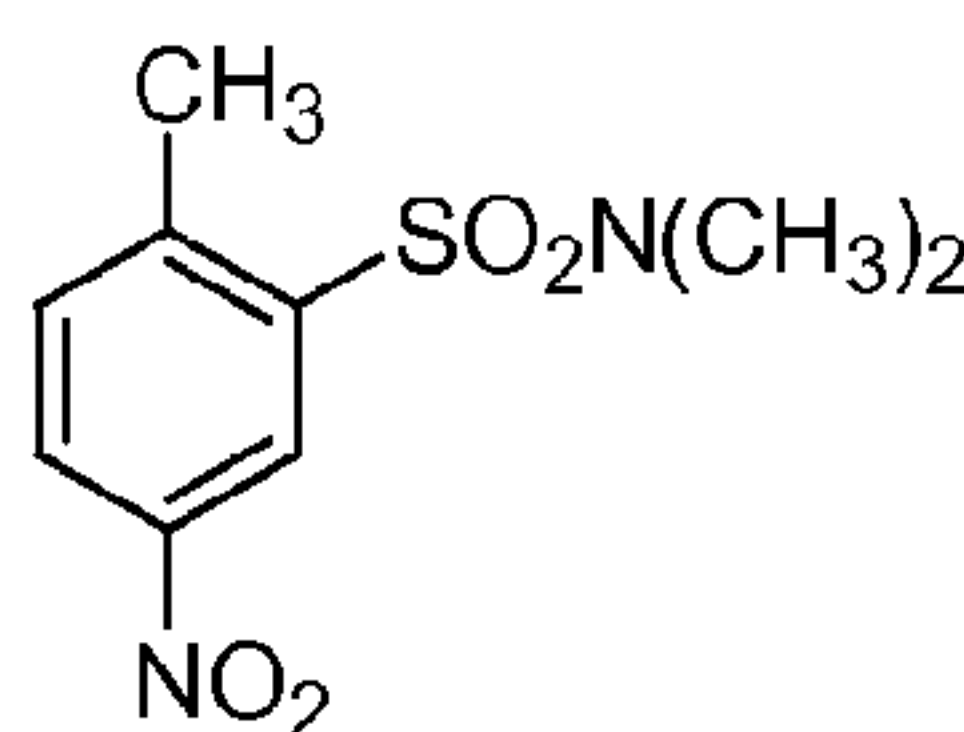
R_6 is C_{1-8} alkyl, OC_{1-4} alkyl, or halo;

R_7 is hydrogen or an ester or amide-forming group;

R_8 is hydrogen or C_{1-6} alkyl;

or a pharmaceutically acceptable salt or solvate thereof.

In one embodiment, a PDE7 inhibitor useful in the methods of the invention has the formula:

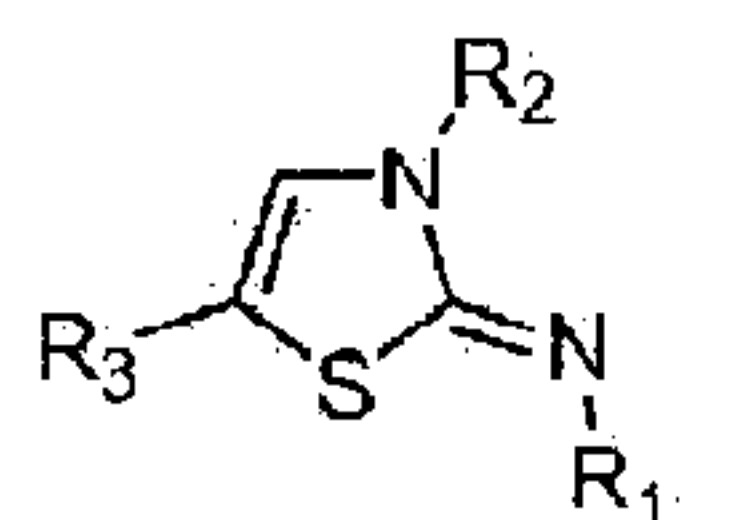


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The preparation of the above compounds is described in U.S. Patent No. 6,617,357, US 20020156064, and *Molecular Pharmacology*, 66:1679-1689, 2004.

In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in U.S. Patent
5 No. 6,852,720, EP 1 348 433, and WO 2003/082277.

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



(9)

10 The substituents for the above compounds are defined as follows:

R₁ is a group selected from cycloalkyl, heterocycloalkyl, aryl and heteroaryl, those groups being optionally substituted by one or more groups, identical or different, selected independently of each other from halogen, trifluoromethyl, nitro, cyano, oxo, NR₄R₅, CO₂R₄, CONR₄R₅, OR₄, S(O)_nR₄, S(O)_nNR₄R₅, tetrazolyl and (C₁-C₆) alkyl
15 which is optionally substituted by 1 to 3 groups, identical or different, selected independently of each other from OR₄, NR₄R₅, and CO₂R₄; wherein n is an integer from 0 to 2 inclusive, R₄ and R₅ are identical or different and independently of each other are a hydrogen atom or a group of formula X₁-R_a, wherein X₁ is a single bond or a (C₁-C₆) alkylene group, and R_a is a group selected from (C₁-C₆) alkyl, cycloalkyl,
20 heterocycloalkyl, aryl, and heteroaryl,

R₂ is a group selected from (C₁-C₆) alkyl, (C₂-C₆) alkenyl, (C₂-C₆) alkynyl, aryl, and cycloalkyl,

R₃ is a group selected from cycloalkyl, heterocycloalkyl, aryl and heteroaryl, these groups being optionally substituted by one or more groups, identical or different,

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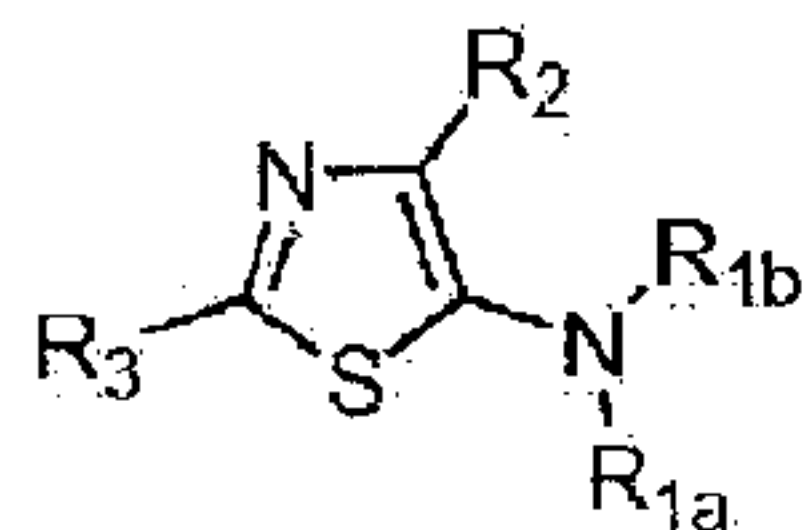
selected independently of each other from halogen, nitro, cyano, trifluoromethyl, oxo, (C₁-C₆) alkyl, OR₆, NR₆R₇, COR₆, CO₂R₆, CONHOH, CONR₆R₇, S(O)_mR₆, S(O)_mNR₆R₇, NR₆COR₇, NR₆SO₂R₇, N(SO₂R₇)₂, NR₆CONR₇R₈, C(=NCN)NR₆R₇, NR₈C(=NCN)NR₆R₇, and tetrazolyl optionally substituted with a (C₁-C₄) alkyl, wherein m is an integer from 0 to 2 inclusive, R₆ and R₇ are identical or different and independently of each other are a hydrogen atom or a group of formula X₂R_b, wherein X₂ is a single bond or a (C₁-C₆) alkylene group, R_b is a group selected from (C₁-C₆) alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, these groups being optionally substituted by 1 to 3 groups, identical or different, selected independently of each other from hydroxy, (C₁-C₆) alkoxy, (C₁-C₆) alkyl, amino, mono(C₁-C₆) alkylamino, di(C₁-C₆) alkylamino (each alkyl amino being identical or different, independently of each other), carboxy, (C₁-C₆) alkoxycarbonyl, and benzyl, and R₈ represents a hydrogen atom or a (C₁-C₆) alkyl group;

a racemic form thereof, an isomer thereof, an N-oxide thereof, or a pharmaceutically acceptable acid or base salt thereof.

The preparation of the above compounds is described in U.S. Patent No. 6,852,720, EP 1 348 433, and WO 2003/082277.

In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in U.S. Patent No. 6,753,340, US 20030191167, EP 1 348 701, and WO 2003/082839 .

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



(10)

-109-

The substituents for the above compounds are defined as follows:

R_{1a} is a group selected from hydrogen, (C₁-C₆) alkyl and aryl(C₁-C₆) alkyl,

R_{1b} is a group selected from cycloalkyl, heterocycloalkyl, aryl and heteroaryl, those groups being optionally substituted by one or more groups, identical or different, selected independently of each other from halogen, trifluoromethyl, nitro, cyano, oxo, NR₄R₅, CO₂R₄, CONR₄R₅, OR₄, S(O)_nR₄, S(O)_nNR₄R₅, tetrazolyl, and (C₁-C₆) alkyl which is optionally substituted by 1 to 3 groups, identical or different, selected independently of each other from OR₄, NR₄ R₅, and CO₂R₄, wherein n is an integer from 0 to 2 inclusive, R₄ and R₅ are identical or different and independently of each other are a hydrogen atom or a group of formula X₁-R_a, wherein X₁ is a single bond or a (C₁-C₆) alkylene group, and R_a is a group selected from (C₁-C₆) alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl,

R₂ is a group selected from (C₁-C₆) alkyl, (C₂-C₆) alkenyl, (C₂-C₆) alkynyl, aryl and cycloalkyl,

R₃ is a group selected from cycloalkyl, heterocycloalkyl, aryl and heteroaryl, these groups being optionally substituted by one or more groups, identical or different, selected independently of each other from halogen, nitro, cyano, trifluoromethyl, oxo, (C₁-C₆) alkyl, OR₆, NR₆R₇, COR₆, CO₂R₆, CONHOH, CONR₆R₇, S(O)_mR₆, S(O)_mNR₆R₇, NR₆COR₇, NR₆SO₂R₇, N(SO₂R₇)₂, NR₆CONR₇R₈, C(=N-CN)NR₆R₇, NR₈C(=N-CN)NR₆R₇, and tetrazolyl optionally substituted with a (C₁-C₄) alkyl, wherein m is an integer from 0 to 2 inclusive, R₆ and R₇ are identical or different and independently of each other are a hydrogen atom or a group of formula X₂-R_b, wherein X₂ is a single bond or a (C₁-C₆) alkylene group, R_b is a group selected from (C₁-C₆) alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, these groups being optionally substituted by 1 to 3 groups, identical or different, selected independently of each other from hydroxy, (C₁-C₆) alkoxy, (C₁-C₆) alkyl, amino, mono(C₁-C₆)

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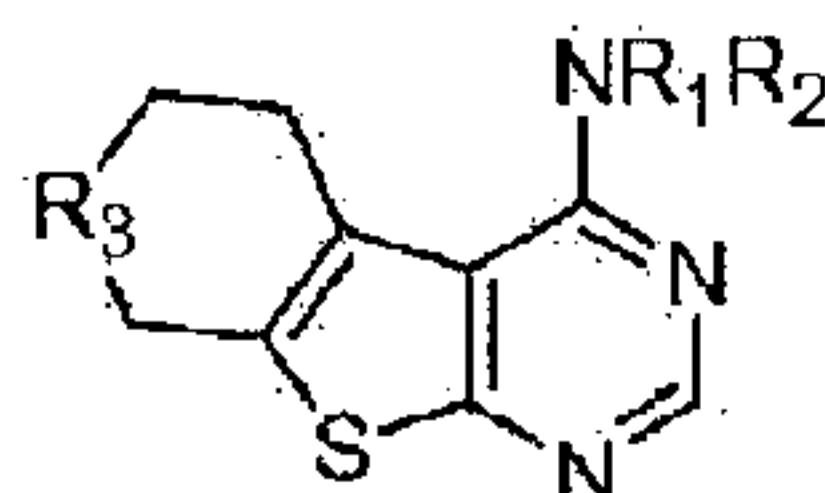
alkylamino, di(C₁-C₆) alkylamino (each alkyl amino being identical or different, independently of each other), carboxy, (C₁-C₆) alkoxy carbonyl, and benzyl, and R₈ is a hydrogen atom or a (C₁-C₆) alkyl group, or

a racemic form thereof, an isomer thereof, an N-oxide thereof or a
5 pharmaceutically acceptable acid or base salt thereof.

The preparation of these compounds is described in U.S. Patent No. 6,753,340, US 20030191167, EP 1 348 701, and WO 2003/082839.

In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in U.S. Patent
10 No. 6,849,638, US 20030119829, and WO 2002/088138.

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



(11)

15 The substituents for the above compounds are defined as follows:

R₁ and R₂ are independently selected from the group consisting of hydrogen, alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, cycloalkyl of 3-7 carbon atoms, fully saturated heterocycle of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S and O, aryl of 6-12 carbon atoms, that may be
20 substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of 6-12 carbon atoms or heteroaryl of 4-11 carbon atoms and 1, 2 heteroatoms selected from N, S, and O,
25 heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which

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may be substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of 6-12 carbon atoms or
5 heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and R₄-R₅, or R₁ and R₂ combine to form, together with the nitrogen atom to which they are attached, a 5-7 membered saturated ring which may contain 1-2 additional heteroatoms selected from the group consisting of NH, NR₈, S and O, or combine to form, together with the nitrogen atom to which they are attached, a 5-7 membered unsaturated ring that
10 may contain 1-2 additional heteroatoms selected from the group consisting of N, S and O, wherein said saturated or unsaturated ring may be substituted with 1-2 substituents selected from the group consisting of OH, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-7 carbon atoms, fully saturated heterocycle of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S, and
15 O, halogen, haloalkyl of 1-2 carbon atoms and a number of halogen atoms up to the perhalo level, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, and R₉-R₁₀; or

R₁ and R₂ combine to form, together with the nitrogen atom to which they are attached, an 8-10 membered bicyclic saturated ring;

20 R₃ is selected from the group consisting of NH, S, S(=O)₂, and O;

R₄ is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, C(=C), S(=O)₂, and C(=O)O;

R₅ is selected from hydrogen, OH, alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atom, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, aryl of
25 6-12 carbon atoms, which may be substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen,

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haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
aryl of 6-12 carbon atoms and heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms
selected from N, S, and O, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected
5 from N, S, and O, which may be substituted with alkyl of 1-6 carbon atoms, alkenyl of
2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen,
haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
aryl of 6-12 carbon atoms and heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms
10 selected from N, S, and O, cycloalkyl of 3-7 carbon atoms, fully saturated heterocycle of
2-6 carbon atoms and 1-2 heteroatoms selected from NH, S and O, and NR_6R_7 ,

R_6 and R_7 are independently selected from hydrogen, alkyl of 1-8 carbon atoms,
alkenyl of 2-8 carbon atoms, and alkynyl of 2-8 carbon atoms, or R_6 and R_7 combine
together with the nitrogen atom to which they are attached to form a 5-7 membered,
15 unsaturated ring which may contain 1-2 additional heteroatoms selected from N, S and O
or to form a 5-7 membered, saturated ring which may contain 1-2 additional heteroatoms
selected from NH, S, and O;

R_8 is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms,
alkynyl of 2-8 carbon atoms, $\text{R}_{11}\text{-R}_{12}$, cycloalkyl of 3-7 carbon atoms, fully saturated
20 heterocycle of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S, and O, aryl of
6-12 carbon atoms, which may be substituted with alkyl of 1-6 carbon atoms, alkenyl of
2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen,
haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
25 aryl of 6-12 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms
selected from N, S, and O, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected

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from N, S, and O, which may be substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, 5 aryl of 6-12 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S, and O;

R₉ is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, and alkynyl of 2-8 carbon atoms,

R₁₀ is selected from OH, aryl of 6-12 carbon atoms, which may be substituted 10 with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of 6-12 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S, and O, and heteroaryl of 15 4-11 carbon atoms and 1-2 heteroatoms selected from N, S, and O, which may be substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of 6-12 carbon atoms or 20 heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S, and O;

R₁₁ is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, and alkynyl of 2-8 carbon atoms; and

R₁₂ is selected from cycloalkyl of 3-7 carbon atoms, fully saturated heterocycle of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S, and O, aryl of 6-12 carbon 25 atoms, which may be substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, haloalkyl of

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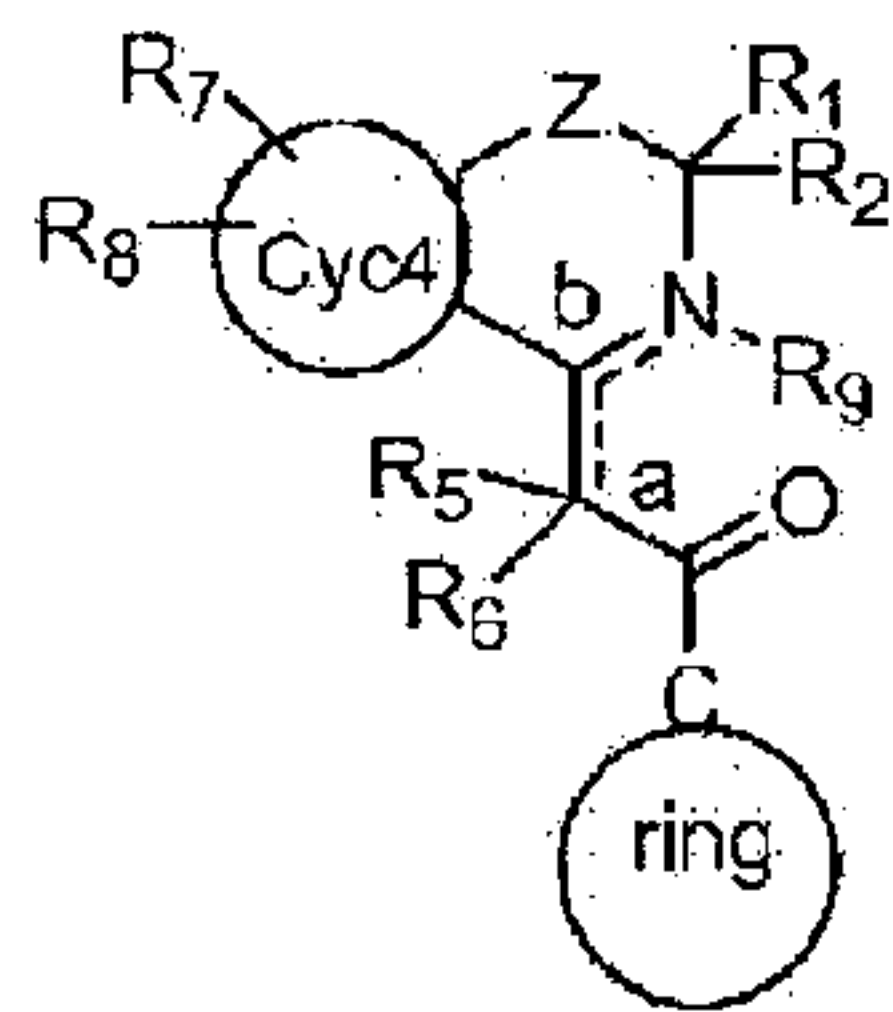
1-6 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of
 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of
 6-12 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from
 N, S, and O, and heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S
 5 and O, which may be substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon
 atoms, alkynyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, haloalkyl of
 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of
 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of
 6-12 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from
 10 N, S and O;

and pharmaceutically acceptable salts thereof.

The preparation of these compounds is described in U.S. Patent No. 6,849,638,
 US 20030119829, and WO 2002/088138.

In another embodiment, PDE7 inhibitors useful in the methods of the invention
 15 are selected from those compounds generally or specifically disclosed in US 2005222138
 and WO 2003/064389.

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the
 formula:



20 (12)

The substituents for the above compounds are defined as follows:

R₁ and R₂ are each independently, (1) hydrogen atom, or (2) C₁₋₈ alkyl, or

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R_1 and R_2 may be taken together with the carbon atom to which they are attached to form Cyc1,

wherein R_1 and R_2 do not represent hydrogen atom at the same time;

Z is (1) CR_3R_4 , (2) O, (3) S, or (4) a bond;

5 R_3 and R_4 are each independently, (1) hydrogen atom, (2) C_{1-8} alkyl, (3) C_{1-8} alkoxy, or (4) hydroxy, or

R_3 and R_4 may be taken together with the carbon atom to which they are attached to form Cyc1 or C(O);

R_5 and R_6 are each independently, (1) hydrogen atom, or (2) C_{1-8} alkyl, or

10 R_5 and R_6 may be taken together with the carbon atom to which they are attached to form Cyc1;

Cyc1, which is represented by R_1 and R_2 , R_3 and R_4 , R_5 and R_6 is, each independently, (1) C_{3-10} cycloalkyl, or (2) 3-10 membered monocyclic hetero-ring comprising 1-2 of heteroatom selected from oxygen, nitrogen and sulfur, and Cyc1 may
15 be substituted with R_{10} ;

R_{10} is (1) C_{1-8} alkyl, (2) C_{1-8} alkoxy, (3) hydroxy, (4) $COOR_{11}$, (5) oxo, (6) SO_2R_{12} , or (7) COR_{13} ;

R_{11} is hydrogen atom, or C_{1-8} alkyl;

R_{12} and R_{13} are (1) C_{1-8} alkyl, or (2) phenyl which may be substituted with C_{1-8}
20 alkyl;

R_7 and R_8 are each independently, (1) hydrogen atom, (2) C_{1-8} alkyl, (3) C_{1-8} alkoxy, (4) hydroxy, (5) cyano, (6) halogen atom, (7) $COOR_{14}$, (8) $CONR_{15}R_{16}$, (9) Cyc2, (10) C_{2-8} alkenyl, (11) C_{2-8} alkynyl, (12) $NR_{51}R_{52}$, (13) nitro, (14) formyl, (15) C_{2-8} acyl, (16) C_{1-8} alkyl substituted with hydroxy, C_{1-8} alkoxy, Cyc2, $NR_{51}R_{52}$, or
25 NR_{53} -Cyc2, (17) $NR_{54}COR_{55}$, (18) $NR_{56}SO_2R_{57}$, (19) $SO_2NR_{58}R_{59}$, (20) C_{2-8} alkenyl substituted with $COOR_{14}$, (21) $CH=N-OH$, (22) C_{1-8} alkylene- NR_{60} -(C_{1-8} alkylene)- R_{61} ,

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(23) C₁₋₈ alkylthio, (24) C₁₋₈ alkyl substituted with 1-3 of halogen atom, (25) C₁₋₈ alkoxy substituted with 1-3 of halogen atom, (26) C₁₋₈ alkoxy substituted with Cyc2, (27) O-Cyc2, (28) OSO₂R₆₅, or (29) CH=N-OR₁₃₇;

R₁₄ is hydrogen atom, or C₁₋₈ alkyl;

5 R₁₅ and R₁₆ are each independently hydrogen atom or C₁₋₈ alkyl;

R₅₁ and R₅₂, R₅₈ and R₅₉ are each independently, hydrogen atom, or C₁₋₈ alkyl;

R₅₃, R₅₄, R₅₆, and R₆₀ are each independently, hydrogen atom, or C₁₋₈ alkyl;

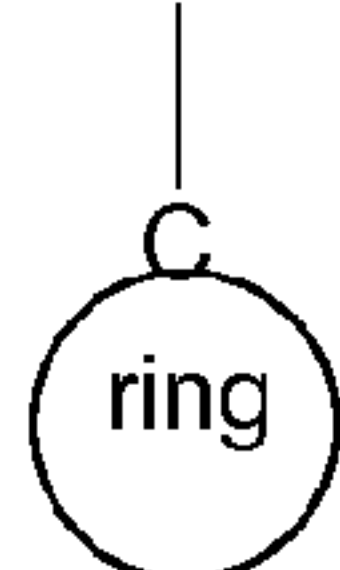
R₅₅ is hydrogen atom, C₁₋₈ alkyl, or C₁₋₈ alkoxy; R₅₇ is C₁₋₈ alkyl;

R₆₁ is NR₆₂R₆₃ or hydroxy;

10 R₆₂ and R₆₃ are each independently, hydrogen atom, or C₁₋₈ alkyl;

R₆₅ is C₁₋₈ alkyl;

R₁₃₇ is C₁₋₈ alkyl;



(hereinafter it is abbreviated as ring) is Cyc2 wherein the group which attaches to carbonyl is carbon;

15 R₇, R₈, and Cyc2 represented by ring are each independently, (1) C₃₋₁₅ mono-, bi- or tri-cyclic (fused or spiro)carboring, or (2) 3-15 membered mono-, bi- or tri-cyclic (fused or spiro)heteroring comprising 1-4 of heteroatom selected from oxygen, nitrogen and sulfur;

Cyc2 may be substituted with 1-5 of R₁₇ or R_{17'};

20 R₁₇ is (1) C₁₋₈ alkyl, (2) C₂₋₈ alkenyl, (3) C₂₋₈ alkynyl, (4) C₁₋₈ alkoxy, (5) C₁₋₈ alkylthio, (6) hydroxy, (7) halogen atom, (8) nitro, (9) oxo, (10) carboxy, (11) formyl, (12) cyano, (13) NR₁₈R₁₉, (14) phenyl, phenoxy or phenylthio, which may be substituted with 1-5 of R₂₀, (15) C₁₋₈ alkyl, C₂₋₈ alkenyl, C₁₋₈ alkoxy or C₁₋₈ alkylthio, which may be substituted with 1-5 of R₂₁ (16) OCOR₂₂, (17) CONR₂₃R₂₄, (18) SO₂NR₂₅R₂₆ (19)

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COOR₂₇, (20) COCOOR₂₈, (21) COR₂₉, (22) COCOR₃₀, (23) NR₃₁COR₃₂, (24) SO₂R₃₃, (25) NR₃₄SO₂R₃₅, or (26) SOR₆₄;

R₁₈ and R₁₉, R₃₁ and R₃₄ are each independently, hydrogen atom, or C₁₋₈ alkyl;

R₂₀ and R₂₁ are C₁₋₈ alkyl, C₁₋₈ alkoxy, hydroxy, halogen atom, nitro, or
5 COOR₃₆;

R₂₂ and R₆₄ are each independently C₁₋₈ alkyl;

R₂₃, R₂₄, R₂₅ and R₂₆ are each independently hydrogen atom, C₁₋₈ alkyl, or phenyl;

R₂₇, R₂₈, R₂₉, R₃₀, R₃₂, R₃₃ and R₃₅ are (1) C₁₋₈ alkyl, (2) C₂₋₈ alkenyl, (3) C₁₋₈
10 alkyl substituted with 1-5 of R₃₇, (4) diphenylmethyl, (5) triphenylmethyl, (6) Cyc3, (7) C₁₋₈ alkyl or C₂₋₈ alkenyl substituted with Cyc3, (8) C₁₋₈ alkyl substituted with O-Cyc3, S-Cyc3 or SO₂-Cyc3;

R₃₆ is hydrogen atom, or C₁₋₈ alkyl;

R₃₇ is C₁₋₈ alkoxy, C₁₋₈ alkylthio, benzyloxy, halogen atom, nitro or COOR₃₈;

15 R₃₈ is hydrogen atom, C₁₋₈ alkyl or C₂₋₈ alkenyl;

Cyc3 is (1) C₃₋₁₅ mono-, bi- or tri-cyclic (fused or spiro)carboring, or (2) 3-15 membered mono-, bi- or tri-cyclic (fused or spiro)heteroring comprising 1-4 of heteroatom selected from oxygen, nitrogen and sulfur;

Cyc3 may be substituted with 1-5 of R₃₉;

20 R₃₉ is (1) C₁₋₈ alkyl, (2) C₂₋₈ alkenyl, (3) C₂₋₈ alkynyl, (4) C₁₋₈ alkoxy, (5) C₁₋₈ alkylthio, (6) hydroxy, (7) halogen atom, (8) nitro, (9) oxo, (10) cyano, (11) benzyl, (12) benzyloxy, (13) C₁₋₈ alkyl, C₁₋₈ alkoxy or C₁₋₈ alkylthio substituted with 1-5 of R₄₀, (14) phenyl, phenoxy, phenylthio, phenylsulfonyl or benzoyl which may be substituted with 1-5 of R₄₁, (15) OCOR₄₂, (16) SO₂R₄₃, (17) NR₄₄COR₄₅, (18) SO₂NR₄₆R₄₇, (19)
25 COOR₄₈, or (20) NR₄₉R₅₀;

R₄₀ is halogen atom;

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R₄₁ is C₁₋₈ alkyl, C₁₋₈ alkoxy, halogen atom, or nitro;

R₄₂, R₄₃ and R₄₅ are C₁₋₈ alkyl;

R₄₄ and R₄₈ are hydrogen atom or C₁₋₈ alkyl;

R₄₆ and R₄₇, R₄₉ and R₅₀ are each independently, hydrogen atom or C₁₋₈ alkyl;

5 R_{17'} is (1) SH, (2) NR₆₆CHO, (3) Cyc5, (4) C₁₋₈ alkyl, C₂₋₈ alkenyl or C₂₋₈ alkynyl substituted with Cyc5, (5) CO-(NH-amino acid residue-CO)_n-OH, (6) NR₆₇CONR₆₈R₆₉, (7) CONR₇₀NR₇₁R₇₂, (8) CONR₇₃OR₇₄, (9) CONR₇₅COR₇₆, (10) C(S)NR₇₇R₇₈, (11) CONR₇₉C(S)COOR₈₀, (12) NR₈₁COCOOR₈₂, (13) NR₈₃COOR₈₄, (14) CONR₈₅C(S)R₈₆, (15) OCOR₈₇, (16) SOR₈₈, (17) CONR₈₉R₉₀,
10 (18) SO₂NR₉₁R₉₂, (19) COOR₉₃, (20) COCOOR₉₄, (21) COR₉₅, (22) COCOR₉₆, (23) NR₉₇COR₉₈, (24) SO₂R₉₉, (25) NR₁₀₀SO₂R₁₀₁, or (26) NR₁₀₂R₁₀₃;

n is an integer of 1 or 2;

R₆₆, R₇₃, R₇₅, R₇₇, R₇₉, R₈₁, R₈₃, R₈₅, R₉₇, R₁₀₀ and R₁₀₂ are hydrogen atom, or C₁₋₈ alkyl;

15 R₆₇ and R₆₈, R₇₀ and R₇₁ are each independently, hydrogen atom, or C₁₋₈ alkyl;
R₈₉ and R₉₁ are (1) hydrogen atom, (2) C₁₋₈ alkyl, (3) phenyl, or (4) C₁₋₈ alkyl substituted with cyano or C₁₋₈ alkoxy;

R₁₀₃ is Cyc6;

R₆₉, R₇₂, R₇₄, R₇₆, R₇₈, R₈₀, R₈₂, R₈₄, R₈₆, R₈₇, R₈₈, R₉₀ and R₉₂ are
20 (1) hydrogen atom, (2) C₁₋₈ alkyl, (3) C₂₋₈ alkenyl, (4) C₂₋₈ alkynyl, (5) C₁₋₈ alkyl substituted with 1-5 of R₁₀₄, (6) diphenylmethyl, (7) triphenylmethyl, (8) Cyc6, (9) C₁₋₈ alkyl or C₂₋₈ alkenyl substituted with Cyc6, or (10) C₁₋₈ alkyl substituted with O-Cyc6, S-Cyc6 or SO₂-Cyc6;

R₁₀₄ is (1) C₁₋₈ alkoxy, (2) C₁₋₈ alkylthio, (3) benzyloxy, (4) halogen atom,
25 (5) nitro, (6) COOR₁₀₅, (7) cyano, (8) NR₁₀₆R₁₀₇, (9) N₁₀₈COR₁₀₉, (10) hydroxy, (11) SH, (12) SO₃H, (13) S(O)OH, (14) OSO₃H, (15) C₂₋₈ alkenyloxy, (16) C₂₋₈

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alkynyloxy, (17) COR₁₁₀, (18) SO₂R₁₁₁, or (19) C₁₋₈ alkoxy or C₁₋₈ alkylthio substituted with hydroxy;

R₁₀₅ is hydrogen atom, C₁₋₈ alkyl, or C₂₋₈ alkenyl;

R₁₀₆ and R₁₀₇ are each independently, hydrogen atom, or C₁₋₈ alkyl;

5 R₁₀₈ is hydrogen atom, or C₁₋₈ alkyl;

R₁₀₉ and R₁₁₁ are C₁₋₈ alkyl;

R₁₁₀ is C₁₋₈ alkyl, or halogen atom;

R₉₃, R₉₄, R₉₅, R₉₆, R₉₈, R₉₉ and R₁₀₁ are (1) C₂₋₈ alkynyl, (2) C₁₋₈ alkyl substituted with R₁₂₈ which may be substituted with 1-4 of R₂₉, (3) Cyc8, (4) C₁₋₈ alkyl or C₂₋₈ alkenyl substituted with Cyc8, or (5) C₁₋₈ alkyl substituted with O-Cyc8, S-Cyc8 or SO₂-Cyc8; R₁₂₈ is (1) cyano, (2) NR₁₀₆R₁₀₇, (3) NR₁₀₈COR₁₀₉, (4) hydroxy, (5) SH, (6) SO₃H, (7) S(O)OH, (8) OSO₃H, (9) C₂₋₈ alkenyloxy, (10) C₂₋₈ alkynyloxy, (11) COR₁₁₀, (12) SO₂R₁₁₁, or (13) C₁₋₈ alkoxy or C₁₋₈ alkylthio substituted with hydroxy;

R₁₂₉ has the same meaning as R₁₀₄;

15 Cyc5 and Cyc6 may be substituted with 1-5 of R₁₁₂;

R₁₁₂ is (1) C₁₋₈ alkyl, (2) C₂₋₈ alkenyl, (3) C₂₋₈ alkynyl, (4) C₁₋₈ alkoxy, (5) C₁₋₈ alkylthio, (6) hydroxy, (7) halogen atom, (8) nitro, (9) oxo, (10) cyano, (11) benzyl, (12) benzyloxy, (13) C₁₋₈ alkyl, C₁₋₈ alkoxy or C₁₋₈ alkylthio substituted with 1-5 of R₁₁₃, (14) phenyl, phenoxy, phenylthio or benzoyl, which may be substituted with 1-5 of R₁₁₄, (15) COR₁₁₅, (16) SO₂R₁₁₆, (17) NR₁₁₇COR₁₁₈, (18) SO₂NR₁₁₉R₁₂₀, (19) COOR₁₂₁, (20) NR₁₂₂R₁₂₃, (21) COR₁₂₄, (22) CONR₁₂₅R₁₂₆, (23) SH, (24) C₁₋₈ alkyl substituted with hydroxy or NR₁₂₇-benzoyl, or (25) Cyc7;

R₁₁₃ is halogen atom;

R₁₁₄ is C₁₋₈ alkyl, C₁₋₈ alkoxy, halogen atom, or nitro;

25 R₁₁₅, R₁₁₆ and R₁₁₈ are C₁₋₈ alkyl;

R₁₁₇, R₁₂₁, R₁₂₄ and R₁₂₇ are hydrogen atom, or C₁₋₈ alkyl;

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R₁₁₉ and R₁₂₀, R₁₂₂ and R₁₂₃, R₁₂₅ and R₁₂₆ are each independently, hydrogen atom or C₁₋₈ alkyl;

Cyc7 may be substituted with 1-5 group selected from (1) C₁₋₈ alkyl, (2) C₁₋₈ alkoxy, (3) halogen atom, or (4) nitro;

5 Cyc8 may be substituted with R₁₃₀, and it further may be substituted with 1-4 of R₁₃₁;

R₁₃₀ is (1) COR₁₂₄, (2) CONR₁₂₅R₁₂₆, (3) SH, (4) C₁₋₈ alkyl substituted with hydroxy or NR₁₂₇-benzoyl, or (5) Cyc7;

R₁₃₁ has the same meaning as R₁₁₂;

10 Cyc5, Cyc6, Cyc7 and Cyc8 are (1) C₃₋₁₅ mono-, bi- or tri-cyclic (fused or spiro)carboring, or (2) 3-15 membered mono-, bi- or tri-cyclic (fused or spiro)heteroring comprising 1-4 of heteroatom selected from 1-4 of oxygen, nitrogen or sulfur;

wherein when R_{17'} is Cyc5, Cyc5 is not phenyl which may be substituted with 1-5 selected from C₁₋₈ alkyl, C₁₋₈ alkoxy, hydroxy, halogen atom, nitro, COOH, or
15 COO(C₁₋₈ alkyl);

wherein Cyc7 is not phenyl;

Cyc4 is (1) C₅₋₇ monocyclic carboring, or (2) 5-7 membered monocyclic heteroring comprising 1-2 of heteroatom selected from oxygen, nitrogen and sulfur; (abbreviated as dashed line a hereafter;) and (abbreviated as dashed line b hereafter;) are
20 (1) a bond, or (2) a double bond;

R₉ (1) absent or (2) is hydrogen atom;

wherein

(1) when dashed line a is a bond, dashed line b is a double bond, and R₉ is absent,
25 (2) when dashed line a is a double bond, dashed line b is a bond, and R₉ is hydrogen atom and R₆ is absent, and

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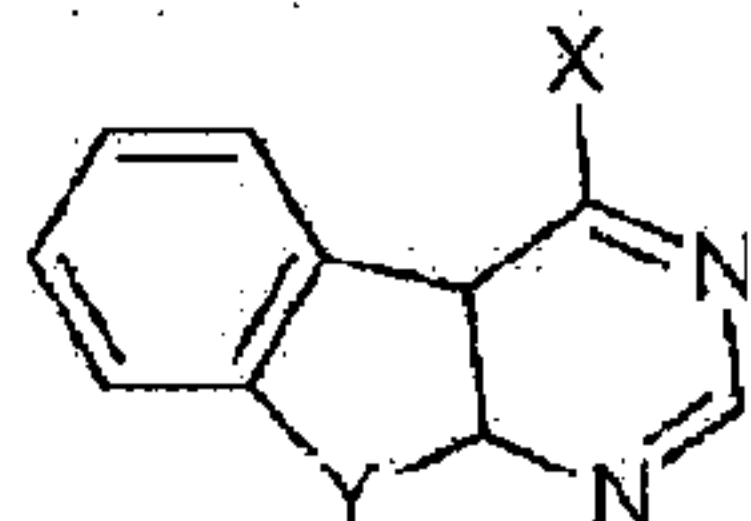
(3) 2-(3,3-dimethyl-3,4-dihydro-(2H)-isoquinolin-1-ylidene)-1-phenylethan-1-one is excluded, or a pharmacologically acceptable salt thereof.

The preparation of these compounds is described in US 2005222138 and WO 2003/064389.

5

In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in WO 2003/057149.

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



10

(13)

The substituents for the above compounds are defined as follows:

(1) X is selected from halogen and NR_1R_2 ,

(2) Y is selected from NR_3 , S, and O, with the proviso that Y is not S when

15 X is Cl,

(3) R_1 and R_2 are independently selected from hydrogen, alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, cycloalkyl of 3-7 carbon atoms, polycycloalkyl of 5-9 carbon atoms, heterocycloalkyl of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S, and O, aryl of 6-12 carbon atoms, which may be substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of 6-12 carbon atoms, or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S, and O, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which

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may be substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of 6-12 carbon atoms, or
5 heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S, and O, and R_4R_5 , or R_1 and R_2 combine to form, together with the nitrogen atom to which they are attached, a 5-7 membered monocyclic saturated ring, which optionally contains 1-2 additional heteroatoms selected from the group consisting of NH, NR_6 , S, and O, or combine to form, together with the nitrogen atom to which they are attached, a
10 6-10 membered fused polycyclic saturated ring, which optionally contains 1-2 additional heteroatoms selected from the group consisting of NH, NR_6 , S, and O, or combine to form, together with the nitrogen atom to which they are attached, a 5-7 membered unsaturated ring, which optionally contains 1-2 additional heteroatoms selected from the group consisting of N, S, and O, wherein said monocyclic saturated ring, polycyclic
15 saturated ring or unsaturated ring may be substituted with 1-2 substituents selected from the group consisting of OH, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-7 carbon atoms, heterocycloalkyl of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S, and O, halogen, haloalkyl of 1-2 carbon atoms and a number of halogen atoms up to the perhalo level, alkoxy of
20 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, and R_7R_8 ,

(4) R_3 is selected from hydrogen, alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, cycloalkyl of 3-7 carbon atoms, and heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S, and O, which
25 may be substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, haloalkyl of 1-6 carbon atoms

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and a number of halogen atom up to the perhalo level, haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of 6-12 carbon atoms, or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S, and O,

(5) R_4 is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, $C(=O)$, $S(=O)_2$, and $C(=O)O$,

(6) R_5 is selected from hydrogen, OH, alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, alkynyl of 2-8 carbon atoms, alkoxy of 1-8 carbon atoms, thioxy of 1-8 carbon atoms, aryl of 6-12 carbon atoms, which may be substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of 6-12 carbon atoms, or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S, and O, heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S, and O, which may be substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of 6-12 carbon atoms, or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S, and O, cycloalkyl of 3-7 carbon atoms, heterocycloalkyl of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S, and O, and NR_9R_{10} ,

(7) R_6 and R_7 are independently selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, and alkynyl of 2-8 carbon atoms,

(8) R_8 is selected from OH, aryl of 6-12 carbon atoms, which may be substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, haloalkyl of 1-6 carbon atoms

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and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of 6-12 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S, and O, and heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S, and O, which
 5 may be substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of 6-12 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S, and O;

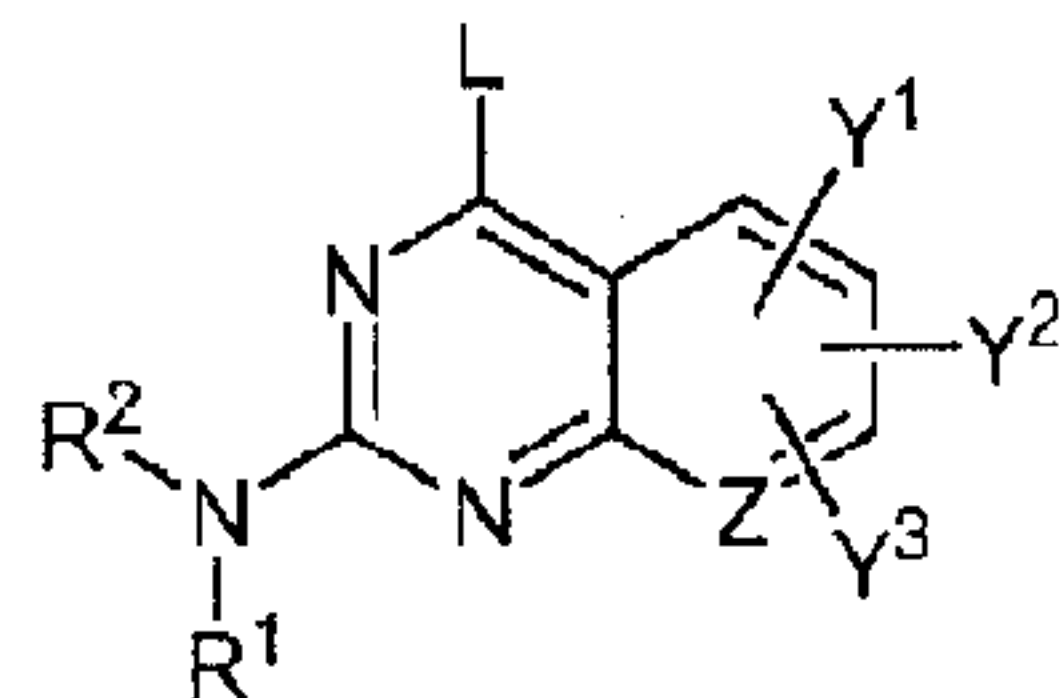
(9) R_9 and R_{10} are independently selected from hydrogen, alkyl of 1-8 carbon
 10 atoms, alkenyl of 2-8 carbon atoms, and alkynyl of 2-8 carbon atoms, or R_9 and R_{10} combine together with the nitrogen atom to which they are attached to form a 5-7 membered, unsaturated ring which may contain 1-2 additional heteroatoms selected from N, S, and O, or to form a 5-7 membered, saturated ring which may contain 1-2 additional heteroatoms selected from NH, NR_{11} , S, and O;

15 (10) R_1 is selected from alkyl of 1-8 carbon atoms, alkenyl of 2-8 carbon atoms, and alkynyl of 2-8 carbon atoms, and pharmaceutically acceptable salts thereof.

The preparation of these compounds is described in WO 2003/057149.

In another embodiment, PDE7 inhibitors useful in the methods of the invention
 20 are selected from those compounds generally or specifically disclosed in US 20030092721, U.S. Patent No. 7,022,849, WO 2002/102315, and US 2006116516.

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



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(14)

The substituents for the above compounds are defined as follows: R_1 is H or alkyl;

R_2 is (a) heteroaryl or heterocyclo, either of which may be optionally substituted
5 with one to three groups T1, T2, T3; or (b) aryl fused to a heteroaryl or heterocyclo ring
wherein the combined ring system may be optionally substituted with one to three groups
T1, T2, T3;

L is (a) OR_4 , $C(O)R_4$, $C(O)OR_4$, SR_4 , NR_3R_4 , $C(O)NR_3R_4$, $NR_3SO_2R_{4b}$,
halogen, nitro, or haloalkyl; or (b) alkyl, aryl, heteroaryl, heterocyclo, or cycloalkyl any
10 of which may be optionally substituted with one to three groups T1a, T2a and/or T3a;

Y_1 , Y_2 and Y_3 are independently (a) hydrogen, halo, or $-OR_{4a}$; or (b) alkyl,
alkenyl, or alkynyl, any of which may be optionally substituted with one to three groups
T1b, T2b and/or T3b;

R_3 and R_4 are independently H, alkyl, alkenyl, aryl, (aryl) alkyl, heteroaryl,
15 (heteroaryl) alkyl, cycloalkyl, (cycloalkyl) alkyl, heterocyclo, or (heterocyclo) alkyl, any
of which may be optionally substituted with one to three groups T1a, T2a and/or T3a; or

R_3 and R_4 together with the nitrogen atom to which they are attached may
combine to form a 4- to 8-membered heterocyclo ring optionally substituted with one to
three groups T1a, T2a and/or T3a;

20 R_{4a} is hydrogen, alkyl, alkenyl, aryl, heteroaryl, (aryl) alkyl, (heteroaryl) alkyl,
heterocyclo, (heterocyclo) alkyl, cycloalkyl, or (cycloalkyl) alkyl, any of which may be
optionally substituted with one to three groups T1b, T2b and/or T3b;

R_{4b} is alkyl, alkenyl, aryl, (aryl) alkyl, heteroaryl, (heteroaryl) alkyl, cycloalkyl,
(cycloalkyl) alkyl, heterocyclo, or (heterocyclo) alkyl, any of which may be optionally
25 substituted with one to three groups T1a, T2a and/or T3a;

Z is N or CH;

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T1-1b, T2-2b, and T3-3b are each independently;

- (1) hydrogen or T6, where T6 is (i) alkyl, (hydroxy)alkyl, (alkoxy)alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkenyl, (cycloalkenyl)alkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl, or (heteroaryl)alkyl; (ii) a group
 5 (i) which is itself substituted by one or more of the same or different groups (i); or (iii) a group (i) or (ii) which is independently substituted by one or more of the following groups (2) to (13) of the definition of T1-1b, T2-2b and T3-3b;

- (2) -OH or -OT6;
 (3) -SH or -ST6;
 10 (4) -C(O)_tH, -C(O)_tT6, or -O-C(O)T6, where t is 1 or 2;
 (5) -SO₃H, -S(O)_tT6, or S(O)_tN(T9)T6;
 (6) halo;
 (7) cyano;
 (8) nitro;
 15 (9) -T4-NT7T8;
 (10) -T4-N(T9)-T5-NT7T8;
 (11) -T4-N(T10)-T5-T6;
 (12) -T4-N(T10)-T5-H; and
 (13) oxo;

- 20 T4 and T5 are each independently a single bond, T11S(O)_tT12-, T11C(O)T12-, T11C(S)T12, T11OT12, T11ST12, T11OC(O)T12, T11C(O)OT12, T11C(=NT9a)T12, or T11C(O)C(O)T12;

T7, T8, T9, T9a and T10 are:

- (1) each independently hydrogen or a group provided in the definition of T6,
 25 or

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(2) T7 and T8 may together be alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached, which ring is unsubstituted or substituted with one or more groups listed in the description of T1-1b, T2-2b and T3-3b, or

5 (3) T7 or T8, together with T9, may be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with one or more groups listed in the description of T1-1b, T2-2b and T3-3b, or

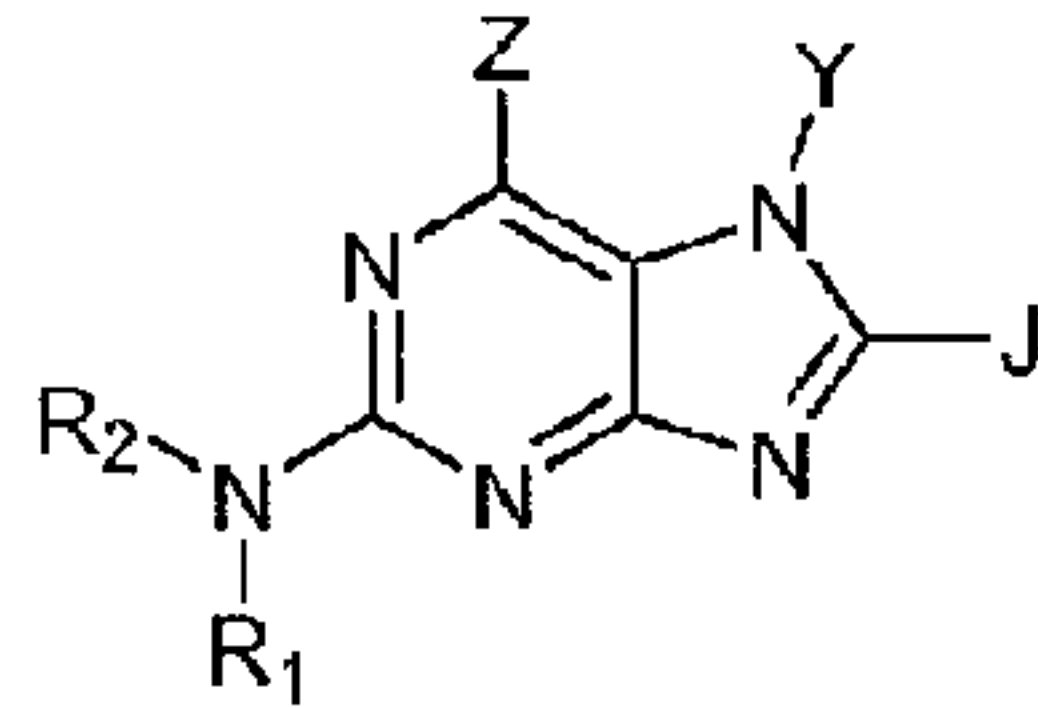
(4) T7 and T8 or T9 and T10 together with the nitrogen atom to which they
10 are attached may combine to form a group N=CT13T14 where T13 and T14 are each independently H or a group provided in the definition of T6; and T11 and T12 are each independently a single bond, alkylene, alkenylene, or alkynylene.

The preparation of these compounds is described in US 20030092721, U.S. Patent No. 7,022,849, WO 2002/102315, and US 2006116516.

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In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in U.S. Patent No. 6,838,559, U.S. 20030100571, and WO 2002/102314.

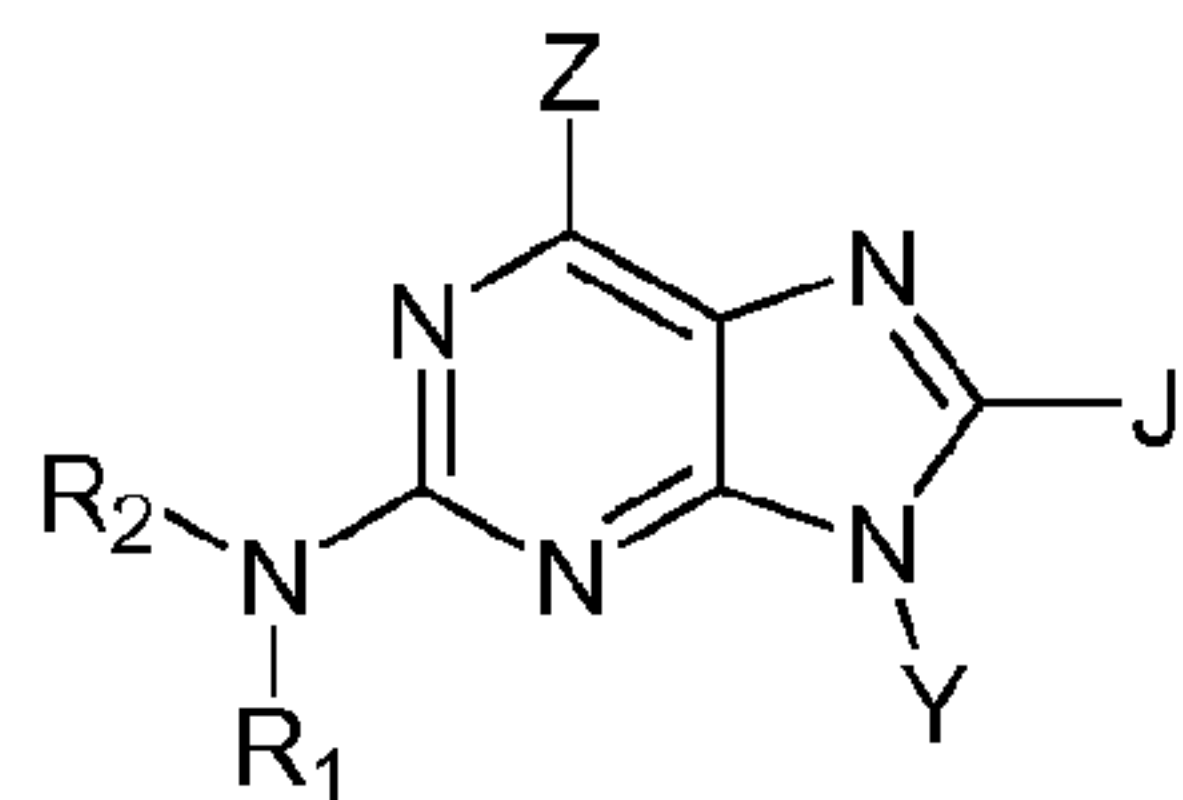
In one embodiment, PDE7 inhibitors useful in the
20 methods of the invention have the formulas:



(15A)

and

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(15B)

The substituents for the above compounds are defined as follows:

R_1 is H or alkyl;

5 R_2 is (a) heteroaryl, or heterocyclo, either of which may be optionally substituted with one to three groups T1, T2, T3; (b) aryl substituted with one to three groups T1, T2, T3 provided that at least one of T1, T2, T3 is other than H; or (c) aryl fused to a heteroaryl or heterocyclo ring wherein the combined ring system may be optionally substituted with one to three groups T1, T2, T3;

10 Y is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclo, heteroaryl, (aryl)alkyl or (heteroaryl) alkyl any of which may be optionally substituted with one to three groups T1a, T2a, T3a;

J is (a) hydrogen, halo, or OR_4 , or (b) alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclo, or, cycloalkyl any of which may be optionally substituted with one to three
15 groups T1b, T2b, T3b;

Z is (a) OR_4 , SR_4 , NR_3R_4 , $NR_3SO_2R_{4a}$ halogen, nitro, haloalkyl; or (b) alkyl, aryl, heteroaryl, heterocyclo, or cycloalkyl any of which may be optionally substituted with one to three groups T1c, T2c, T3c;

R_3 is H, alkyl, alkenyl, aryl, (aryl)alkyl, heteroaryl, (heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclo or (heterocyclo)alkyl any of which may be optionally
20 independently substituted where valance allows with one to three groups T1c, T2c, T3c;

R_4 is alkyl, alkenyl, aryl, (aryl)alkyl, heteroaryl, (heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclo or (heterocyclo)alkyl any of which may be optionally

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independently substituted where valance allows with one to three groups T1d, T2d, or T3d; or

R₃ and R₄ together with the nitrogen atom to which they are attached may combine to form a 4 to 8 membered heterocyclo ring optionally substituted with one to
 5 three groups T1c, T2c, or T3c;

R_{4a} is hydrogen, alkyl, alkenyl, aryl, heteroaryl, (aryl)alkyl, (heteroaryl)alkyl, heterocyclo, (heterocyclo)alkyl, cycloalkyl or (cycloalkyl)alkyl any of which may be optionally substituted with one to three groups T1d, T2d or T3d;

T1, T1a, T1b, T1c, T1d, T2, T2a, T2b, T2c, T2d, T3, T3a, T3b, T3c, and T3d
 10 (hereinafter abbreviated as T1-1d, T2-2d, and T3-3d) are independently

(1) hydrogen or T6, where T6 is

(a) alkyl, (hydroxy) alkyl, (alkoxy) alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl) alkyl, cycloalkenyl, (cycloalkenyl) alkyl, aryl, (aryl) alkyl, heterocyclo, (heterocyclo) alkyl, heteroaryl, or (heteroaryl) alkyl;

15 (b) a group (a) which is itself substituted by one or more of the same or different groups (a); or

(c) a group (a) or (b) which is independently substituted by one or more (preferably 1 to 3) of the following groups (2) to (13) of the definition of T1-1d, T2-2d and T3-3d,

20 (2) OH or OT6,

(3) SH or ST6,

(4) C(O)^t H, C(O)^t T6, or OC(O)T6, where t is 1 or 2;

(5) SO₃ H, S(O)^t T6, or S(O)^t N(T9)T6,

(6) halo,

25 (7) cyano,

(8) nitro,

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- (9) T4NT7 T8,
- (10) T4N(T9)-T5NT7 T8,
- (11) T4N(T10)-T5-T6,
- (12) T4N(T10)-T5H,

5 (13) oxo,

T4 and T5 are each independently a single bond, T11-S(O)_t-T12, T11-C(O)-T12, T11-C(S)-T12, T11-O-T12, -T11S-T12, -T11OC(O)-T12, -T11-C(O)O-T12, -T11C(=NT9a)-T12, or T11-C(O)-C(O)-T12;

T7, T8, T9, T9a and T10 are

10 (1) each independently hydrogen or a group provided in the definition of T6,
or

(2) T7 and T8 may together be alkylene or alkenylene, completing a 3- to 8-membered saturated or unsaturated ring together with the atoms to which they are attached, which ring is unsubstituted or substituted with one or more groups listed in the
15 description of T1-1d, T2-2d and T3-3d, or

(3) T7 or T8, together with T9, may be alkylene or alkenylene completing a 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with one or more groups listed in the description of T1-1d, T2-2d and T3-3d, or

20 (4) T7 and T8 or T9 and T10 together with the nitrogen atom to which they are attached may combine to form a group N=CT13 T14 where

T13 and T14 are each independently H or a group provided in the definition of T6; and

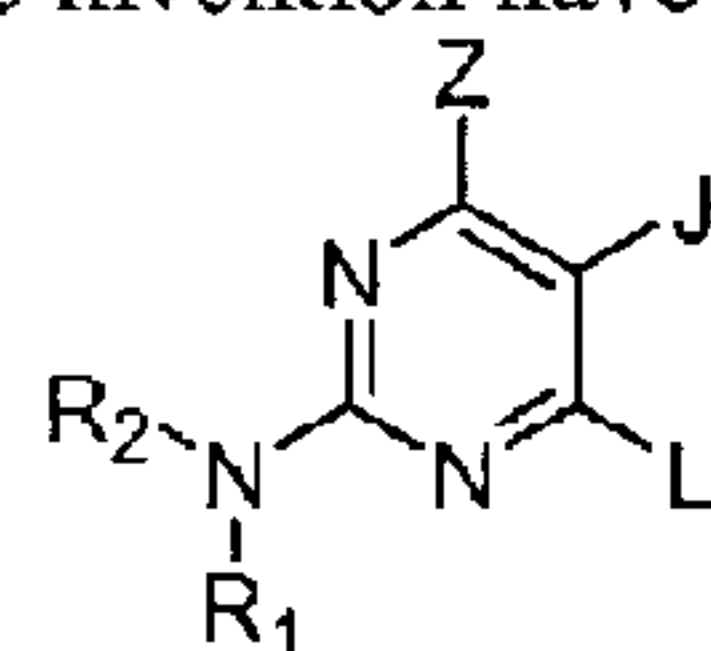
T11 and T12 are each independently a single bond, alkylene, alkenylene, or
25 alkynylene.

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The preparation of these compounds is described in U.S. Patent No. 6,838,559, U.S. 20030100571, and WO 2002/102314.

In another embodiment, PDE7 inhibitors useful in the methods of the invention
5 are selected from those compounds generally or specifically disclosed in U.S. Patent No. 7,087,614, U.S. 20030162802, and WO 2002/102313.

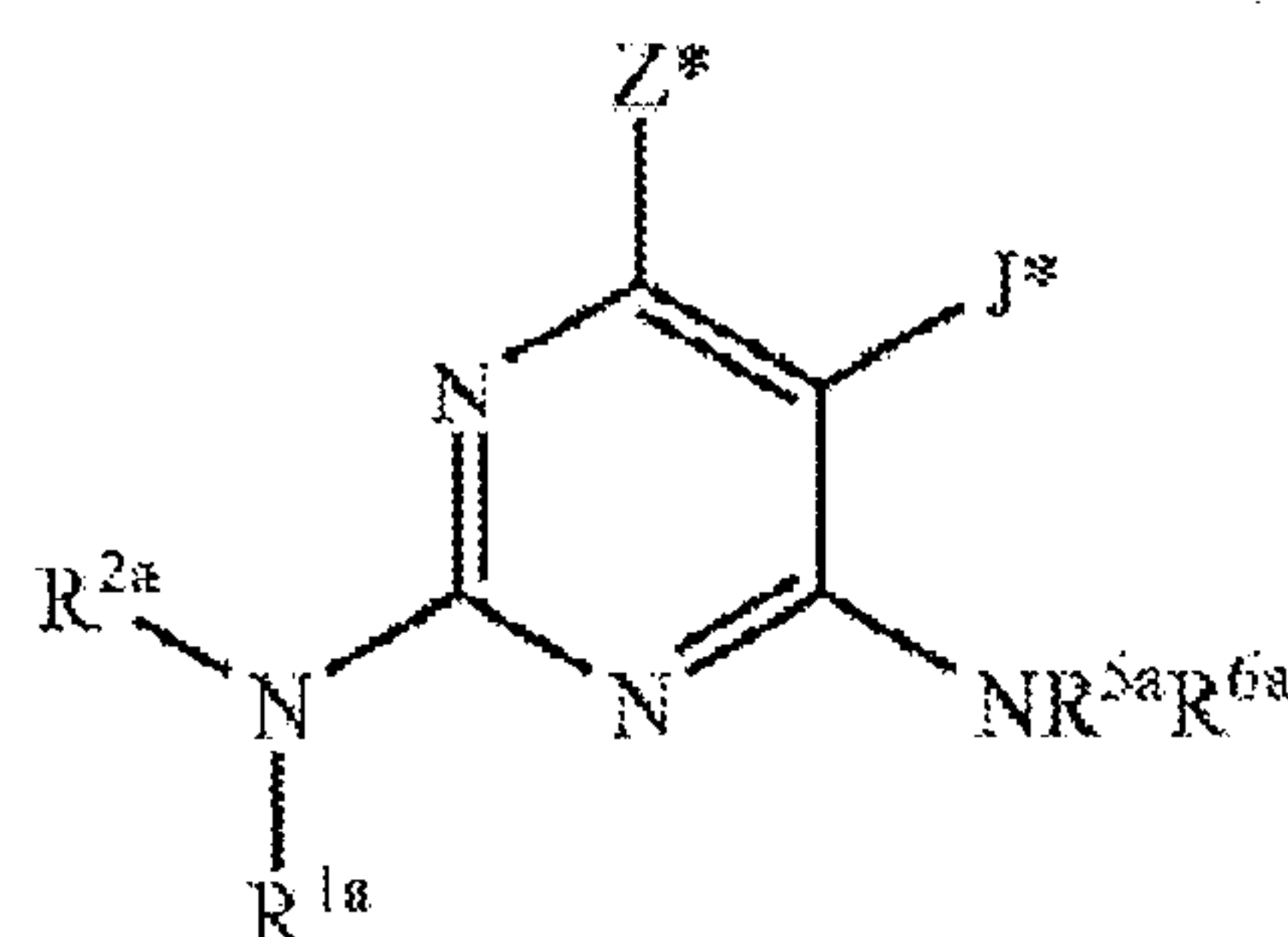
In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



10 (16)

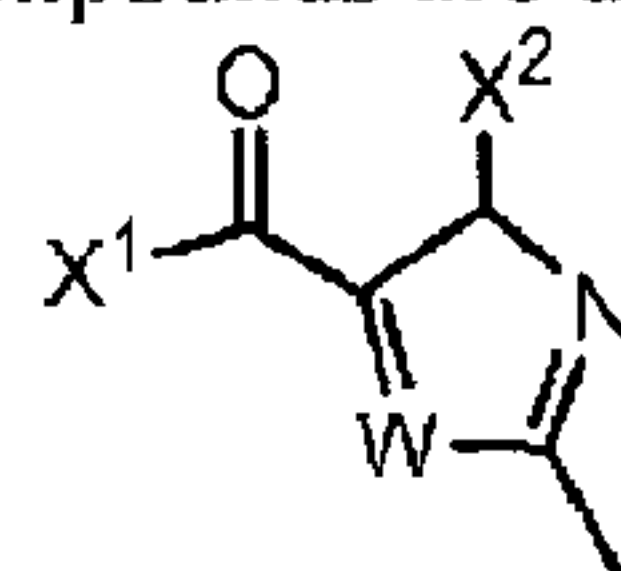
The substituents for the above compounds are described below.

In a related embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



15 (16a)

The substituents for the above compounds are defined as follows:



R_{1a} is hydrogen or alkyl; R_{2a} is alkyl;
W is S; X₁ is alkoxy; and X₂ is

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Z* is halogen, haloalkyl, oxazolyl, NR_{3a}R_{4a}, C(O)-N(H)-alkylene-COOH, or phenyl which is unsubstituted or substituted with heteroaryl, CO_tH, or CO_tT₆;

R_{3a} is hydrogen or alkyl;

R_{4a} is alkyl, alkoxy, unsubstituted or substituted (heteroaryl) alkyl, unsubstituted
 5 or substituted heterocyclo, unsubstituted or substituted (heterocyclo) alkyl, or (aryl) alkyl wherein the aryl group is substituted with one or two groups T1 and/or T2 and/or further substituted with a group T3; or R_{3a} and R_{4a} together with the nitrogen atom to which they are attached combine to form an unsubstituted or substituted heterocyclo ring;

R_{5a} is an unsubstituted or substituted (heteroaryl) alkyl, or (aryl) alkyl wherein the
 10 aryl group is substituted with one or two groups T1 and/or T2 and/or further substituted with a group T3; or R_{5a} and R_{6a} together with the nitrogen atom to which they are attached combine to form an unsubstituted or substituted heterocyclo ring; R_{6a} is hydrogen or alkyl; J* is hydrogen or alkyl; T1 and T2 are independently alkoxy, alkoxy carbonyl, heteroaryl, SO₃H, or SO₂R_{8a} where R_{8a} is alkyl, amino, alkylamino or
 15 dialkylamino; or T1 and T2 together with the aryl ring to which they are attached combine to form a bicyclic ring; T3 is H, alkyl, halo, haloalkyl, or cyano; t is 1 or 2; and T6 is alkyl, haloalkyl, cycloalkyl, alkoxy, or heteroaryl.

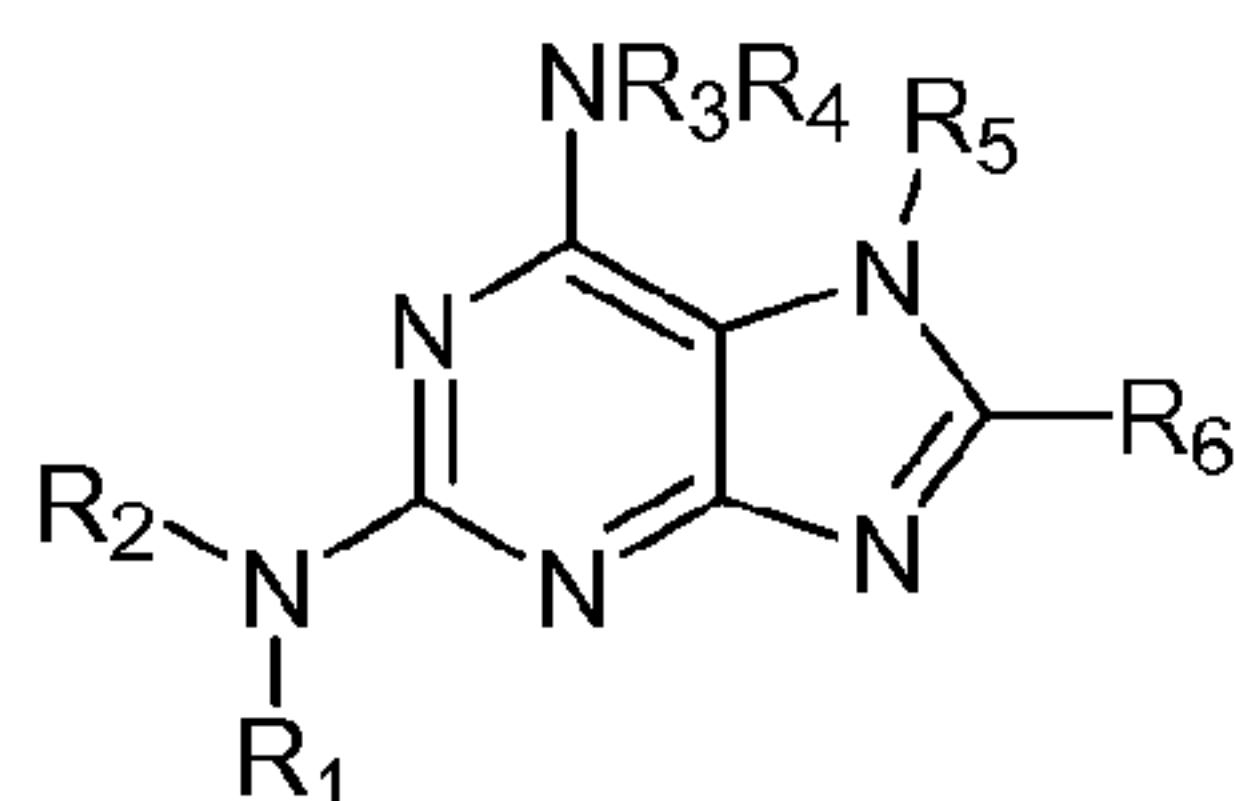
The preparation of these compounds is described in U.S. Patent No. 7,087,614, U.S. 20030162802, and WO 2002/102313.

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In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in US 20030104974, WO 2002/088080, and WO 2002/088079.

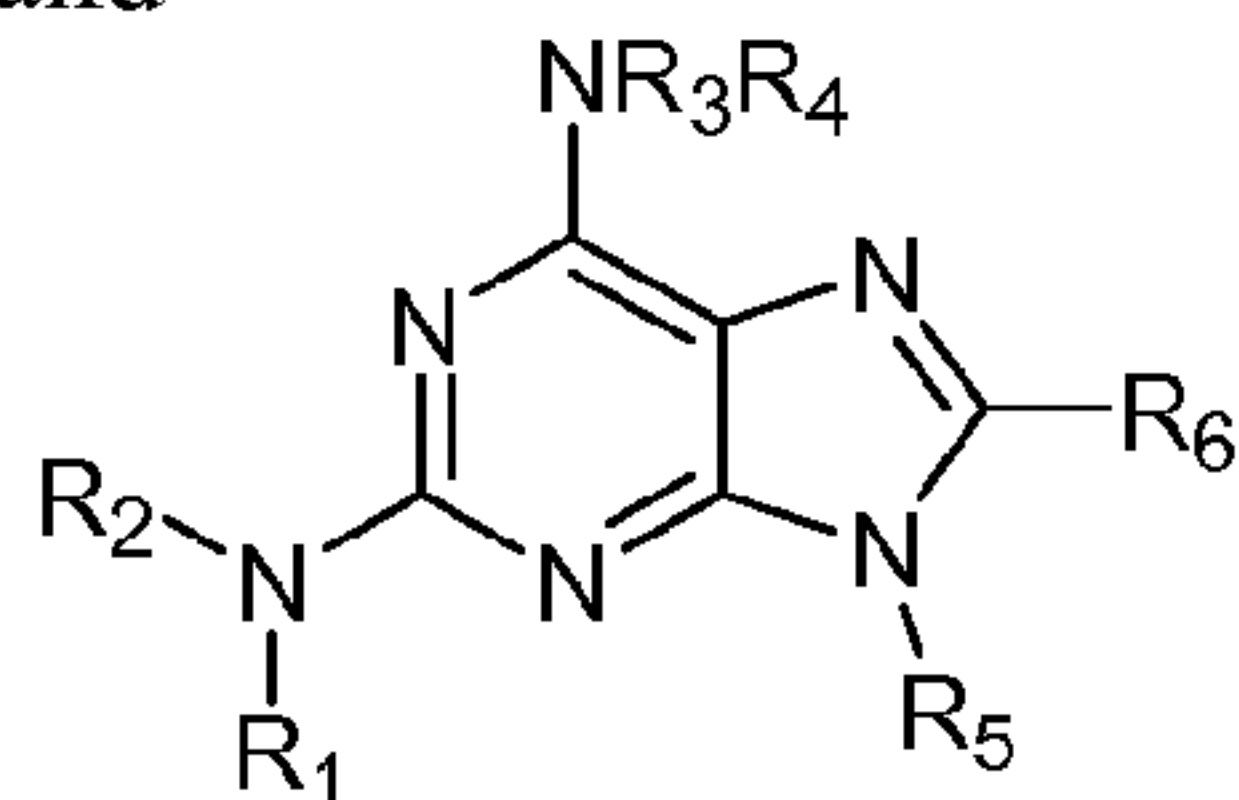
In one embodiment, PDE7 inhibitors useful in the
 25 methods of the invention have the formulas:

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(17A)

and

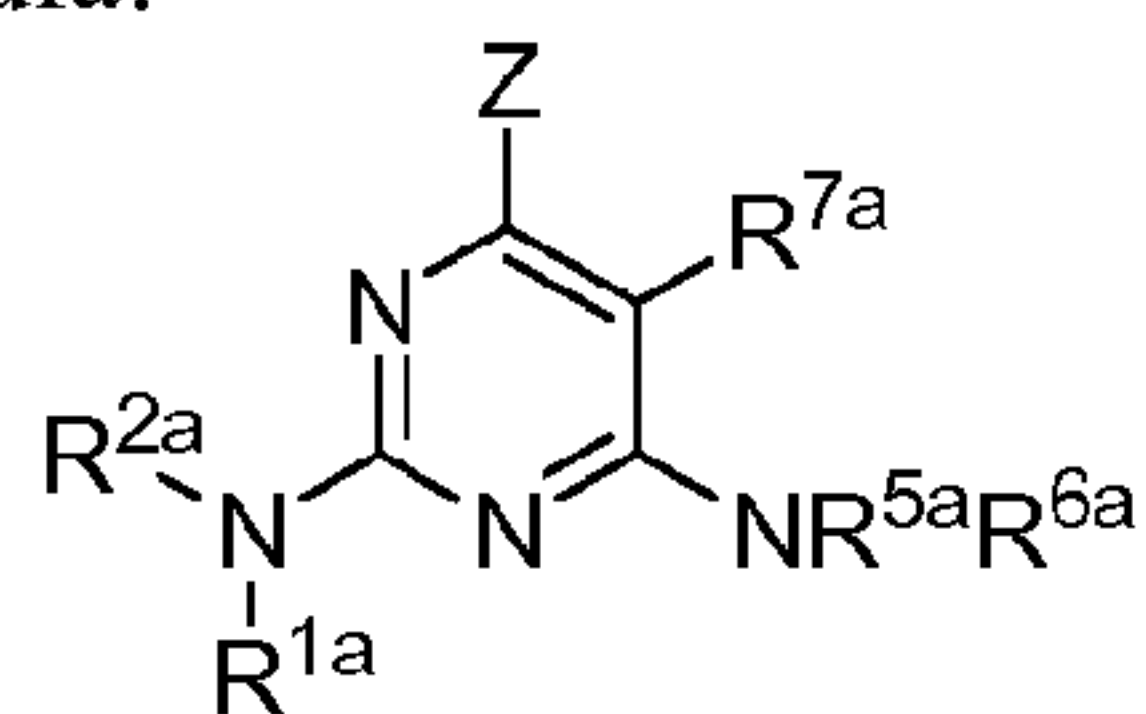


(17B)

The substituents for the above compounds are defined as follows:

R_1 is H or alkyl; R_2 is optionally substituted heteroaryl, or 4-substituted aryl; R_3 is hydrogen or alkyl; R_4 is alkyl, optionally substituted (aryl)alkyl, optionally substituted (heteroaryl)alkyl, optionally substituted heterocyclo, or optionally substituted (heterocyclo)alkyl; or R_3 and R_4 together with the nitrogen atom to which they are attached may combine to form an optionally substituted heterocyclo ring; R_5 is alkyl, optionally substituted (aryl)alkyl, or optionally substituted (heteroaryl)alkyl; and R_6 is hydrogen or alkyl.

In a related embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:

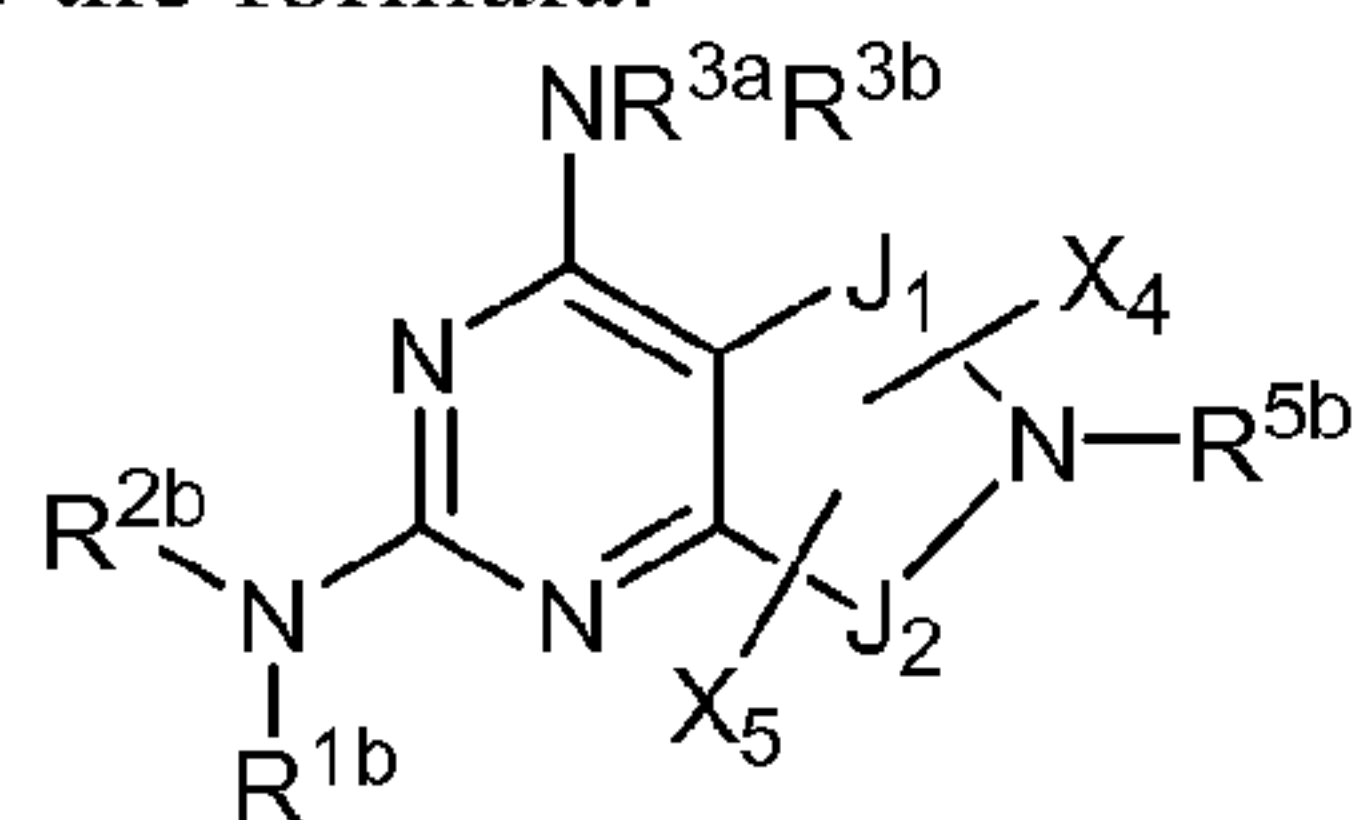


wherein R_{1a} is H or alkyl; R_{2a} is optionally substituted heteroaryl; Z is halogen, alkyl, substituted alkyl, haloalkyl, or $NR_{3a}R_{4a}$; R_{3a} is hydrogen or alkyl; R_{4a} is alkyl, optionally substituted (heteroaryl) alkyl, optionally substituted heterocyclo, optionally substituted (heterocyclo) alkyl, or (aryl) alkyl wherein the aryl group is substituted with

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one or two groups T1 and T2 and optionally further substituted with a group T3; or R_{3a} and R_{4a} together with the nitrogen atom to which they are attached may combine to form an optionally substituted heterocyclo ring; R_{5a} is (aryl) alkyl wherein the aryl group is substituted with one or two groups T1 and T2 and optionally further substituted with a group T3; R_{6a} is hydrogen or alkyl; R_{7a} is hydrogen or alkyl; T1 and T2 are independently alkoxy, alkoxycarbonyl, heteroaryl or SO₂R_{8a} where R_{8a} is alkyl, amino, alkylamino or dialkylamino; or T1 and T2 together with the atoms to which they are attached may combine to form a ring (e.g., benzodioxole); T3 is H, alkyl, halo, haloalkyl or cyano.

10 In another related embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:

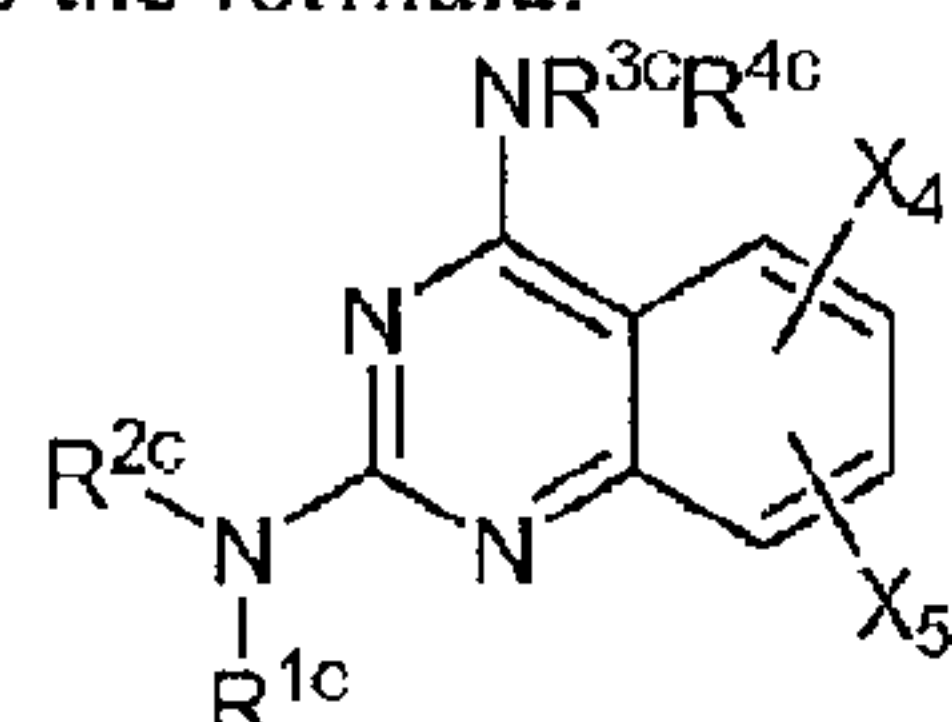


wherein R_{1b} is H or alkyl; R_{2b} is optionally substituted heteroaryl; R_{3b} is H or alkyl; R_{4b} is optionally substituted (aryl)alkyl; R_{5b} is H, alkyl, or C(O)(CH₂)_vOYR_{6b},
 15 where Y is a bond or C(O), R_{6b} is hydrogen or alkyl, and v is an integer from 0 to 2;
 J₁ and J₂ are independently optionally substituted C₁₋₁₃ alkylene, provided that J₁ and J₂ are not both greater than C₂ alkylene; X₄ and X₅ are optional substituents bonded to any available carbon atom in one or both of J₁ and J₂, independently selected from hydrogen, OR₇, NR₈R₉, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted
 20 alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocycloalkyl, or heteroaryl; R₇ is hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, cycloalkyl, substituted cycloalkyl, C(O)alkyl, C(O)substituted alkyl, C(O)cycloalkyl, C(O)substituted cycloalkyl, C(O)aryl, C(O)substituted aryl, C(O)O-alkyl, C(O)O-substituted alkyl, C(O)heterocycloalkyl, C(O)heteroaryl, aryl, substituted aryl, heterocycloalkyl and

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heteroaryl; and R_8 and R_9 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, alkynyl, C(O) alkyl, C(O) substituted alkyl, C(O) cycloalkyl, C(O)substituted cycloalkyl, C(O)aryl, C(O)substituted aryl, C(O)O alkyl, C(O)O substituted alkyl, C(O) heterocycloalkyl, C(O) heteroaryl, S(O)₂alkyl, S(O)₂ substituted alkyl, S(O)₂ cycloalkyl, S(O)₂ substituted cycloalkyl, S(O)₂aryl, S(O)₂substituted aryl, S(O)₂ heterocycloalkyl, S(O)₂ heteroaryl, aryl, substituted aryl, heterocycloalkyl, and heteroaryl, or R_8 and R_9 taken together with the nitrogen atom to which they are attached complete an optionally substituted heterocycloalkyl or heteroaryl ring.

10 In a further related embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



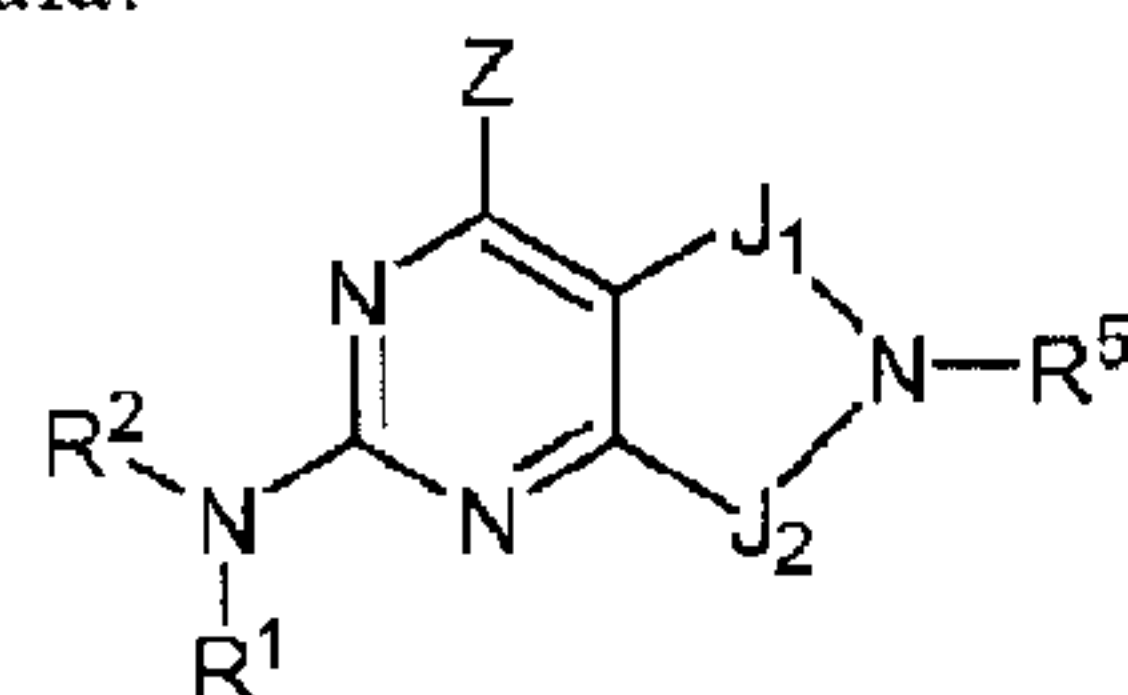
wherein R_{1c} is H or alkyl; R_{2c} is optionally substituted heteroaryl; R_{3c} is H or alkyl; R_{4c} is optionally substituted (aryl)alkyl; and X_4 and X_5 are optional substituents bonded to any available carbon atom in one or both of J_1 and J_2 , independently selected from hydrogen, OR_7 , NR_8R_9 , alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocycloalkyl, or heteroaryl.

The preparation of these compounds is described in US 20030104974, WO 2002/088080, and WO 2002/088079.

In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in US 20030092908 and WO 2002/087513.

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In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



(18)

5 The substituents for the above compounds are defined as follows:

R_1 is hydrogen or alkyl;

R_2 is (a) heteroaryl, or heterocyclo, either of which may be optionally substituted with one to three groups T1, T2, T3; (b) aryl substituted with one to three groups T1, T2, T3 provided that at least one of T1, T2, T3 is other than H; or (c) aryl fused to a
10 heteroaryl or heterocyclo ring wherein the combined ring system may be optionally substituted with one to three groups T1, T2, T3;

Z is NR_3R_4 , $NR_3SO_2R_{4a}$, OR_4 , SR_4 , haloalkyl, or halogen;

R_3 and R_4 are independently H, alkyl, alkenyl, aryl, (aryl)alkyl, heteroaryl, (heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclo or (heterocyclo)alkyl any of
15 which may be optionally independently substituted where valance allows with one to three groups T1a, T2a, or T3a; or

R_3 and R_4 may be taken together with the nitrogen atom to which they are attached to form a heterocyclo or heteroaryl ring optionally independently substituted where valance allows with one to three groups T1a, T2a, or T3a;

20 R_{4a} is alkyl, alkenyl, aryl, (aryl)alkyl, heteroaryl, (heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclo or (heterocyclo)alkyl any of which may be optionally independently substituted where valance allows with one to three groups T1a, T2a, or T3a;

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R_{3b} and R_{4b} are independently H, alkyl, alkenyl, aryl, (aryl)alkyl, heteroaryl, (heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclo or (heterocyclo)alkyl;

R_5 is

(1) hydrogen, or cyano;

5 (2) alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl or (heteroaryl)alkyl, any of which may be optionally independently substituted where valance allows with one to three groups T1b, T2b, or T3b; or

(3) $C(O)R_6$, $C(O)OR_6$, $C(O)-C(O)OR$, or SO_2R_{6a} ;

10 R_6 is H, alkyl, alkenyl, $NR_{3b}R_{4b}$, heterocyclo, (heterocyclo)alkyl, (hydroxy)alkyl, (alkoxy)alkyl, (aryloxy)alkyl, ($NR_{3b}R_{4b}$)alkyl, heteroaryl, aryl or (aryl)alkyl, any of which may be optionally independently substituted where valance allows with one to three groups T1b, T2b, or T3b;

15 R_{6a} is alkyl, alkenyl, $NR_{3b}R_{4b}$, heterocyclo, (heterocyclo)alkyl, (hydroxy)alkyl, (alkoxy)alkyl, (aryloxy)alkyl, ($NR_{3b}R_{4b}$)alkyl, heteroaryl, aryl or (aryl)alkyl, any of which may be optionally independently substituted where valance allows with one to three groups T1b, T2b, or T3b;

J_1 and J_2 are independently optionally substituted C_{1-3} alkylene, provided that J_1 and J_2 are not both greater than C_2 alkylene; and

20 T1-1b, T2-2b, and T3-3b are each independently

(1) hydrogen or T6, where T6 is (i) alkyl, (hydroxy)alkyl, (alkoxy)alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkenyl, (cycloalkenyl)alkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl, or (heteroaryl)alkyl; (ii) a group (i) which is itself substituted by one or more of the same or different groups (i); or (iii) a group (i) or (ii) which is independently substituted by one or more (preferably 1 to 3) of the following groups (2) to (13) of the definition of T1-1b, T2-2b, and T3-3b,

25

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- (2) OH or OT6,
 (3) SH or ST6,
 (4) C(O)_tH, C(O)_tT6, or OC(O)T6, where t is 1 or 2,
 (5) SO₃H, S(O)_tT6, or S(O)_tN(T9)T6,
 5 (6) halo,
 (7) cyano,
 (8) nitro,
 (9) T4-NT7T8,
 (10) T4-N(T9)-T5-NT7T8,
 10 (11) T4-N(T10)-T5-T6,
 (12) T4-N(T10)-T5H,
 (13) oxo,
- T4 and T5 are each independently (1) a single bond, (2) T11-S(O)_t-T12, (3) T11-C(O)-T12, (4) T11-C(S)-T12, (5) -T11-O-T12, (6) T11-S-T12, (7) T11-O-C(O)-T12,
 15 (8) T11-C(O)-O-T12, (9) T11-C(=NT9a)-T12, or (10) T11-C(O)-C(O)-T12,
- T7, T8, T9, T9a and T10,
- (1) are each independently hydrogen or a group provided in the definition of T6, or
- (2) T7 and T8 may together be alkylene or alkenylene, completing a 3- to
 20 8-membered saturated or unsaturated ring together with the atoms to which they are attached, which ring is unsubstituted or substituted with one or more groups listed in the description of T1-1b, T2-2b, and T3-3b, or
- (3) T7 or T8, together with T9, may be alkylene or alkenylene completing a
 3- to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which
 25 they are attached, which ring is unsubstituted or substituted with one or more groups listed in the description of T1-1b, T2-2b, and T3-3b, or

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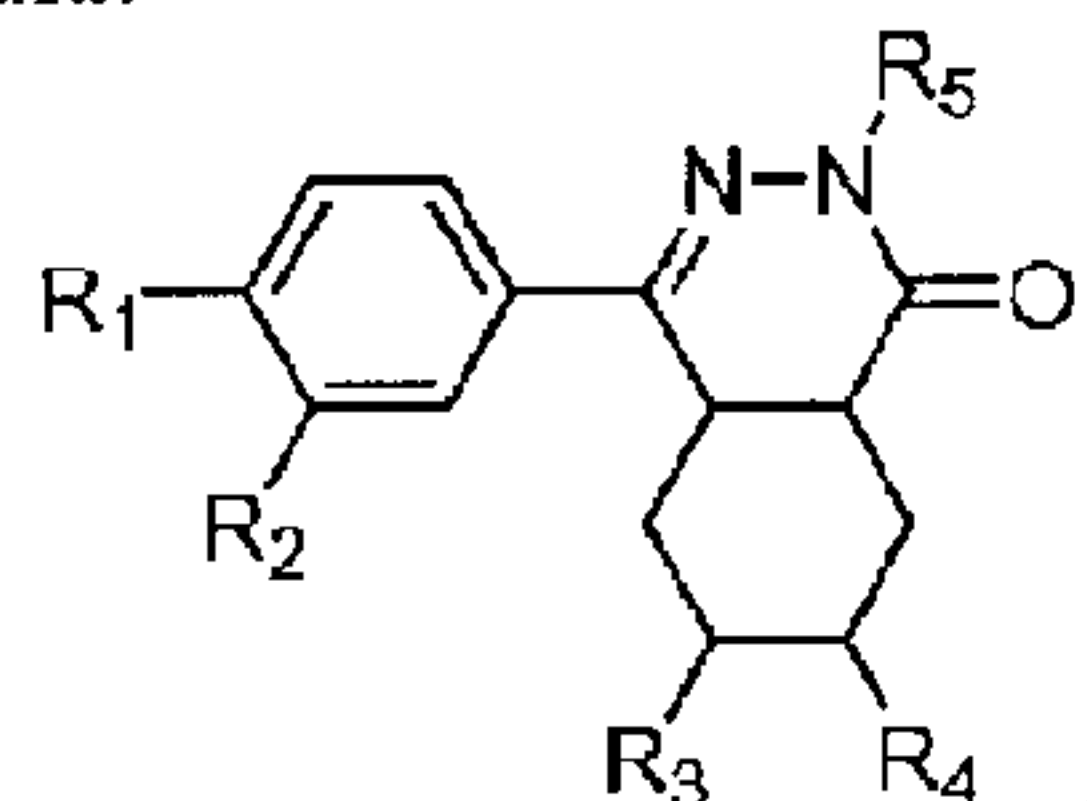
(4) T7 and T8 or T9 and T10 together with the nitrogen atom to which they are attached may combine to form a group N=CT13T14 where T13 and T14 are each independently H or a group provided in the definition of T6; and

T11 and T12 are each independently a single bond, alkylenc, alkenylenc, or alkynylene.

The preparation of these compounds is described in US 20030092908 and WO 2002/087513.

In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in US 20040127707 and WO 2002/085906.

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



(19)

The substituents for the above compounds are defined as follows:

R₁ is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R₂ is fluorine, bromine, or chlorine,

R₃ and R₄ are both hydrogen or together form an additional bond,

R₅ is R₆, C_mH_{2m}-R₇, C_nH_{2n}-C(O)R₈, CH(R₉)₂, C_pH_{2p}-Y-Aryl₁, R₁₂ or R₂₆,

wherein

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R₆ 1-8C-alkyl, 3-10C-cycloalkyl, 3-7C-cycloalkylmethyl, 3-7C-alkenyl, 3-7C-alkynyl, phenyl-3-4C-alkenyl, 7-10C-polycycloalkyl, naphthyl, pyridyl, pyrazinyl, pyridazinyl, pyrimidyl, quinazolinyl, quinoxalinyl, cinnolyl, isoquinolyl, quinolyl, indanyl, indazolyl, benzoxazolyl, benzothiazolyl, oxazolyl, thiazolyl, N-methylpiperidyl, tetrahydropyranyl, 6-methyl-3-trifluoromethyl-pyridin-2-yl, 1,3,4-trimethyl-1H-pyrazolo[3,4-b]pyridin-6-yl, 3-thiophen-2-yl[1,2,4]thiadiazol-5-yl, 1,1-dioxide-tetrahydrothiophen-3-yl, 1-oxo-1,3-dihydro-isobenzofuran-5-yl, 4-(4-yl-but-1-oxy)benzoic acid, or an unsubstituted or by R₆₁ and/or R₆₂ substituted phenyl radical, wherein

10 R₆₁ is hydroxyl, 1-4C-alkyl, 1-4C-alkoxy, nitro, cyano, halogen, carboxyl, hydroxycarbonyl-1-4C-alkyl, 1-4C-alkoxycarbonyl, hydroxy-1-4C-alkyl, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, aminosulfonyl, mono- or di-1-4C-alkylaminosulfonyl, 4-methylphenylsulfonamido, imidazolyl; tetrazol-5-yl, 2-(1-4C-alkyl)tetrazol-5-yl or
15 2-benzyltetrazol-5-yl and

R₆₂ is 1-4C-alkyl, 1-4C-alkoxy, nitro, or halogen,

R₇ is hydroxyl, halogen, cyano, nitro, nitroxy(O-NO₂), carboxyl, carboxyphenoxy, phenoxy, 1-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonyloxy, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonyl, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, amino, mono- or di-1-4C-alkylamino, or an unsubstituted or by R₇₁ and/or R₇₂ substituted piperidyl, piperazinyl, pyrrolidinyl or morpholinyl radical, wherein

R₇₁ is hydroxyl, 1-4C-alkyl, hydroxy-1-4C-alkyl or 1-4C-alkoxycarbonyl, and

R₇₂ is 1-4C-alkyl, carboxyl, aminocarbonyl or 1-4C-alkoxycarbonyl,

25 R₈ is an unsubstituted or by R₈₁ and/or R₈₂ substituted phenyl, naphthyl, phenanthrenyl or anthracenyl radical, wherein

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R₈₁ is hydroxyl, halogen, cyano, 1-4C-alkyl, 1-4C-alkoxy, carboxyl, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, 1-4C-alkylcarbonyloxy, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine, and

5 R₈₂ is hydroxyl, halogen, 1-4C-alkyl, 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

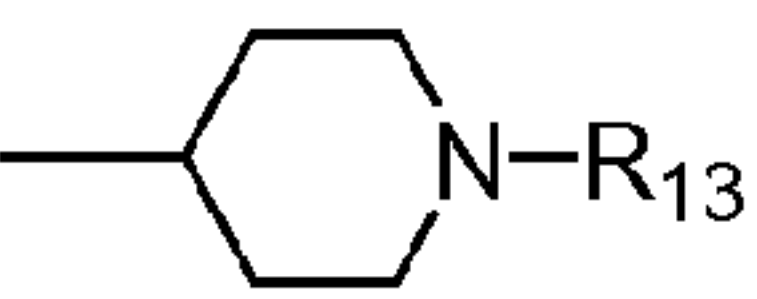
R₉ is C_qH_{2q}-phenyl,

Y is a bond or O (oxygen),

Aryl₁ is an unsubstituted phenyl, naphthyl, pyridyl, pyrazinyl, pyridazinyl,
10 pyrimidinyl, quinazolinyl, quinoxalinyl, cinnolinyl, isoquinolyl, quinolyl, coumarinyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzotriazolyl, N-benzosuccinimidyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, furyl, thienyl, pyrrolyl, a 2-(1-4C-alkyl)-thiazol-4-yl radical, or a phenyl radical substituted by R₁₀ and/or R₁₁, wherein

R₁₀ is hydroxyl, halogen, nitro, cyano, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy,
15 carboxyl, hydroxycarbonyl-1-4C-alkyl, 1-4C-alkylcarbonyloxy, 1-4C-alkoxycarbonyl, amino, mono- or di-1-4C-alkylamino, 1-4C-alkylcarbonylamino, aminocarbonyl, mono- or di-1-4C-alkylamino-carbonyl, imidazolyl or tetrazolyl, and R₁₁ is hydroxyl, halogen, nitro, 1-4C-alkyl or 1-4C-alkoxy,

m is an integer from 1 to 8, n is an integer from 1 to 4, p is an integer from 1 to 6,
20 q is an integer from 0 to 2,

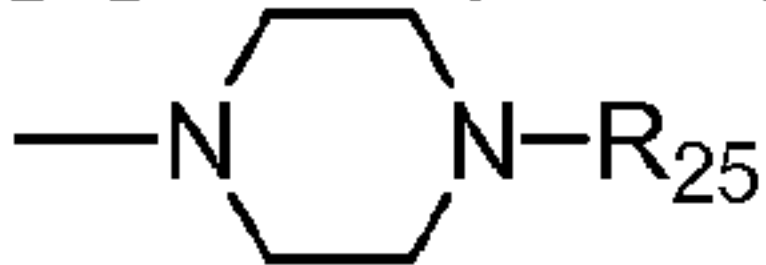
R₁₂ is a radical of formula (a) 

wherein R₁₃ is S(O)₂-R₁₄, S(O)₂-(CH₂)_r-R₁₅, (CH₂)_s-S(O)₂-R₁₆, C(O)-R₁₇, C(O)-(CH₂)_r-R₁₈, (CH₂)_s-C(O)-R₁₉, Hetaryl₁, Aryl₂ or Aryl₃-1-4C-alkyl, R₁₄ is 1-4C-alkyl, 5-dimethylaminonaphthalin-1-yl, N(R₂₀)R₂₁, phenyl or phenyl substituted by R₂₂ and/or

25 R₂₃, R₁₅ is N(R₂₀)R₂₁, R₁₆ is N(R₂₀)R₂₁,

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R_{17} is 1-4C-alkyl, hydroxycarbonyl-1-4C-alkyl, phenyl, pyridyl, 4-ethyl-piperazin-2,3-dion-1-yl, 2-oxo-imidazolidin-1-yl or $N(R_{20})R_{21}$, R_{18} is $N(R_{20})R_{21}$, R_{19} is $N(R_{20})R_{21}$, phenyl, phenyl substituted by R_{22} and/or R_{23} and/or R_{24} , R_{20} and R_{21} are independent from each other hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkylmethyl or phenyl, or R_{20} and R_{21} together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-ring, 1-pyrrolidinyl-ring, 1-piperidinyll-ring, 1-hexahydroazepino-ring or a 1-piperazinyll-ring of formula (b)

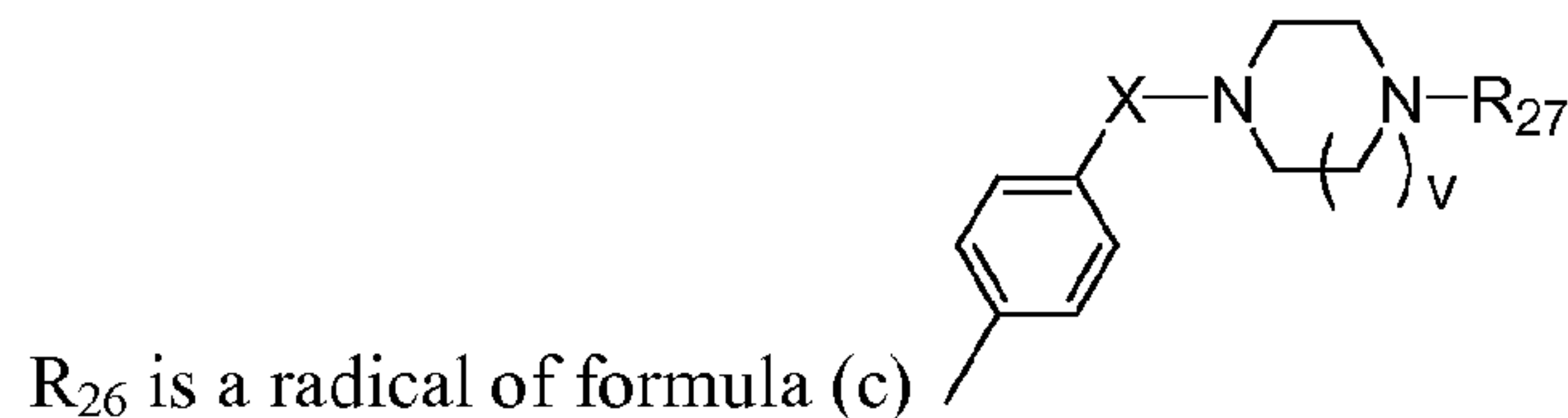
5 

wherein R_{25} is pyrid-4-yl, pyrid-4-ylmethyl, 1-4C-alkyl-dimethylamino, dimethylaminocarbonylmethyl, N-methyl-piperidin-4-yl, 4-morpholino-ethyl or tetrahydrofuran-2-ylmethyl-, R_{22} is halogen, nitro, cyano, carboxyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, amino, mono-or di-1 4C-alkylamino, aminocarbonyl 1-4C-alkylcarbonylamino or mono-or di-1-4C-alkylaminocarbonyl-, R_{23} is halogen, amino, nitro, 1-4C-alkyl or 1-4C-alkoxy, R_{24} is halogen,

15 Hetaryl₁ is pyrimidin-2-yl, thieno-[2,3-d]pyrimidin-4-yl, 1-methyl-1H-pyrazolo-[3,4-d]pyrimidin-4-yl, thiazolyl, imidazolyl or furanyl, Aryl₂ is pyridyl, phenyl or phenyl substituted by R_{22} and/or R_{23} , Aryl₃ is pyridyl, phenyl, phenyl substituted by R_{22} and/or R_{23} , 2-oxo-2H-chromen-7-yl or 4-(1,2,3-thiadiazol-4-yl)phenyl,

r is an integer from 1 to 4, s is an integer from 1 to 4,

20



wherein R_{27} is $C(O)R_{28}$, $(CH_2)_t-C(O)R_{29}$, $(CH_2)_uR_{30}$, Aryl₄, Hetaryl₂, phenylprop-1-en-3-yl or 1-methylpiperidin-4-yl, R_{28} hydrogen, 1-4C-alkyl, OR_{31} , furanyl, indolyl, phenyl, pyridyl, phenyl substituted by R_{34} and/or R_{35} or pyridyl substituted by R_{36} and/or

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R_{37} , R_{29} is $N(R_{32})R_{33}$, R_{30} is $N(R_{32})R_{33}$, tetrahydrofuranyl or pyridinyl, R_{31} is 1-4C-alkyl, R_{32} is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl, R_{33} is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkylmethyl, or

R_{32} and R_{33} together and with inclusion of the nitrogen atom to which they are
 5 bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl- or 1-hexahydroazepinyl-
 ring,

Aryl₄ is phenyl, pyridyl, pyrimidinyl, phenyl substituted by R_{34} and/or R_{35} ,
 pyridyl substituted by R_{36} and/or R_{37} , R_{34} is halogen, nitro, 1-4C-alkyl, trifluoromethyl or
 1-4C-alkoxy, R_{35} is halogen or 1-4C-alkyl, R_{36} is halogen, nitro, 1-4C-alkyl,
 10 trifluoromethyl or 1-4C-alkoxy, R_{37} is halogen or 1-4C-alkyl,

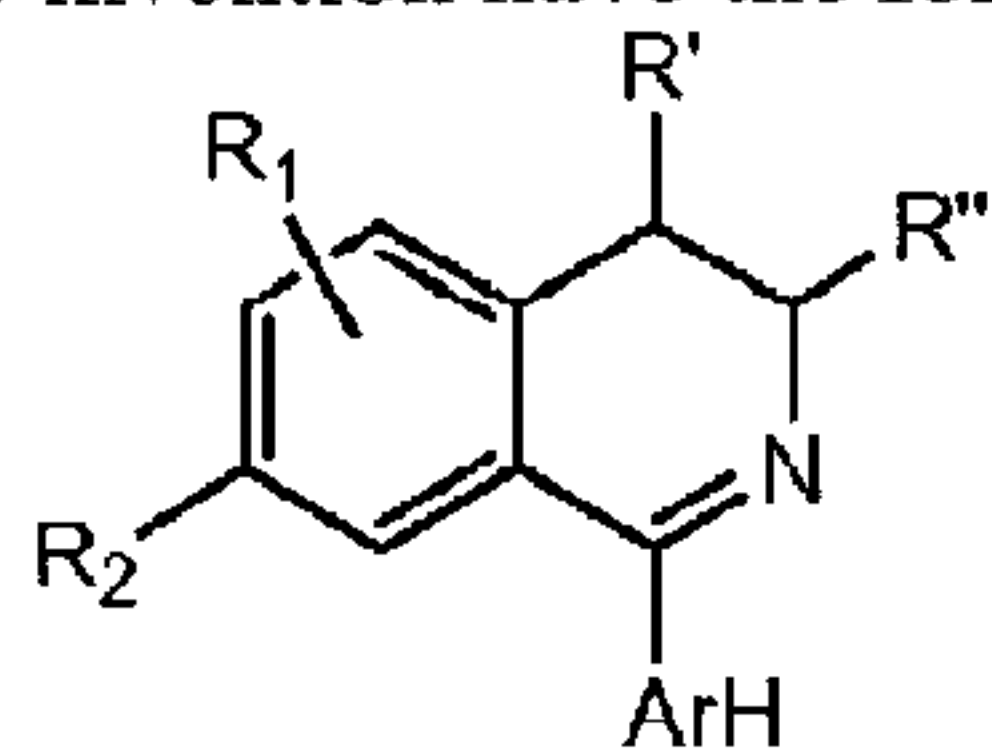
Hetaryl₂ is indol-4-yl, 2-methyl-quinolin-4-yl, 5-chloro-6-oxo-1-phenyl-1,6-
 dihydro-pyridazin-4-yl, 3-phenyl-1,2,4-thiadiazol-5-yl or 3-o-tolyl-1,2,4-thiadiazol-5-yl,

t is an integer from 1 to 4, u is an integer from 1 to 4, v is an integer from 1 to 2,
 X is -C(O)- or -S(O)₂-, and the salts of these compounds.

15 The preparation of these compounds is described in US 20040127707 and
 WO 2002/085906.

In another embodiment, PDE7 inhibitors useful in the methods of the invention
 are selected from those compounds generally or specifically disclosed in U.S. Patent
 20 No. 6,818,651, US 20040044212, and WO 2002/040450.

In one embodiment, PDE7 inhibitors useful in the
 methods of the invention have the formula:

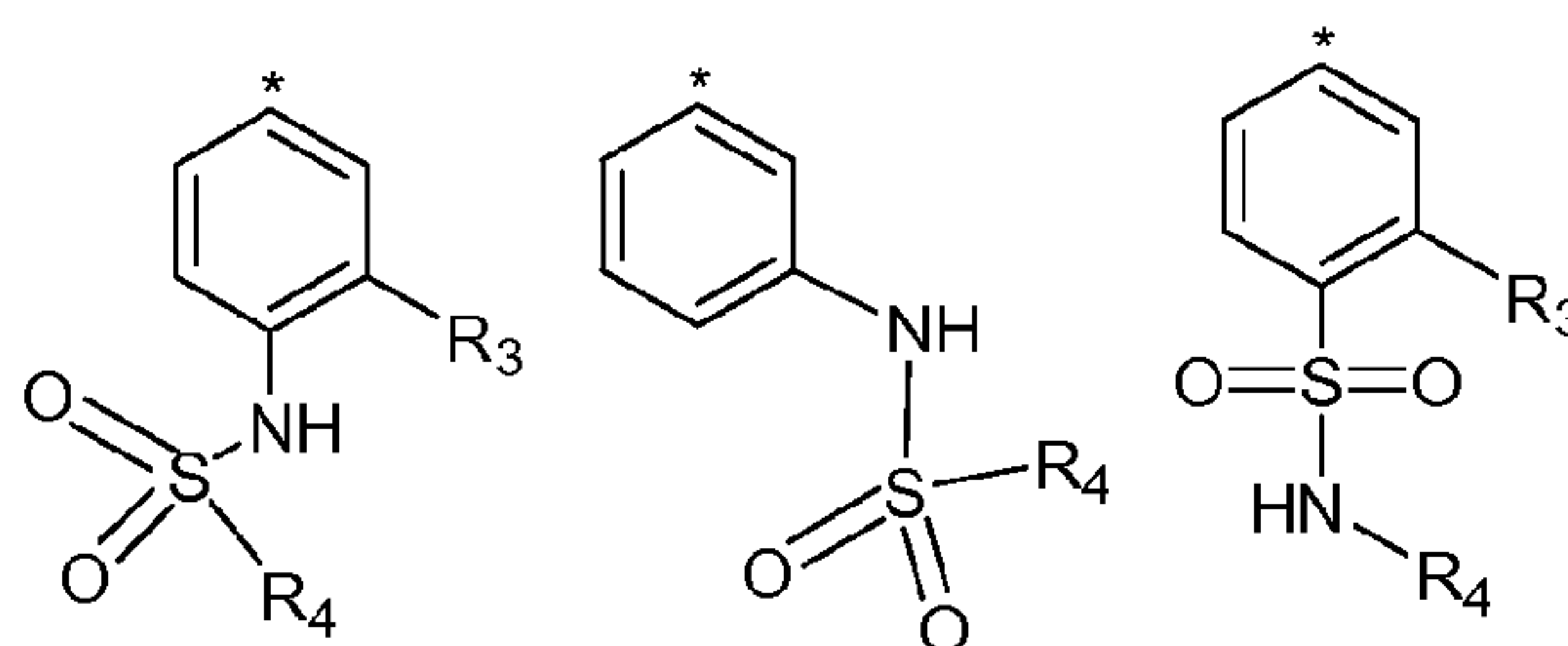


(20)

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The substituents for the above compounds are defined as follows:

either R_1 denotes hydrogen, and R_2 denotes fluorine, chlorine, bromine, cyano, trifluoromethyl or phenoxy, or R_1 denotes hydrogen, fluorine, chlorine, bromine, trifluoromethyl or cyano, and R_2 denotes hydrogen, R' and R'' both denote hydrogen or together represent a bond, and Ar represents a phenyl radical of the formulae IIa, IIb, or IIc



wherein R_3 denotes hydrogen, hydroxyl, nitro, amino, carboxyl, aminocarbonyl, 1-4C-alkoxy, trifluoromethoxy, 1-4C-alkoxycarbonyl or mono- or di-1-4C-alkylaminocarbonyl,

R_4 represents 1-4C-alkyl, naphthalenyl, 5-dimethylaminonaphthalen-1-yl, phenylethen-2-yl, 3,5-dimethylisoxazol-4-yl, 5-chloro-3-methylbenzo[b]thiophen-2-yl, 6-chloro-imidazo[2,1b]-thiazol-5-yl, or represents a phenyl or thiophene radical which is unsubstituted or is substituted by one or more identical or different radicals selected from the group halogen, cyano, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy which is substituted entirely or mainly by fluorine, 1-4C-alkoxy, 1-4C-alkylcarbonylamino, 1-4C-alkoxycarbonyl, phenylsulfonyl or isoxazolyl, or

a hydrate, solvate, salt, hydrate of a salt, or solvate of a salt thereof.

The preparation of these compounds is described in U.S. Patent No. 6,818,651, US 20040044212, and WO 2002/040450.

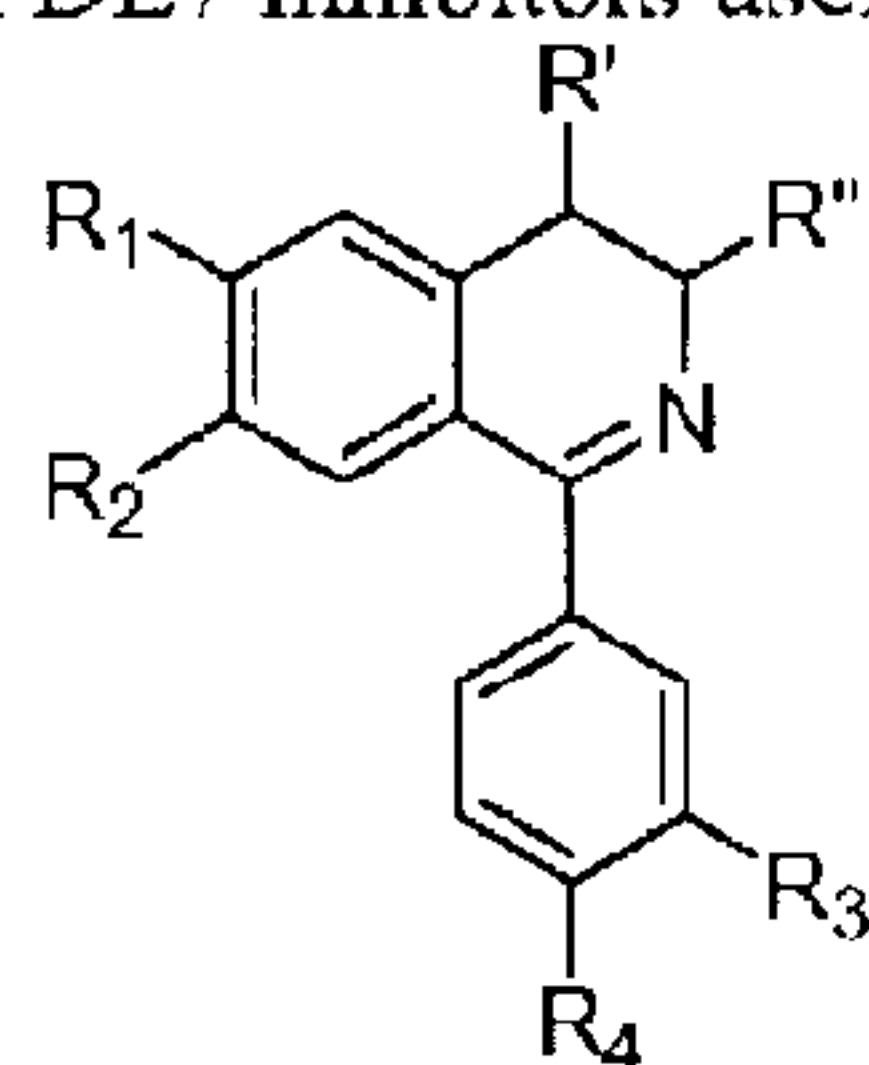
In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in

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WO 2002/040449 .

In one

embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



(21)

5 The substituents for the above compounds are defined as follows:

either R_1 denotes hydrogen and R_2 denotes fluorine, chlorine, bromine, cyano, trifluoromethyl or phenoxy, or

R_1 denotes hydrogen, fluorine, chlorine, bromine, trifluoromethyl or cyano and R_2 denotes hydrogen,

10 R' and R'' both denote hydrogen or together represent a bond,

R_3 denotes hydrogen, hydroxyl, nitro, amino, carboxyl, aminocarbonyl, 1-4C-alkoxy, trifluoromethoxy, 1-4C-alkoxycarbonyl or mono- or di-1-4C-alkylaminocarbonyl and R_4 denotes $C(O)-X-R_5$, $N(H)-C(O)-R_6$ or $N(H)-C(O)-N(H)-R_2$, wherein

X denotes O or $N(H)$,

15 R_5 denotes hydrogen, 1-4C-alkyl, 3-7C-cycloalkylmethyl, 6,6-dimethylbicyclo[3,3,1]hept-2-yl, 3-7C-alkynyl, 1-4C-alkylcarbonyl-1-4C-alkyl, aminocarbonyl-1-4C-alkyl, furan-2-ylmethyl, 2-pyridin-2-yleth-1-yl, 2-pyridin-3-ylmethyl, N-methylpiperidin-3-yl, 1-benzylpiperidin-4-yl, morpholin-4-yl-eth-2-yl, morpholin-4-yl-eth-1-yl, 2-benzo[1,3]dioxol-4-yl-eth-1-yl, chroman-4-yl, 1-
20 methoxycarbonyl-2-indol-3-yl-eth-1-yl, 1,3-bis-methoxycarbonylprop-1-yl, 1-methoxycarbonyl-3-methylsulfanyl-eth-1-yl, 1-methoxycarbonyl-2-thiazol-2-yl-eth-1-yl, or 4-methylthiazol-5-yl-eth-2-yl, or represents a benzyl-, phenyl-eth-1-yl or 1-

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methoxycarbonyl-2-phenyl-eth-2-yl radical which is unsubstituted or substituted by one or more radicals selected from the group halogen, trifluoromethyl and phenyl,

R_6 denotes 2,4-dichlorophenoxymethyl, 2-tert-butoxycarbonylamino-eth-1-yl, 1-acetyl piperidin-4-yl, Ar1 or Ar2-CH=CH-,

5 where Ar1 represents 3-chlorophenyl, 4-trifluoromethoxyphenyl, 3-phenoxyphenyl, indol-5-yl, 2-methylpyridin-5-yl, quinolin-6-yl or 2-benzothiazol-6-yl, Ar2 represents furan-2-yl, furan-3-yl, thiophen-2-yl, indol-3-yl, 3-trifluoromethylphenyl, 3-methoxyphenyl or pyridin-3-yl,

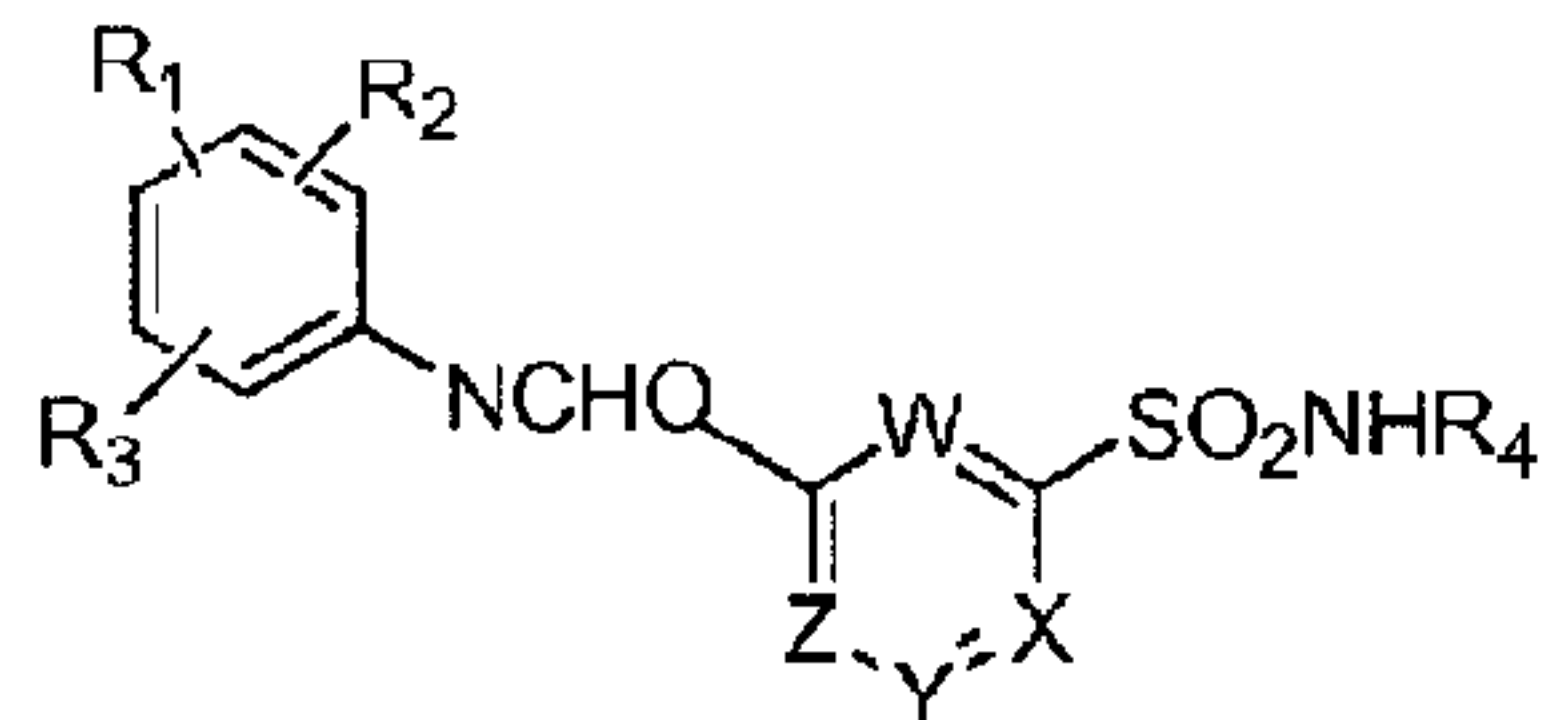
R_7 represents 1-4C-alkyl, 3-7C-alkenyl, 3-7C-cycloalkyl, 1-ethoxycarbonyl-2-phenyl-eth-1-yl, thiophen-2-yleth-1-yl or a phenyl radical which is unsubstituted or substituted by one or more radicals selected from the group halogen, cyano, 1-4C-alkyl, trifluoromethyl, 1-4C-alkylthio, 1-4C-alkoxy, 1-4C-alkoxy which is entirely or predominantly substituted by fluorine, 1-4C-alkylcarbonyl and phenoxy, or

a salt thereof.

15 The preparation of these compounds is described in WO 2002/040449.

In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in WO 2001/098274. In one

20 embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



(22)

The substituents for the above compounds are defined as follows:

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W, X, Y and Z, which may be the same or different, each represents a nitrogen atom or a C(R⁵) group [wherein R₅ is a hydrogen or halogen atom or an alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxy, -NO₂ or -CN group] provided that two or more of W, X, Y, and Z are C(R₅) groups;

5 R₁, R₂ and R₃, which may be the same or different, each is an atom or group -L₁(Alk₁)_rL₂(R₆)_s wherein L₁ and L₂, which may be the same or different, is each a covalent bond or a linker atom or group, r is zero or the integer 1, Alk₁ is an aliphatic or heteroaliphatic chain, s is an integer 1, 2 or 3 and R₆ is a hydrogen or halogen atom or a group selected from alkyl, -OR₇ [where R₇ is a hydrogen atom or an optionally substituted alkyl group], -SR₇, NR₇R₈ [where R₈ is as just defined for R₇ and may be the same or different], -NO₂, CN, CO₂R₇, SO₃H, S(O)R₇, SO₂R₇, OCO₂R₇, CONR₇R₈, OCONR₇R₈, CSNR₇R₈, OCR₇, OCOR₇, N(R₇)COR₈, N(R₇)CSR₈, S(O)NR₇R₈, SO₂NR₇R₈, N(R₇)SO₂R₈, N(R₇)CON(R₈)(R₉) [where R₉ is a hydrogen atom or an optionally substituted alkyl group], N(R₇)CSN(R₈)(R₉), N(R₇)SO₂N(R₈)(R₉),
10 C(R₇)=NO(R₈), cycloaliphatic, heterocycloaliphatic, aryl or heteroaryl group]; provided that one or more of R₁, R₂, or R₃ is a substituent other than a hydrogen atom;

R₄ represents an optionally substituted phenyl, 1- or 2- naphthyl, pyridyl, pyrimidinyl, pyridazinyl, or pyrazinyl group; and

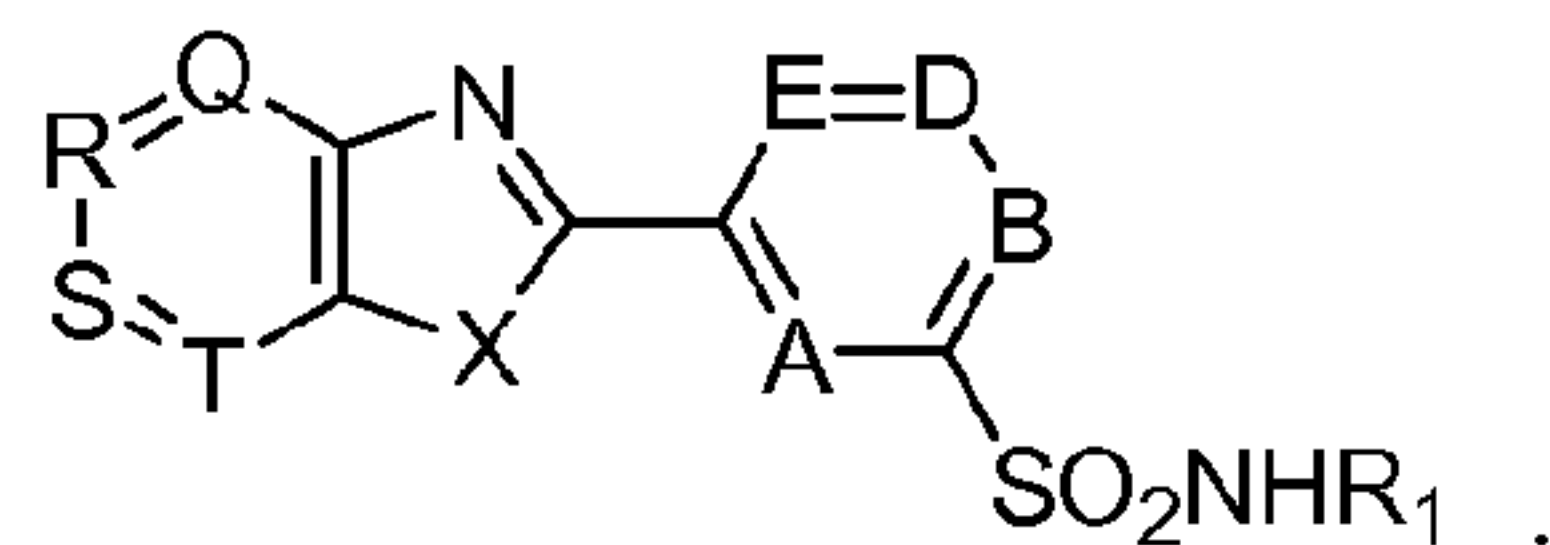
the salts, solvates, hydrates and N-oxides thereof.

20 The preparation of these compounds is described in WO 2001/098274.

In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in WO 2001/074786 .

25 In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:

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(23)

The substituents for the above compounds are defined as follows:

R₁ represents an aryl or heteroaryl group;

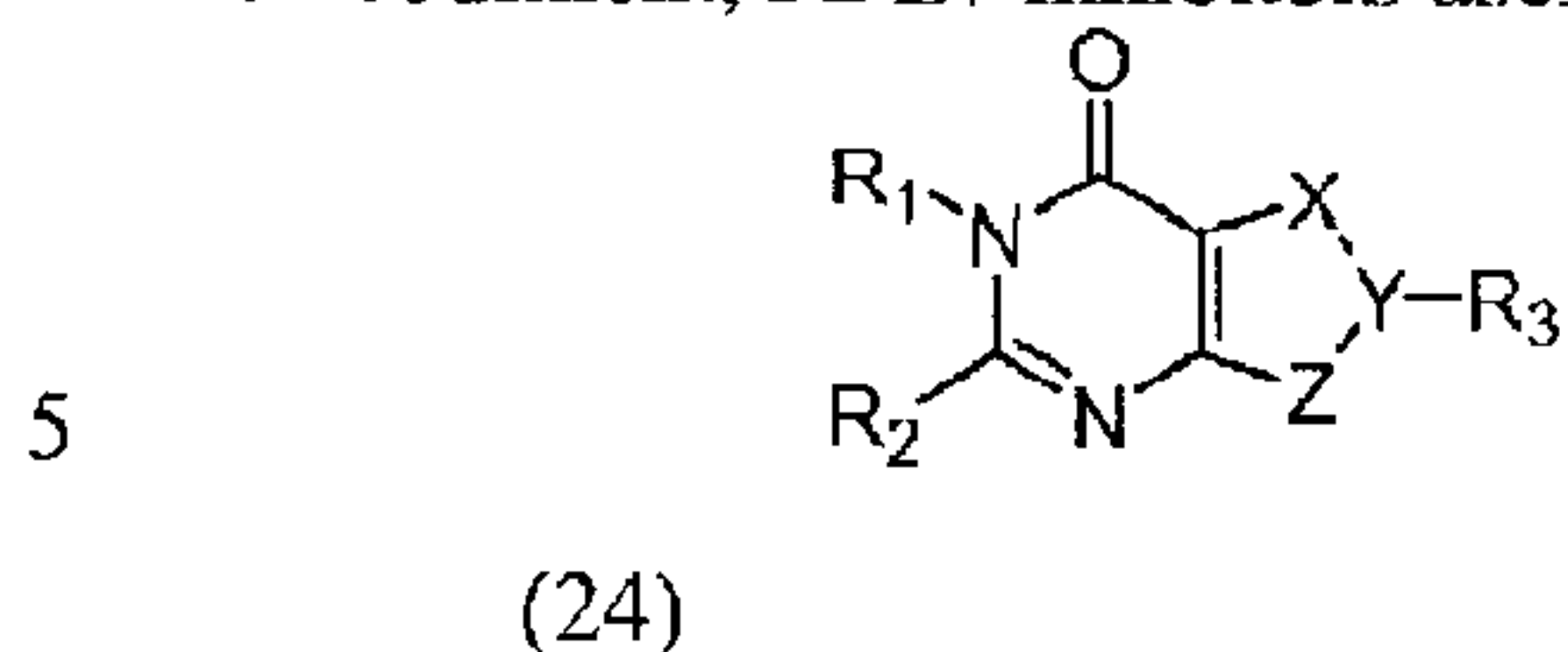
- 5 A, B, P, and E, which may be the same or different, each represents a nitrogen atom or a C(R₂) group [wherein R₂ is a hydrogen or halogen atom or an alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxy, -NO₂ or -CN group] provided that two or more of A, B, D, and E are C(R₂) groups; X represents an oxygen or sulphur atom or a N(R₃) group wherein R₃ is a hydrogen atom or an alkyl group;
- 10 Q, R, S, and T, which may be the same or different each represents a nitrogen atom or a group C(R₄) [wherein R₄ is an atom or group -L₁(Alk₁)^rL₂(R₅)_s wherein L₁ and L₂, which may be the same or different, is each a covalent bond or a linker atom or group, r is zero or the integer 1, Alkyl is an aliphatic or heteroaliphatic chain, s is an integer 1, 2 or 3 and R₅ is a hydrogen or halogen atom or a group selected from alkyl, OR₆ [where
- 15 R₆ is a hydrogen atom or an optionally substituted alkyl group], SR₆, NR₆R₇ [where R₇ is as just defined for R₆ and may be the same or different], NO₂, CN, CO₂R₆, SO₃H, S(O)R₆, SO₂R₆, OCO₂R₆, CONR₆R₇, OCONR₆R₇, CSNR₇R₇, OCR₆, OCOR₆, N(R₆)COR₇, N(R₆)CSR₇, S(O)NR₆R₇, SO₂NR₆R₇, N(R₆)SO₂R₇; N(R₆)CON(R₇)(R₈) [where R₈ is a hydrogen atom or an optionally substituted alkyl group],
- 20 N(R₆)CSN(R₇)(R₈), N(R₆)SO₂N(R₇)(R₈), C(R₆)=NO(R₇) cycloaliphatic, heterocycloaliphatic, aryl or heteroaryl group] provided that two or more of Q, R, S, and T are C(R₄) groups; and the salts, solvates, hydrates and N-oxides thereof.

The preparation of these compounds is described in WO 2001/074786.

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In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in WO 2000/068230.

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



The substituents for the above compounds are defined as follows:

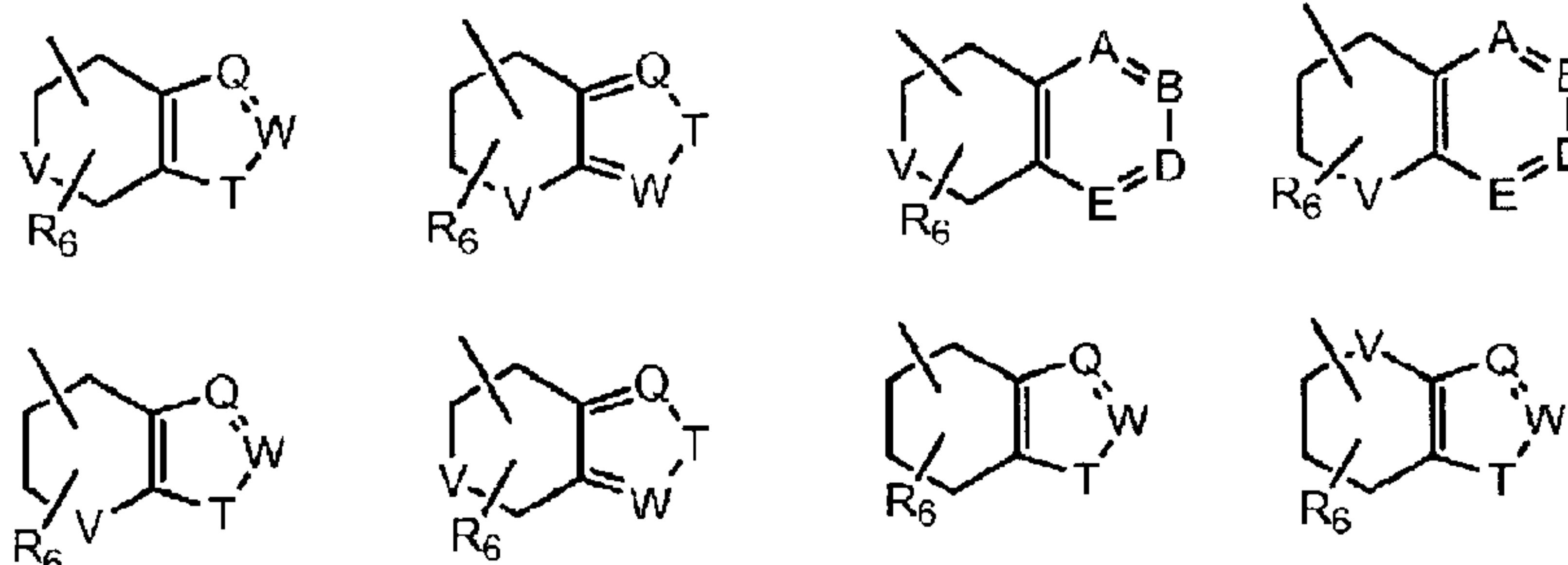
X-Y-Z represents $\text{NR}_4\text{-C=N}$ or N=C-NR_4 ;

R_1 represents H, alkyl, cycloalkyl, cycloalkylalkyl, arylalkyl, heteroarylalkyl or
10 heterocycloalkyl;

R_2 represents OR_8 , NR_8R_9 , SR_{13} , alkyl or CF_3 ;

R_3 represents halogen, alkyl, CF_3 or OR_8 ;

R_4 , which can be attached to either X or Z, is a residue selected from



15 wherein attachment is through any position on the saturated ring, provided the attachment is not at a position adjacent to V, and the saturated ring may be substituted at any position with one or more R_6 ;

A, B, D, and E are the same or different and each represents Cl_nR_5 , N or N-O;

V represents O, S, NR_7 or $\text{C}(\text{L}^1_m\text{R}_{14})(\text{L}^2_n\text{R}_{14})$;

20 Q and W are the same or different and each represents Cl_nR_5 or N;

T represents O, S or NR_7 ;

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L^1 and L^2 are the same or different and each represents $C(R_{15})_2$;

m and n are the same or different and each represents 0, 1, 2, 3, 4 or 5;

the R_5 s are the same or different and each represents H, halogen, alkyl, cycloalkyl, OR_8 , NR_8R_9 , CO_2R_{10} , $CONR_{11}R_{12}$, $CONHOH$, $SO_2NR_{11}R_{12}$, $SON_{11}R_{12}$,
 5 COR_{13} , SO_2R_{13} , SOR_{13} , SR_{13} , CF_3 , NO_2 or CN ;

R_6 represents H, alkyl, cycloalkyl, OR_8 , NR_8R_9 , CO_2R_{10} , $CONR_{11}R_{12}$, $SO_2NR_{11}R_{12}$, $SON_{11}R_{12}$, COR_{13} , SO_2R_{13} , SOR_{13} , SR_{13} , CF_3 , CN or $=O$;

R_7 represents H or alkyl;

R_8 represents H, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl,
 10 heteroarylalkyl, heterocyclo or heterocycloalkyl;

R_9 represents R_8 or alkylcarbonyl, alkoxy carbonyl, alkylsulphonyl, cycloalkylcarbonyl, cycloalkoxy carbonyl, cycloalkylsulphonyl, cycloalkylalkylcarbonyl, cycloalkylalkoxy carbonyl, cycloalkylalkylsulphonyl, arylcarbonyl, arylsulphonyl, heteroarylcarbonyl, heteroarylsulphonyl, heterocyclocarbonyl, heterocyclosulphonyl, arylalkylcarbonyl, arylalkoxy carbonyl, arylalkylsulphonyl, heteroarylalkylcarbonyl, heteroarylalkoxy carbonyl, heteroarylsulphonyl, heterocycloalkylcarbonyl, heterocycloalkoxy carbonyl or heterocycloalkylsulphonyl; or

NR_8R_9 represents a heterocyclic ring such as morpholine;

R_{10} represents H, alkyl, cycloalkyl, cycloalkylalkyl, arylalkyl, heteroarylalkyl or
 20 heterocycloalkyl;

R_{11} and R_{12} are the same or different and are each R_8 , or $NR_{11}R_{12}$ represents a heterocyclic ring such as morpholine;

R_{13} represents alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocyclo or heterocycloalkyl;

25 the R_{14} s are the same or different and are each selected from H alkyl, cycloalkyl, OR_8 , NR_8R_9 , CO_2R_{10} , $CONR_{11}R_{12}$, $CONHOH$, $SO_2NR_{11}R_{12}$, $SON_{11}R_{12}$, COR_{13} ,

-151-

SO₂R₁₃, SOR₁₃, SR₁₃, CF₃, NO₂ and CN, provided that when both m and n represent 0, if one R₁₄ is OR₈, NR₈R₉ or SR₁₃, the other is not OR₈, NR₈R₉ or SR₁₃; and

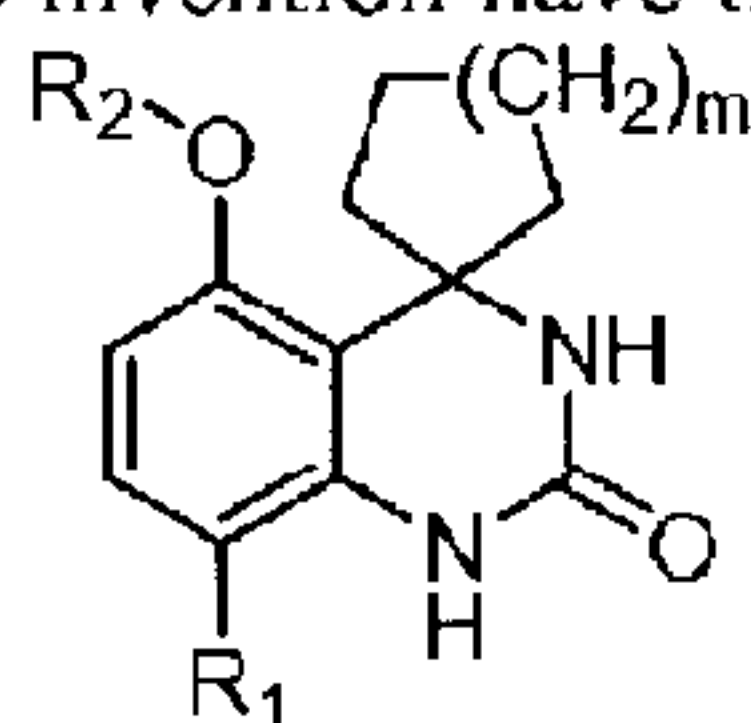
R₁₅ represents H, alkyl or F; or

a pharmaceutically acceptable salt thereof.

5 The preparation of these compounds is described in WO 2000/068230, incorporated herein by reference in its entirety.

In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in
10 US 20040106631, EP 1 400 244, and WO 2004/026818.

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



(25)

15 The substituents for the above compounds are defined as follows:

m is 1, 2 or 3; R₁ is methyl, chloro, bromo or fluoro; R₂ is -Q¹-Q²-Q³-Q⁴ or (C₁-C₆) alkyl, said (C₁-C₆) alkyl is substituted with one to three OR₄, COOR₄, NR₄R₅, NRC(=O)R₄, C(=O)NR₄R₅ or SO₂NR₄R₅;

R₄ is (C₁-C₆) alkyl substituted with one to three F, CN, S(=O)R₆, SO₃H, SO₂R₆,
20 SR₇, C(=O)-NH-SO₂-CH₃, C(=O)R₇, NR'C(=O)R₇, NR'SO₂R₆, C(=O)NR₇R₈, O-C(=O)NR₇R₈ or SO₂NR₇R₈;

R₅ is H or (C₁-C₆) alkyl optionally substituted with one to three F, CN, S(=O)R₆, SO₃H, SO₂R₆, SR₇, C(=O)-NH-SO₂-CH₃, C(=O)R₇, NR'C(=O)R₇, NR'SO₂R₆, C(=O)NR₇R₈, O-C(=O)NR₇R₈ or SO₂NR₇R₈; or

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said (C₁-C₆) alkyl is

(1) substituted with one to three OC(=O)R_{4a}, SR_{4a}, S(=O)R₃, C(=NR₉)R_{4a}, C(=NR₉)-NR_{4a}R_{5a}, NR-C(=NR₉)-NR_{4a}R_{5a}, NRCOOR_{4a}, NR-C(=O)NR_{4a}R_{5a}, NR-SO₂-NR_{4a}R_{5a}, NR-C(=NR₉)-R_{4a} or NR-SO₂-R₃; and

5 (2) optionally substituted with one or two OR_{4a}, COOR_{4a}, C(=O)-R_{4a}, NR_{4a}R_{5a}, NRC(=O)R_{4a}, C(=O)NR_{4a}R_{5a} or SO₂NR_{4a}R_{5a};

R₉ is H, CN, OH, OCH₃, SO₂CH₃, SO₂NH₂ or (C₁-C₆) alkyl; and R₃ is (C₁-C₆) alkyl optionally substituted with one to three F, CN, S(=O)R₆, SO₃H, SO₂R₆, C(=O)-NH-SO₂-CH₃, OR₇, SR₇, COOR₇, C(=O)R₇, O-C(=O)NR₇R₈, NR₇R₈, NR'C(=O)R₇,
10 NR'SO₂R₆, C(=O)NR₇R₈ or SO₂NR₇R₈;

R_{4a} and R_{5a} are the same or different and are H or (C₁-C₆) alkyl optionally substituted with one to three F, CN, S(=O)R₆, SO₃H, SO₂R₆, C(=O)-NH-SO₂-CH₃, OR₇, SR₇, COOR₇, C(=O)R₇, O-C(=O)NR₇R₈, NR₇R₈, NR'C(=O)R₇, NR'SO₂R₆, C(=O)NR₇R₈ or SO₂NR₇R₈;

15 Q¹ is a single bond or (C₁-C₆) alkylene; Q² is a saturated 4- to 6-membered heterocyclyl comprising one or two O or N; Q³ is (C₁-C₆) alkylene; Q⁴ is a 4 to 8-membered, aromatic or non aromatic, heterocyclyl comprising 1 to 4 O, S, S(=O), SO₂, or N, said heterocyclyl being optionally substituted with one to three OR, NRR', -CN or (C₁-C₆) alkyl;

20 R is H or (C₁-C₆) alkyl;

R₆ is (C₁-C₆) alkyl optionally substituted with one or two OR';

R₇ and R₈ are the same or different and are H or (C₁-C₆) alkyl optionally substituted with one or two OR';

R₉ is H, CN, OH, OCH₃, SO₂CH₃, SO₂NH₂ or (C₁-C₆) alkyl;

25 R' is H or (C₁-C₆) alkyl; and R'' is H or (C₁-C₆) alkyl;

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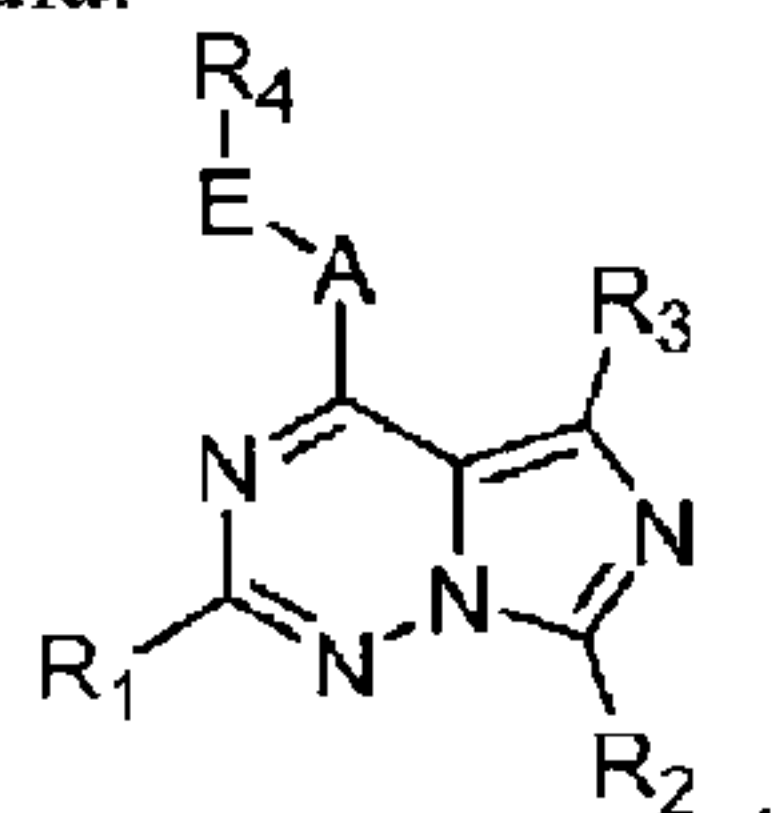
provided that (1) the atom of Q^2 bound to Q^1 is a carbon atom; and (2) the atom of Q^4 bound to Q^3 is a carbon atom;

or a racemic form, isomer, pharmaceutically acceptable derivative thereof.

The preparation of these compounds is described in US 20040106631, EP 1 400
 5 244, and WO 2004/026818.

In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in U.S. Patent No. 6,936,609 and US 20040249148 .

10 In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



(26)

The substituents for the above compounds are defined as follows:

15 R_1 represents (C_6-C_{10}) -aryl, which is optionally identically or differently substituted by radicals selected from the group consisting of halogen, formyl, carbamoyl, cyano, hydroxyl, trifluoromethyl, trifluoromethoxy, nitro, (C_1-C_6) -alkyl or (C_1-C_6) -alkoxy, and optionally by a radical of the formula $SO_2NR_5R_6$, wherein R_5 and R_6 independently of one another denote hydrogen or (C_1-C_6) -alkyl, or NR_5R_6 denotes 4- to
 20 8-membered heterocyclyl, bonded via a nitrogen atom, optionally identically or differently substituted by radicals selected from the group consisting of oxo, halogen, (C_1-C_6) -alkyl and (C_1-C_6) -acyl,

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R_2 represents a saturated or partially unsaturated hydrocarbon radical having 1 to 10 carbon atoms,

R_3 represents methyl or ethyl,

A represents O, S, or NR_7 , wherein R_7 denotes hydrogen or (C_1-C_6) -alkyl optionally substituted by (C_1-C_3) -alkoxy,

E represents a bond or (C_1-C_3) -alkanediyl,

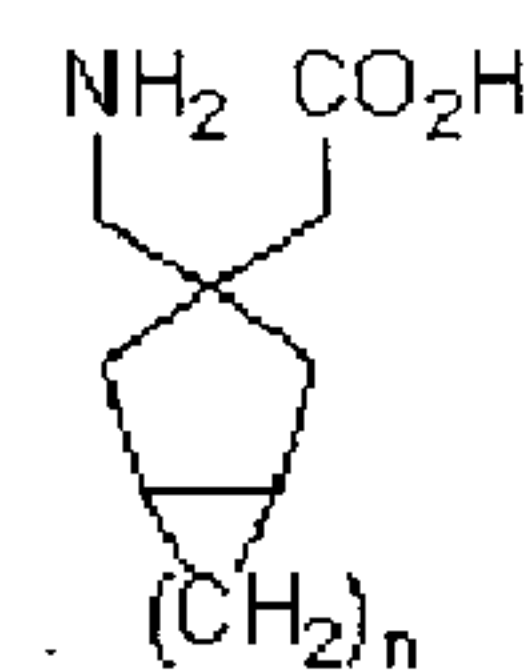
R_4 represents (C_6-C_{10}) -aryl or 5- to 10-membered heteroaryl, where aryl and heteroaryl are optionally identically or differently substituted by radicals selected from the group consisting of halogen, formyl, carboxyl, carbamoyl, $-SO_3H$, aminosulphonyl, cyano, hydroxyl, trifluoromethyl, trifluoromethoxy, nitro, (C_1-C_6) -alkyl, (C_1-C_6) -alkoxy, 1,3-dioxo-propane-1,3-diyl, (C_1-C_6) -alkylthio, (C_1-C_6) -alkylsulphonyl and (C_1-C_6) -alkyl-sulphonyl, $-NR_8R_9$ and optionally methyl-substituted, 5- to 6-membered heteroaryl or phenyl,

wherein R_8 and R_9 independently of one another denote hydrogen, (C_1-C_6) -alkyl or (C_1-C_6) -acyl, or salt thereof.

The preparation of these compounds is described in U.S. Patent No. 6,936,609 and US 20040249148.

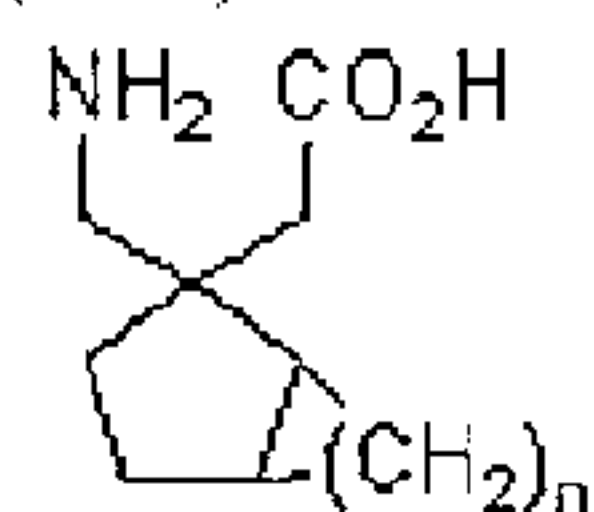
In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in WO 2006/092692.

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formulas:

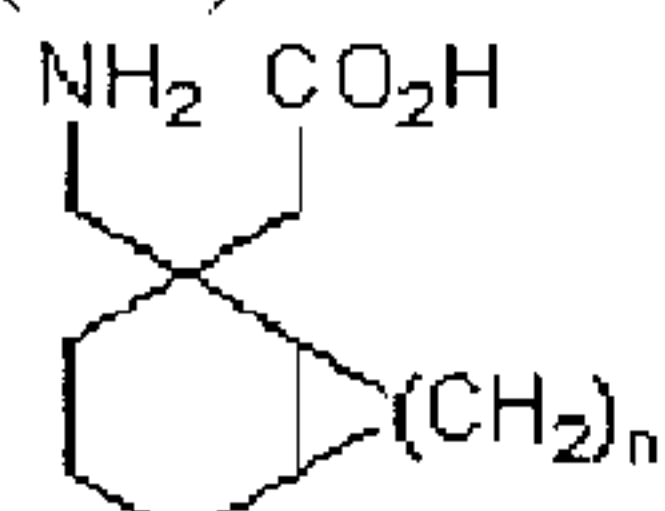


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(27A)

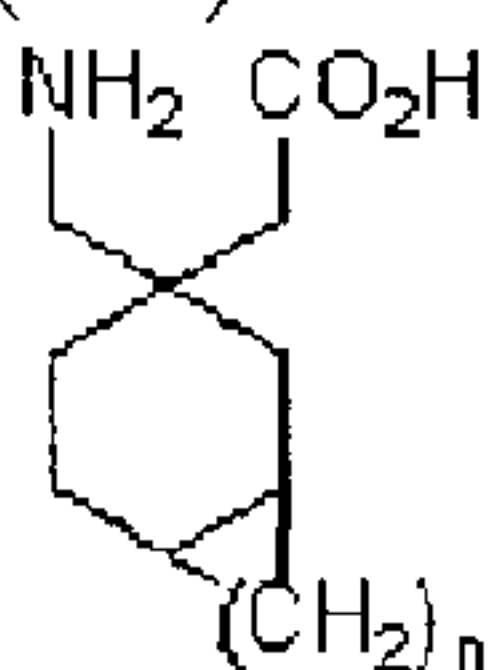


(27B)



5

(27C) and



(27D)

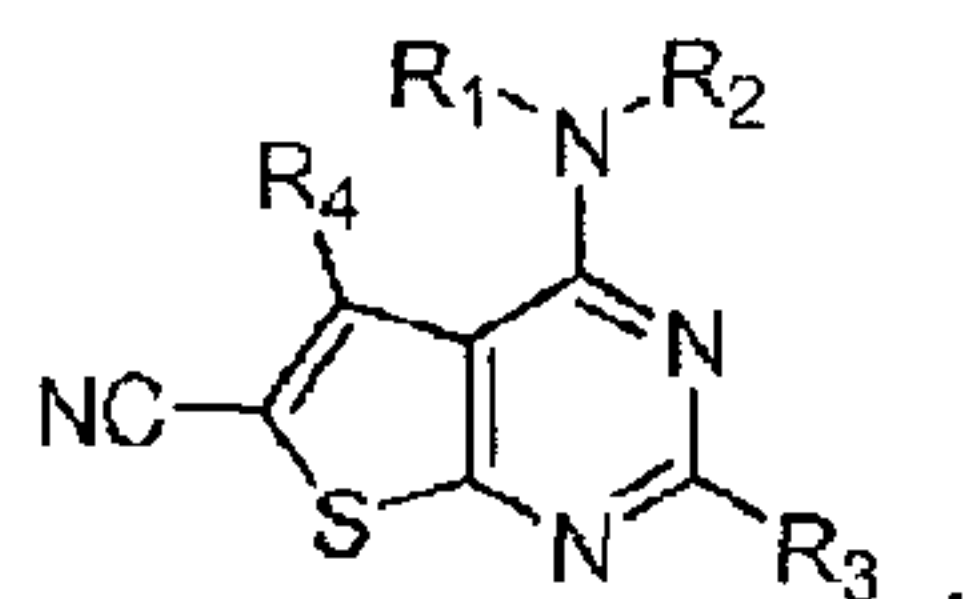
wherein n is an integer of from 1 to 4, and where there are stereocenters, each center may be independently R or S.

10

The preparation of these compounds is described in WO 2006/092692.

In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in US 2006229306 and WO 2004/065391 .

15 one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



(28)

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The substituents for the above compounds are defined as follows:

R₁ and R₂ either

(1) independently represent:

(a) a hydrogen atom;

5 (b) a group selected from alkyl, alkenyl and alkynyl groups, wherein each alkyl, alkenyl and alkynyl group is independently optionally substituted by one or more substituents selected from halogen atoms, hydroxy, alkoxy, aryloxy, alkylthio, hydroxycarbonyl, alcoxycarbonyl, mono- and di-alkylaminoacyl, oxo, amino, and mono- and di-alkylamino groups; or

10 (c) a group of formula (CH₂)_n-R₆, wherein n is an integer from 0 to 4 and R₆ represents a cycloalkyl or cycloalkenyl group;

(2) R₁ and R₂ form, together with the nitrogen atom to which they are attached, a 3- to 8-membered ring comprising from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulphur, which ring is saturated or unsaturated and optionally
15 substituted by one or more substituents selected from halogen atoms, alkyl, hydroxy, alkoxy, acyl, hydroxycarbonyl, alcoxycarbonyl, alkylenedioxy, amino, mono- and di-alkylamino, mono- and di-alkylaminoacyl, nitro, cyano and trifluoromethyl groups;

R₃ is a group of formula (CH₂)_n-G, wherein n is an integer from 0 to 4 and G represents a monocyclic or bicyclic aryl or heteroaryl group comprising from zero to
20 four heteroatoms which group is optionally substituted by one or more substituents selected from:

(1) halogen atoms;

(2) alkyl and alkylene groups, wherein each alkyl and alkylene group is independently optionally substituted by one or more substituents selected from halogen
25 atoms; and

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(3) phenyl, hydroxy, hydroxyalkyl, alkoxy, alkylendioxy, aryloxy, alkylthio, amino, mono- and di-alkylamino, acylamino, nitro, acyl, hydroxycarbonyl, alkoxycarbonyl, cyano, difluoromethoxy and trifluoromethoxy groups;

R₄ represents a hydrogen atom, an alkyl or an aryl group.

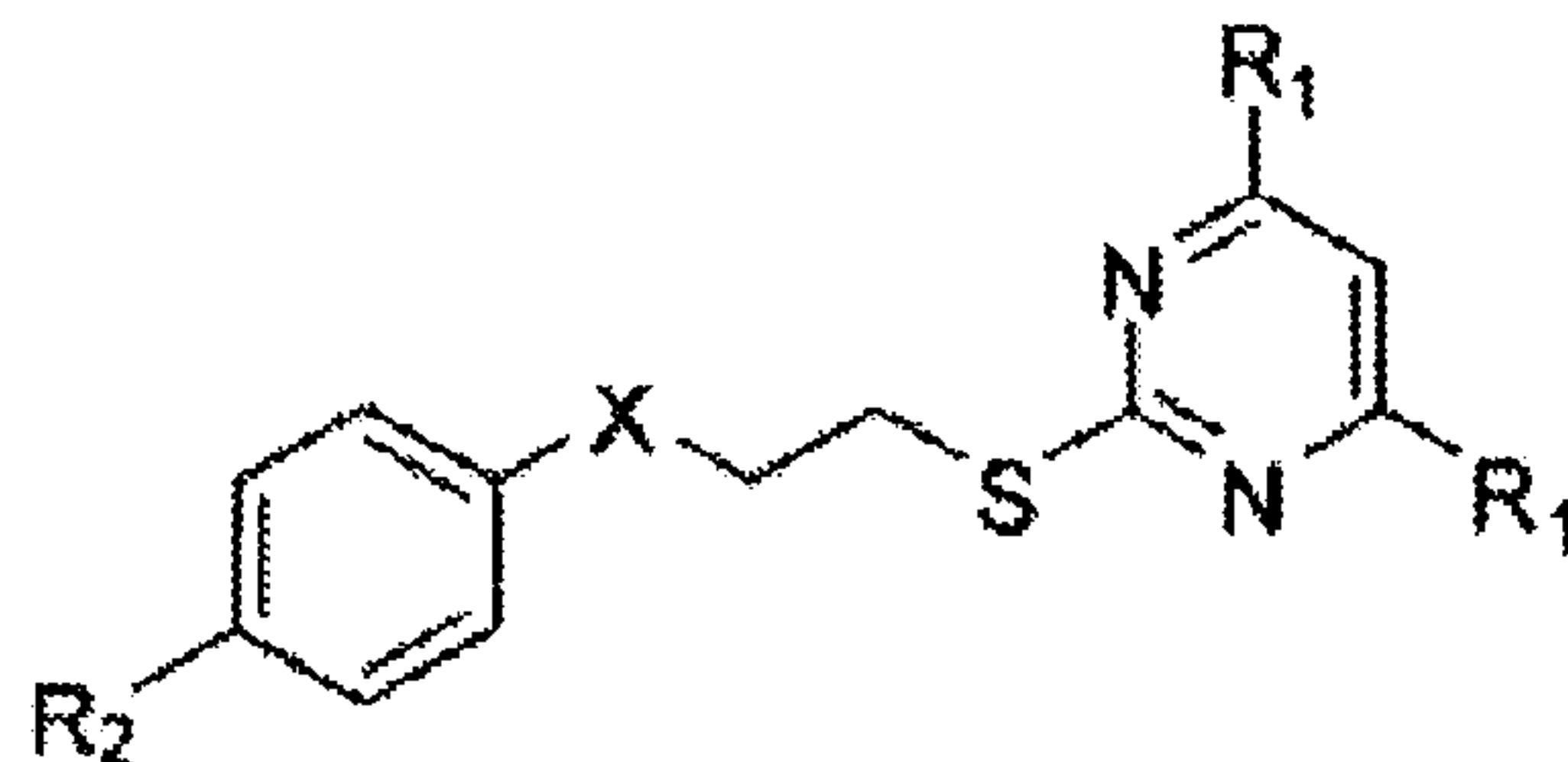
5 The preparation of these compounds is described in US 2006229306 and WO 2004/065391.

Other compounds useful in the methods of the invention include imidazopyridine derivatives (WO 2001/34601), dihydropurine derivatives (WO 2000/68203), pyrrole derivatives (WO 2001/32618), benzothiopyranoimidazolone derivatives (DE 19950647), heterocyclic compounds (WO 2002/87519), guanine derivatives (*Bioorg. Med. Chem. Lett.* 11:1081-1083, 2001), and benzothienothiadiazine derivatives (*Eur. J. Med. Chem.* 36:333, 2001).

15

In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in WO 2008/130619.

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



20

(29)

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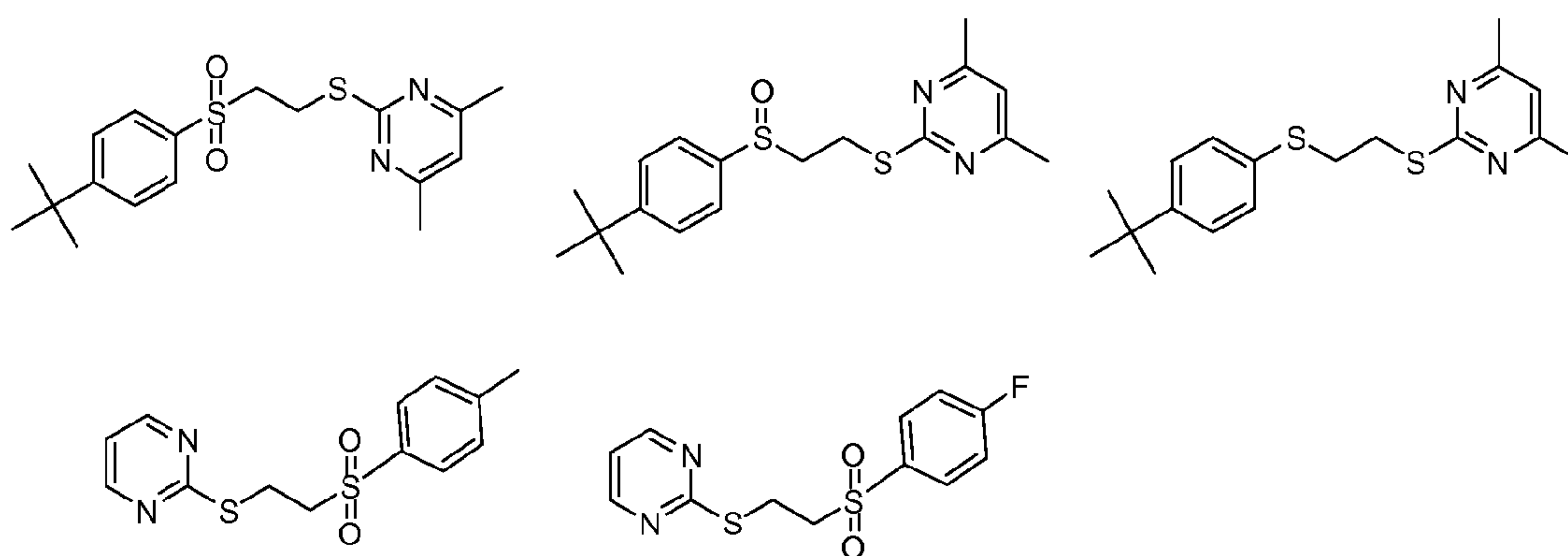
The substituents for the above compounds are defined as follows:

X is SO, or SO₂,

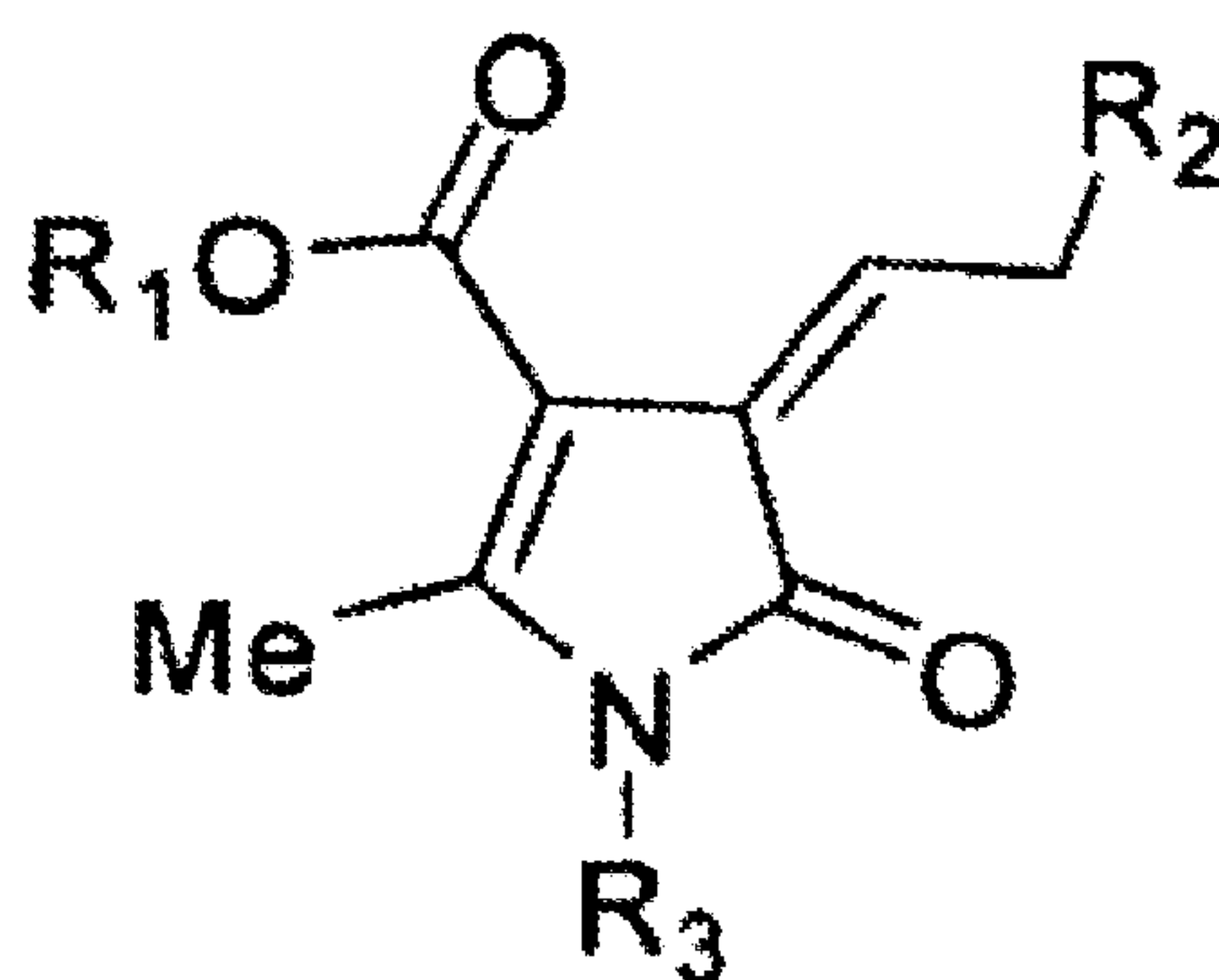
R1 is H, or alkyl,

R2 is alkyl, or halogen.

- 5 In specific embodiments, R1 is Me. In other specific embodiments R1 is F. In certain embodiments R2 is t-Bu. In specific embodiments, R1 is methyl. In more specific embodiments, the compounds are selected from:



- In a related embodiment, PDE7 inhibitors useful in the methods of the invention
10 have the formula:



(30)

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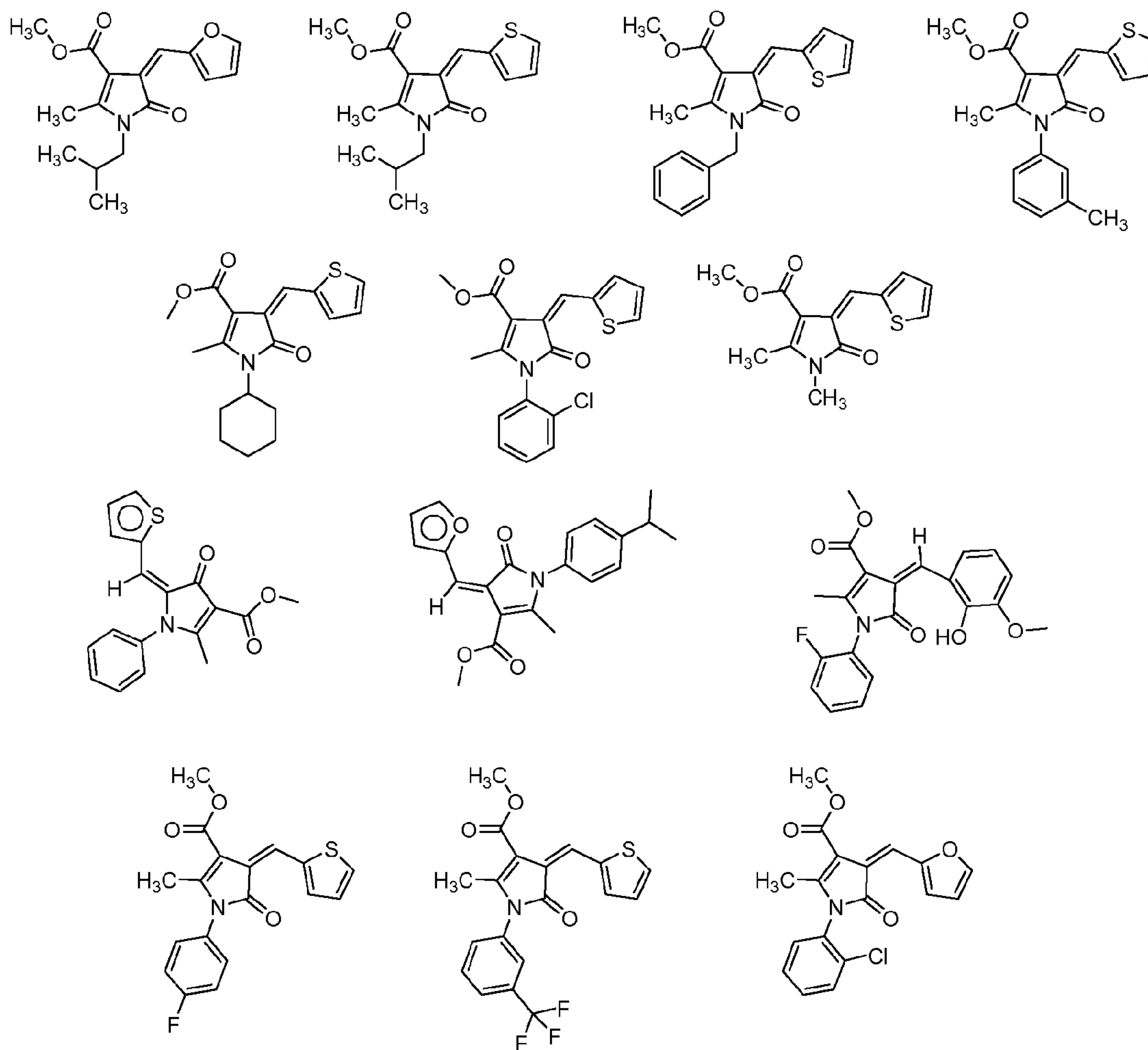
wherein

R1 is alkyl,

R2 is aryl or heteroaryl,

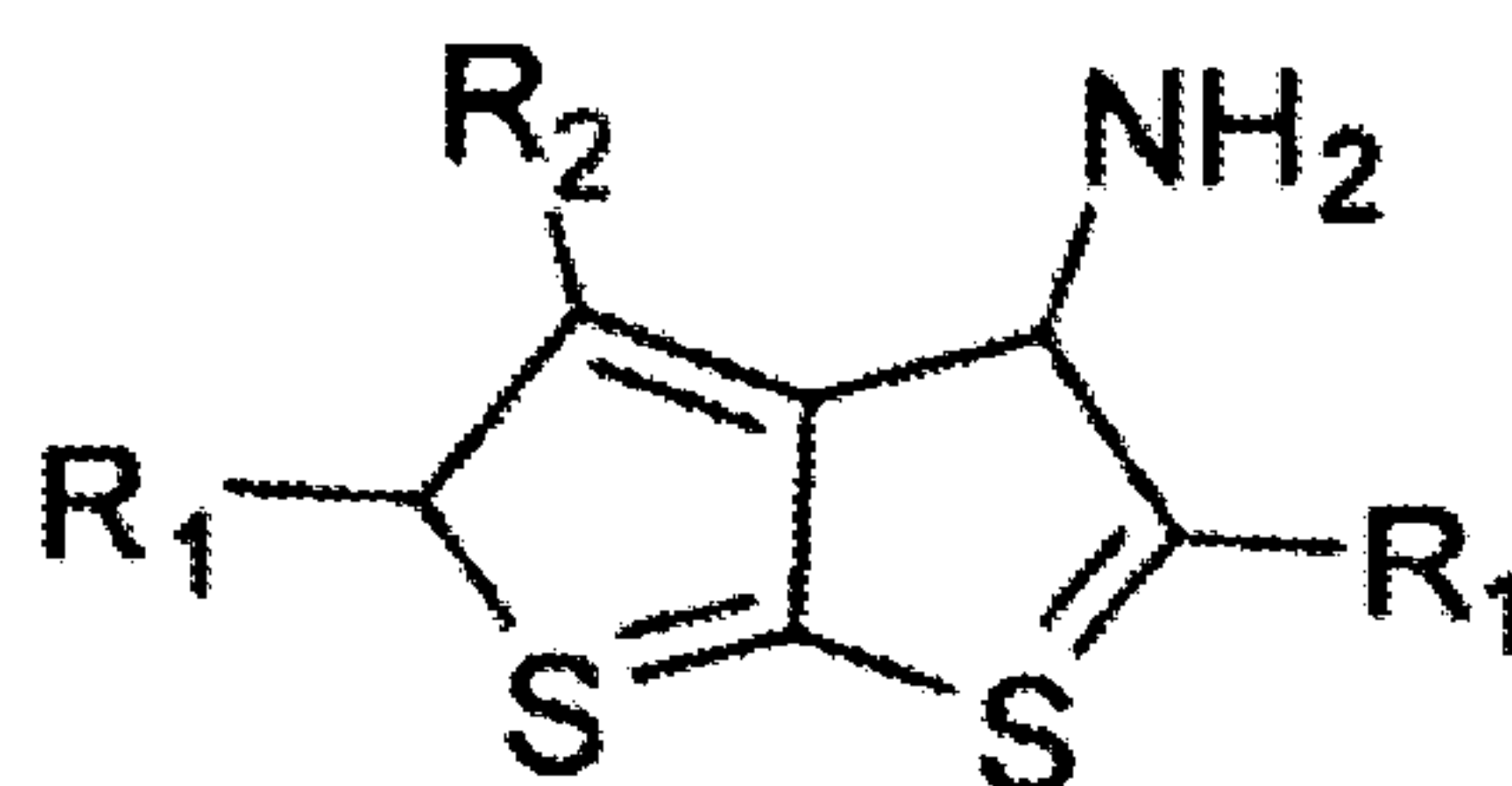
R3 is alkyl, aryl, cycloalkyl, or alkylaryl.

- 5 In specific embodiments, R1 is methyl. In certain embodiments R2 is furanyl or thiophenyl. In other specific embodiments, R2 is substituted phenyl or benzyl. In preferred embodiments, R3 is iso-butyl. In more specific embodiments, the compounds are selected from:



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In another related embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



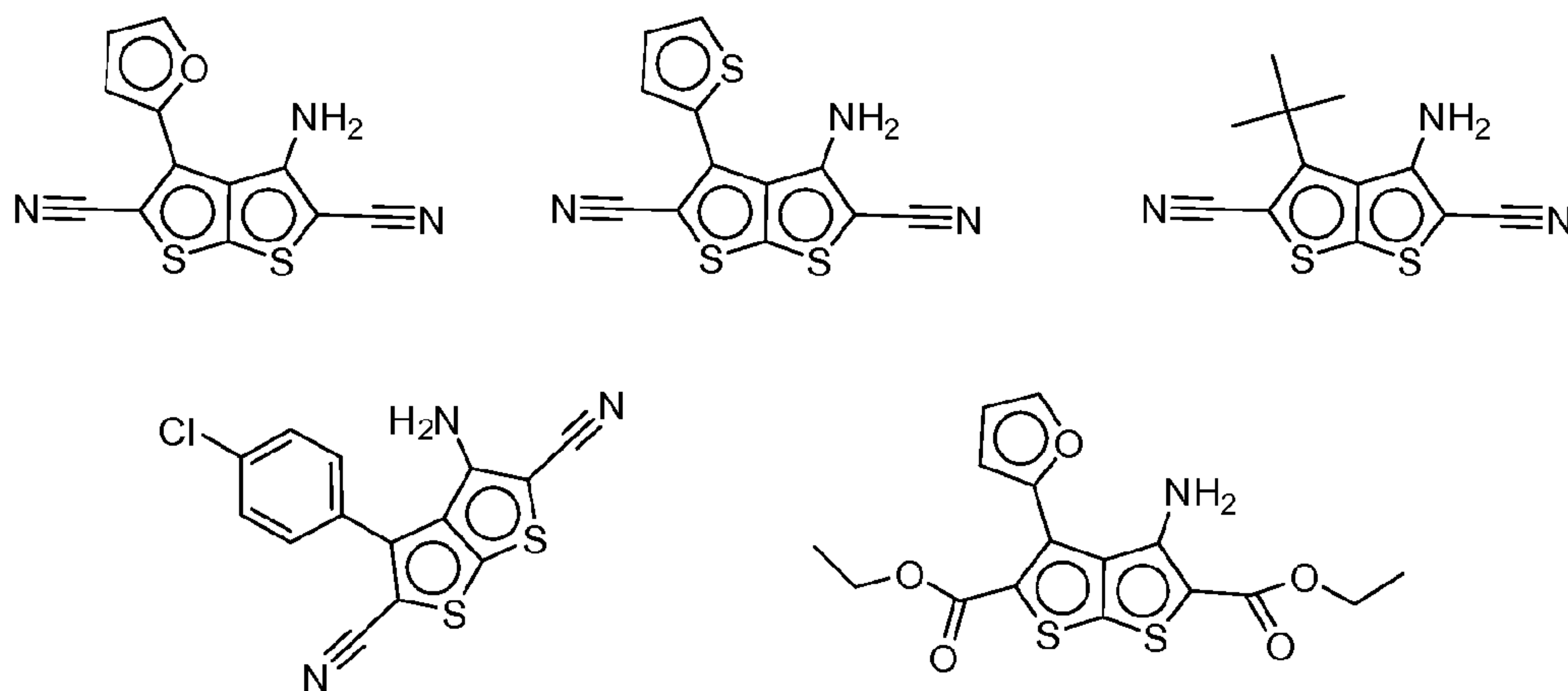
(31)

5 wherein

R1 is nitrile, or alkylcarboxylate,

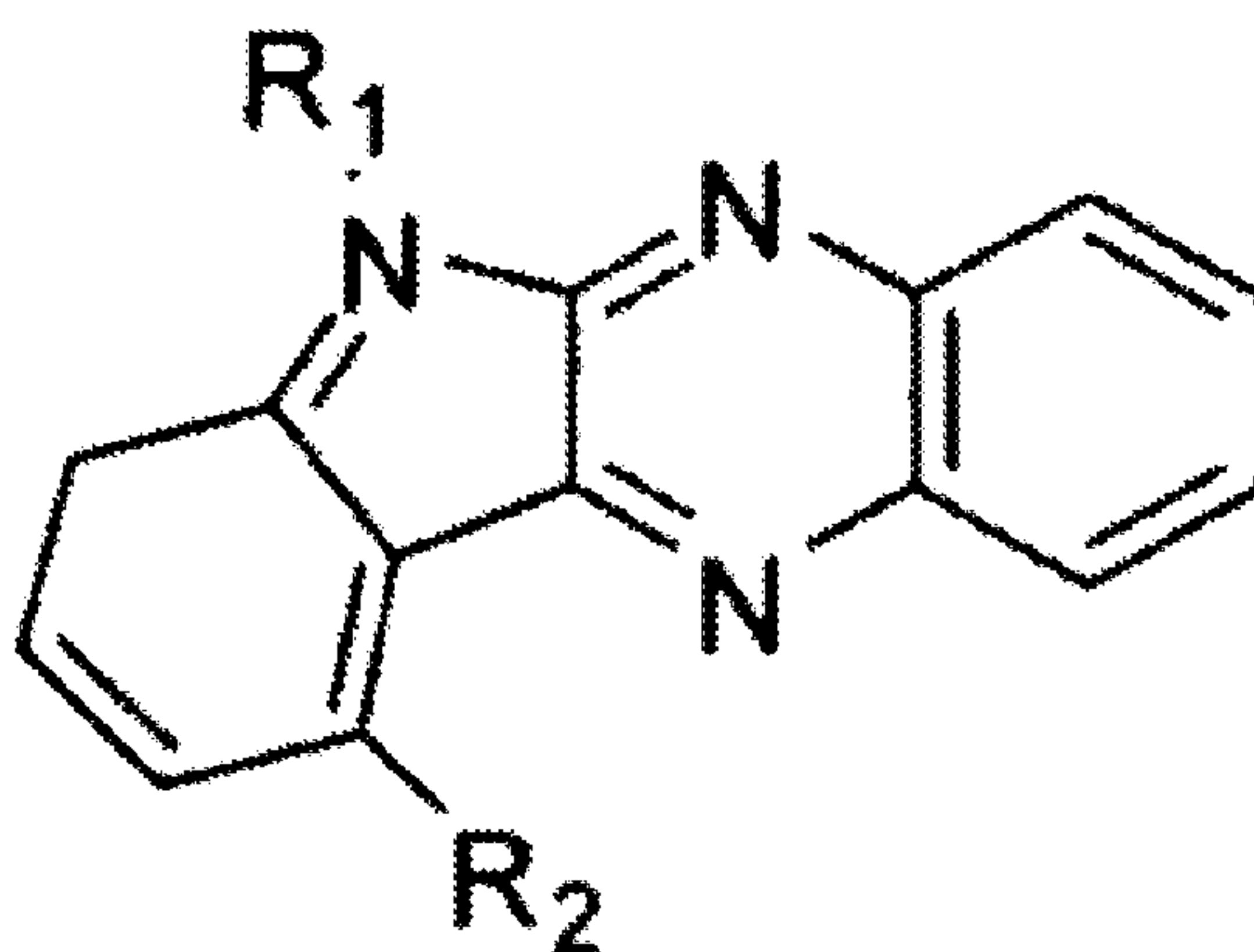
R2 is alkyl, aryl, or heteroaryl.

In specific embodiments, R1 is nitrile or methylcarboxylate. In certain
embodiments, R2 is a five membered heteroaryl. In more specific embodiments, R2 is
10 furanyl, or thienyl. In other embodiments, R2 is a six membered aryl. In more specific
embodiments, R2 is substituted phenyl.



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In another related embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



(32)

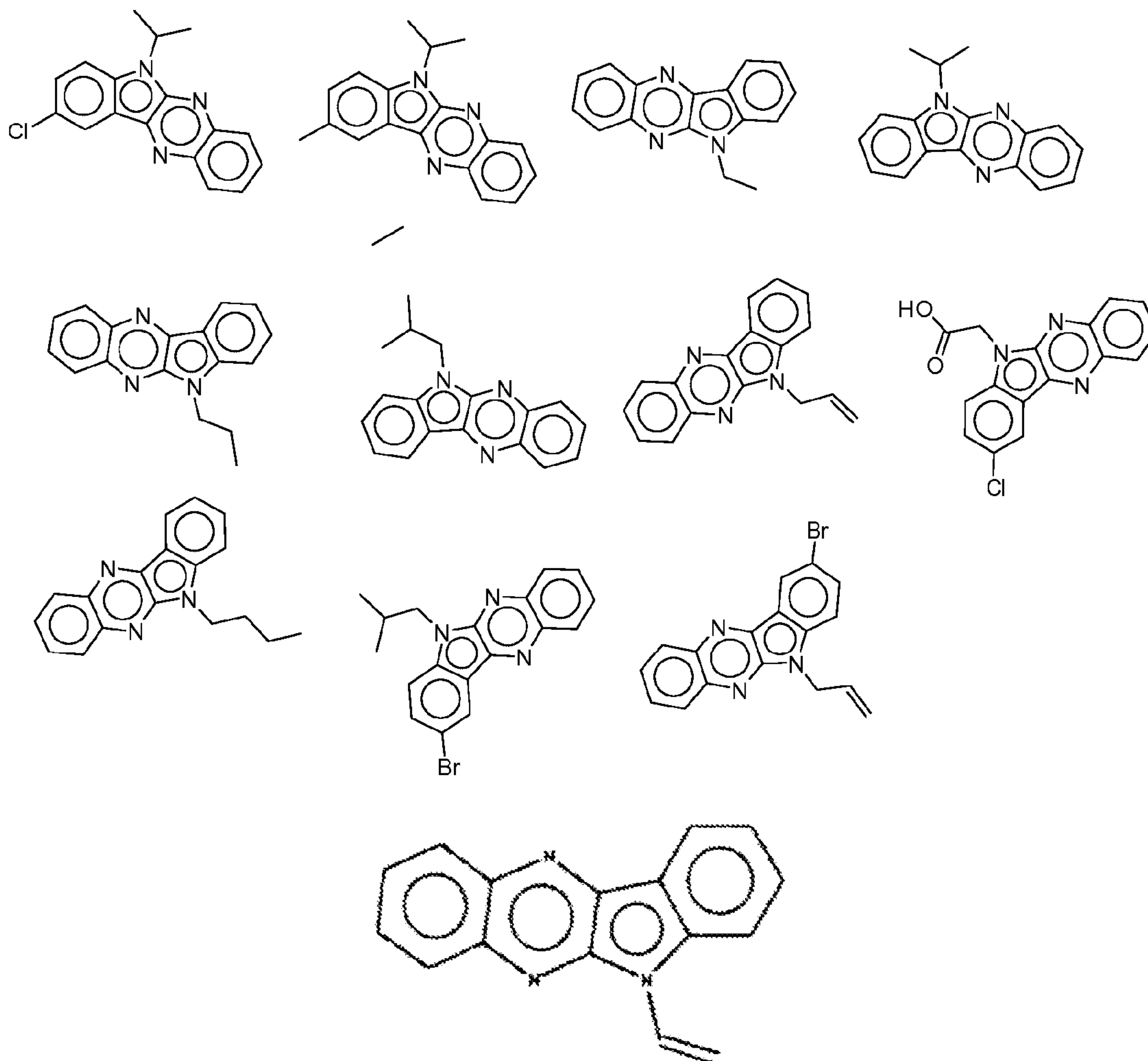
5 wherein

R1 is alkyl, alkenyl, or alkylcarboxylic acid,

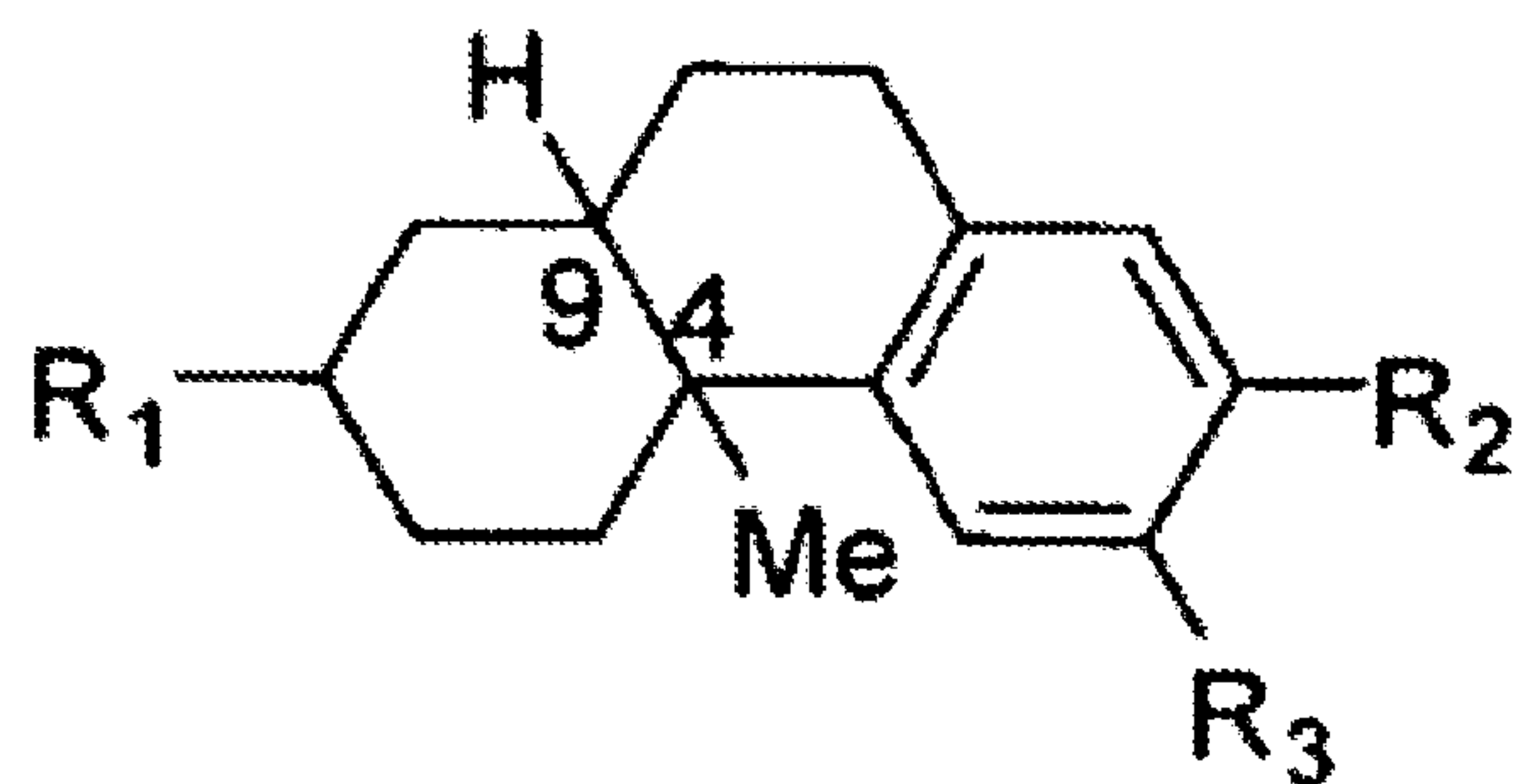
R2 is halogen.

In certain embodiments R1 is butyl. In other embodiments R1 is terminal alkenyl. In more specific embodiments R1 is allyl, or vinyl. In other embodiments, R1 is C₁-
10 ₄alkyl. In specific embodiments R1 is methylcarboxylic acid. In certain embodiments R2 is Cl, or Br. In more specific embodiments, the compounds are selected from:

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In other related embodiments, PDE7 inhibitors useful in the methods of the
 5 invention have the formula:



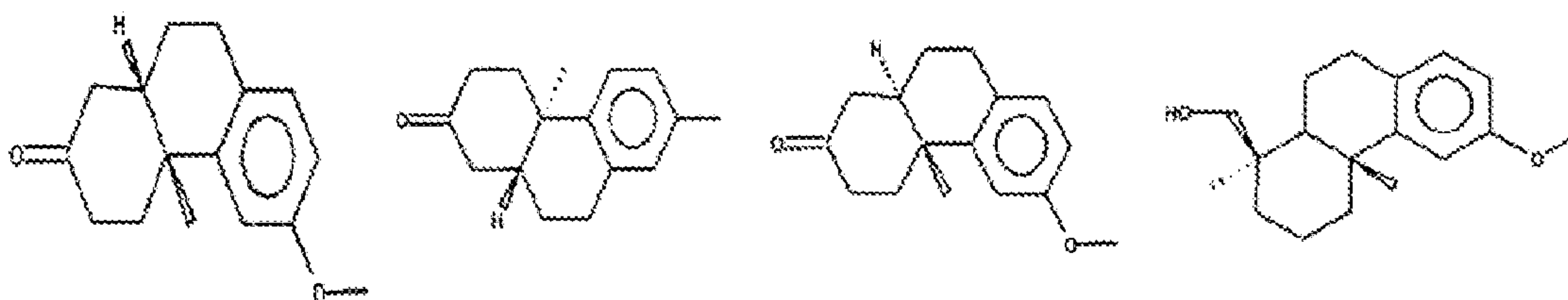
(33)

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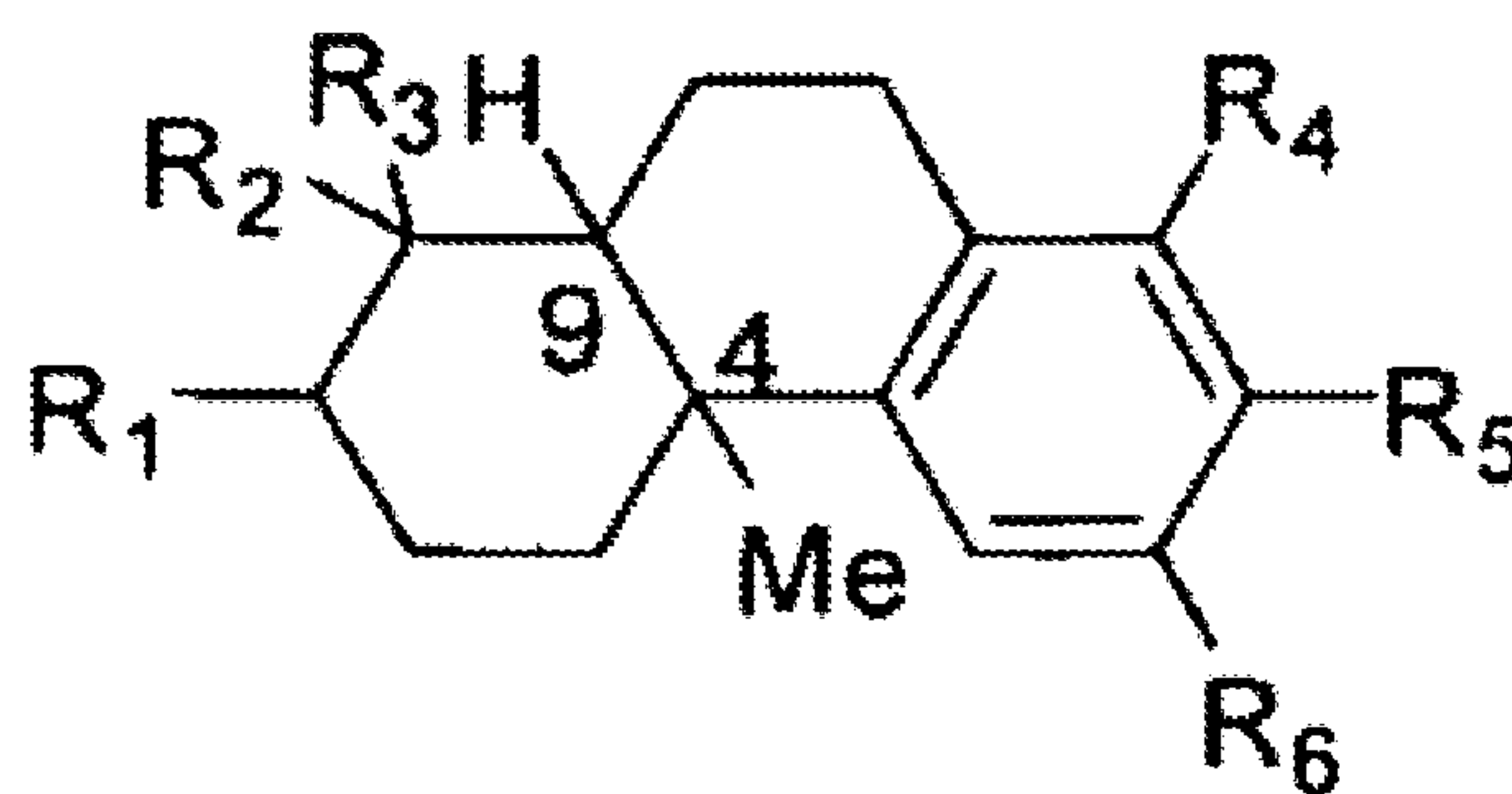
wherein

R1 is CO, or alkylalcohol, R2 is alkyl, R3 is alkoxy, and the C4 and C9 stereocenters are independently (R) or (S).

In certain embodiments R1 is carbonyl, or 2-methylpropan-1-ol. In specific
5 embodiments R2 is methyl. In certain embodiments, R3 is methoxy. In more specific
embodiments the compounds are selected from:



In another related embodiment, PDE7 inhibitors useful in the methods of the
10 invention have the formula:



(34)

wherein

R1 is hydrogen, hydroxyl, carbonyl, or alkylalcohol,

15 R2 and R3 are independently selected from hydrogen, alkyl, alkylcarboxylate, or
carboxylic acid,

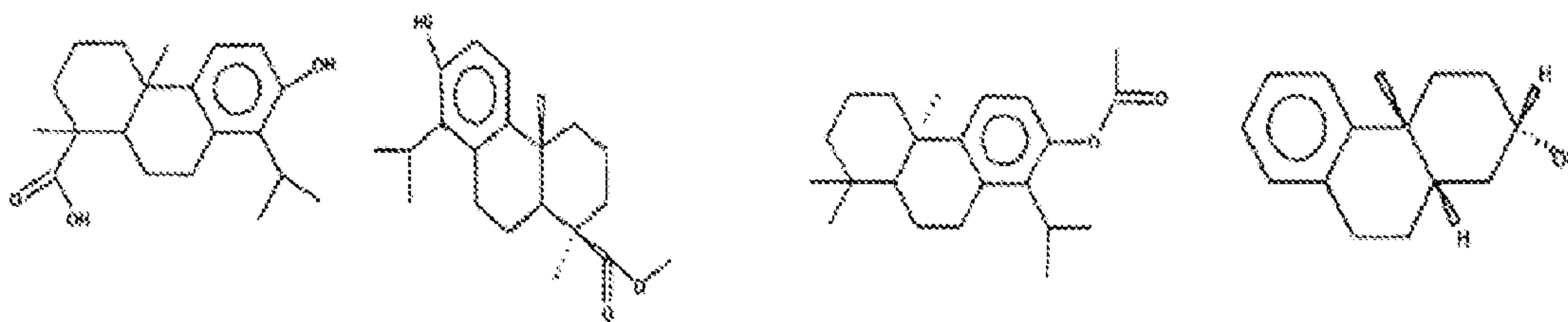
R4 is hydrogen, or alkyl,

R5 is hydrogen, alkyl, hydroxyl, or acetate,

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R6 is hydrogen, or alkoxy, and the C4 and C9 stereocenters are independently (R) or (S).

In certain embodiments R1 is 2-methylpropan-1-ol. In specific embodiments R2 is methyl. In certain embodiments, R2 is methylcarboxylate. In specific embodiments R2 and R3 are both methyl. In other embodiments, R2 is methyl, and R3 is methylcarboxylate. In specific embodiments R4 is iso-propyl. In specific embodiments, R5 is methyl. In certain embodiments, R6 is methoxy. In more specific embodiments the compounds are selected from:



10

In regards to the above compounds, the terms "alkyl", "alkenyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms. Preferred groups have a total of up to 10 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, adamantyl, norbornane, and norbornene. This is also true of groups that include the prefix "alkyl-", such as alkylcarboxylic acid, alkyl alcohol, alkylcarboxylate, alkylaryl, and the like. Examples of suitable alkylcarboxylic acid groups are methylcarboxylic acid, ethylcarboxylic acid, and the like. Examples of suitable alkylalcohols are methylalcohol, ethylalcohol, isopropylalcohol, 2-methylpropan-1-ol, and the like. Examples of suitable alkylcarboxylates are methylcarboxylate,

20

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ethylcarboxylate, and the like. Examples of suitable alkyl aryl groups are benzyl, phenylpropyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl. The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring hetero atom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinoliny, isoquinoliny, indolyl, isoindolyl, thiazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxaliny, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, and so on.

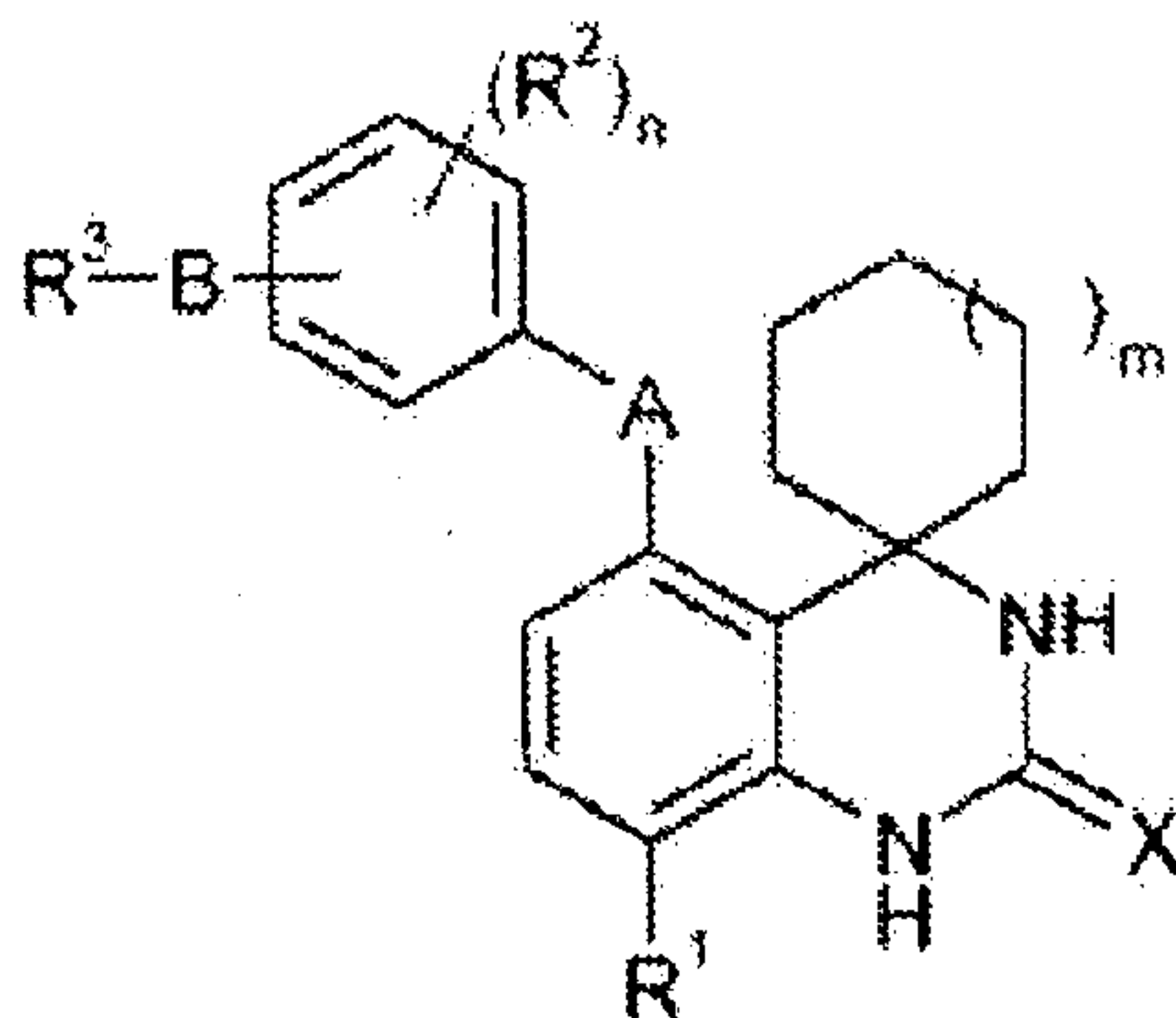
The aryl, and heteroaryl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, methylenedioxy, ethylenedioxy, alkylthio, haloalkyl, haloalkoxy, haloalkylthio, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylthio, arylalkoxy, arylalkylthio, heteroaryl, heteroaryloxy, heteroarylalkoxy, heteroarylalkylthio, amino, alkylamino, dialkylamino, heterocyclyl, heterocycloalkyl, alkylcarbonyl, alkenylcarbonyl, alkoxy carbonyl, haloalkylcarbonyl, haloalkoxy carbonyl, alkylthiocarbonyl, arylcarbonyl, heteroarylcarbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, arylthiocarbonyl, heteroarylthiocarbonyl, alkanoyloxy, alkanoylthio, alkanoylamino, arylcarbonyloxy, arylcarbonylthio, alkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryldiazinyl, alkylsulfonylamino, arylsulfonylamino, arylalkylsulfonylamino, alkylcarbonylamino, alkenylcarbonylamino, arylcarbonylamino, arylalkylcarbonylamino, arylcarbonylaminoalkyl, heteroarylcarbonylamino, heteroarylalkylcarbonylamino, alkylsulfonylamino, alkenylsulfonylamino, arylsulfonylamino, arylalkylsulfonylamino, heteroarylsulfonylamino, heteroarylalkylsulfonylamino, alkylaminocarbonylamino,

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alkenylaminocarbonylamino, arylaminocarbonylamino, arylalkylaminocarbonylamino, heteroarylaminocarbonylamino, heteroarylalkylaminocarbonylamino and, in the case of heterocyclyl, oxo. If other groups are described as being "substituted" or "optionally substituted," then those groups can also be substituted by one or more of the above
 5 enumerated substituents.

In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in WO 2008/142550.

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



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(35)

The substituents for the above compounds are defined as follows:

m is 0, 1 or 2; n is 0, 1, 2 or 3,

X is O, S or N-CN,

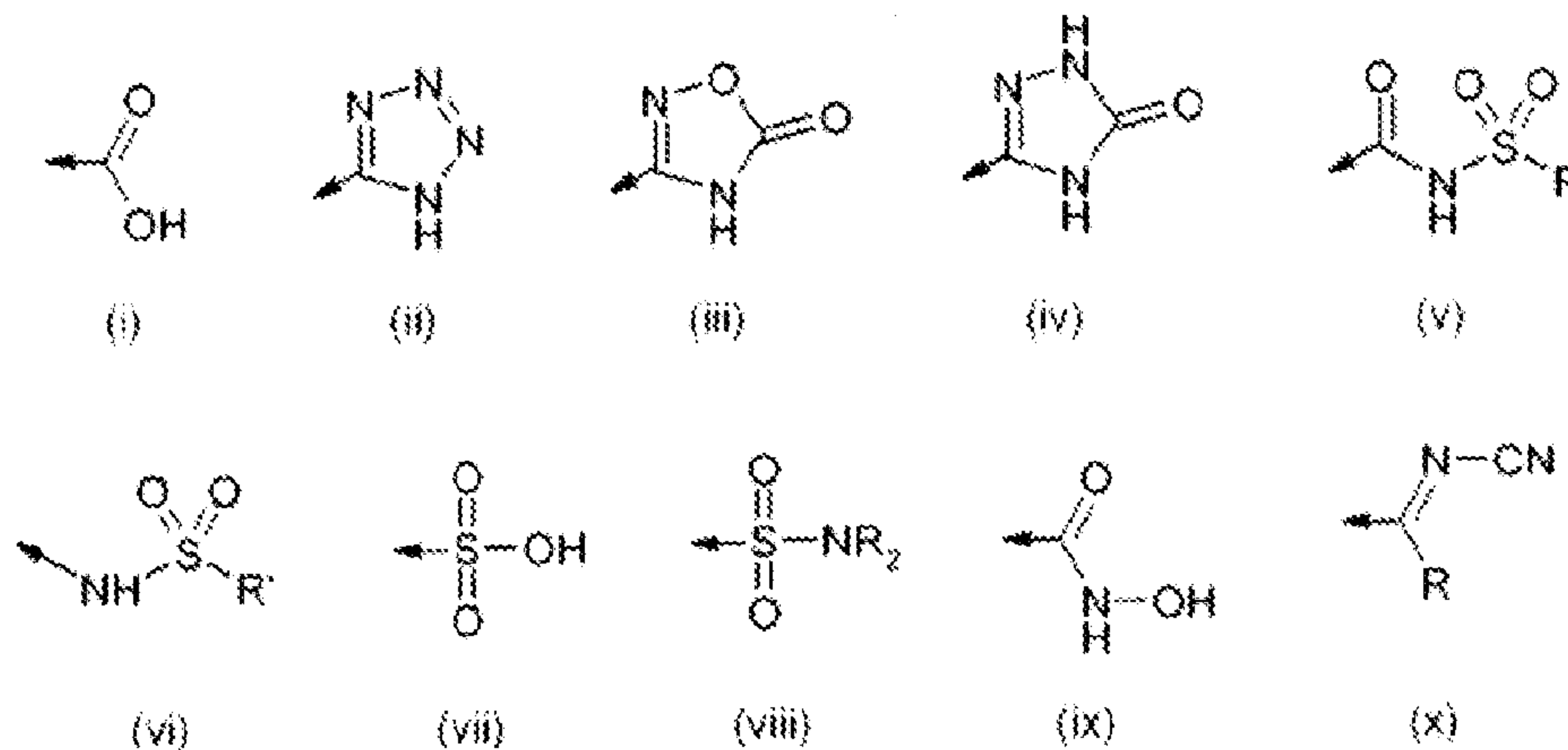
15 R¹ is halogen or CN,

A is a single bond, CH₂, O or S,

B is a single bond, CH₂ or OCH₂, each R² is independently halogen, (C₁₋₆)alkyl (optionally substituted by 1 to 3 fluorine atoms), OH, (C₁₋₆)alkylthio or CN,

R³ is selected from the following groups (i) to (x):

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R is H or (C₁₋₆)alkyl (optionally substituted by 1 to 3 fluorine atoms), R' is (C₁₋₆)alkyl (optionally substituted by 1 to 3 fluorine atoms), or a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof.

In regard to the above compounds, the term "alkyl" denotes a monovalent, straight or branched, saturated hydrocarbon chain containing 1 to 6 carbon atoms. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, 2-methylbutyl, 3-methylbutyl, neopentyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2-ethylbutyl and 2,2-dimethylbutyl. Preferred alkyl groups are particularly methyl and ethyl, especially methyl.

Where stated, alkyl groups may be substituted by 1 to 3 fluorine atoms. The substitution may be at any position on the alkyl chain. Preferably, such fluorinated alkyl groups have 1 to 4 carbon atoms, more preferably 1 or 2 carbon atoms. Mono-, di- and trifluoromethyl groups (especially trifluoromethyl), and mono-, di- and trifluoroethyl groups (especially 2,2,2-trifluoroethyl) are especially preferred.

The term "alkoxy" denotes "alkyl-O-", wherein "alkyl" is as defined above, either in its broadest aspect or a preferred aspect. Preferred alkoxy groups are groups, particularly methoxy and ethoxy. The term "alkylthio" denotes "alkyl-S-", wherein "alkyl" is as defined above, either in its broadest aspect or a preferred aspect. Preferred

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alkylthio groups are (C₁₋₄)alkylthio groups, particularly methylthio and ethylthio. The term "halogen" denotes fluoro, chloro, bromo or iodo. Preferred halogen groups are fluoro and chloro.

Preferably, m is 0 or 1, more preferably 1.

5 Preferably, n is 0 or 1, more preferably 0.

Preferably, X is O or N-CN, more preferably O.

Preferably, R¹ is F or Cl, more preferably Cl.

Preferably, A is a single bond or O, more preferably O.

10 When the group B is OCH₂, the oxygen atom is bonded to the benzene ring and the methylene group to the group R³.

Preferably, B is a single bond.

Preferably, R² is F or Cl, more preferably F.

Preferably, R³ is a group (i), (ii), (iii), (iv), (v) or (vi), more preferably a group (i) or (ii), and especially a group (ii).

15 In one embodiment, the group -B-R³ is present at the 2-position of the phenyl ring (the position of the group A being the 1-position). In other embodiments, the group -B-R³ is present at the 3-position. In further embodiments, the group -B-R³ is present at the 4-position.

20 PDE7 inhibitors useful in the methods of the invention include those in which each variable in the above formula is selected from the suitable and/or preferred groups for each variable. Even more preferred PDE7 inhibitors useful in the methods of the invention include those where each variable in the above formula is selected from the more preferred or most preferred groups for each variable.

25 In a related embodiment, the following PDE7 inhibitors are useful in the methods of the invention:

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5-[(8'-chloro-2'-oxo-2',3'-dihydro-1'H-spiro[cyclohexane-1,4'-quinazolin]-5'-yl)]-
2-fluorobenzoic acid,

3-(8'-chloro-2'-oxo-2',3'-dihydro-1'H-spiro[cyclohexane-1,4'-quinazolin]-5'-
yl)benzoic acid,

5 5-[(8'-chloro-2'-oxo-2',3'-dihydro-1'H-spiro[cyclohexane-1,4'-quinazolin]-4'-yl)]-
2-fluorobenzoic acid,

8-chloro-5'-[4-fluoro-3-(2H-tetrazol-5-yl)phenyl]-1'H-spiro[cyclohexane-1,4'-
quinazolin]-2'(3'H)-one,

10 [3-(8'-chloro-2'-oxo-2',3'-dihydro-1'H-spiro[cyclohexane-1,4'-quinazolin]-5'-
yl)phenoxy]acetic acid,

2-[(8'-chloro-2'-oxo-2',3'-dihydro-1'H-spiro[cyclohexane-1,4'-quinazolin]-5'-
yl)oxy]-3-fluorobenzoic acid,

2-[(8'-chloro-2'-oxo-2',3'-dihydro-1'H-spiro[cyclopentane-1,4'-quinazolin]-5'-
oxy]-3-fluorobenzoic acid,

15 3-chloro-2-[(8'-chloro-2'-oxo-2',3'-dihydro-1'H-spiro[cyclohexane-1,4'-
quinazolin]-5'-yl)oxy]benzoic acid,

3-chloro-2-[(8'-fluoro-2'-oxo-2',3'-dihydro-1'H-spiro[cyclohexane-1,4'-
quinazolin]-5'-yl)oxy]benzoic acid,

20 8'-chloro-5'-[2-fluoro-6-(2H-tetrazol-5-yl)phenoxy]-1'H-spiro[cyclohexane-1,4'-
quinazolin]-2'(3'H)-one,

8'-chloro-5'-[4-fluoro-2-(1H-tetrazol-5-yl)phenoxy]-1'H-spiro[cyclohexane-1,4'-
quinazolin]-2'(3'H)-one,

8'-chloro-5'-[6-fluoro-2-(1H-tetrazol-5-yl)phenoxy]-1'H-spiro[cyclohexane-1,4'-
quinazolin]-2'(3'H)-one,

25 8'-chloro-5'-[4-fluoro-2-(1H-tetrazol-5-yl)phenoxy]-1'H-spiro[cyclopentane-1,4'-
quinazolin]-2'(3'H)-one,

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8'-chloro-5'-[6-fluoro-2-(1H-tetrazol-5-yl)phenoxy]-1'H-spiro[cyclopentane-1,4'-quinazolin]-2'(3'H)-one,

8'-chloro-5'-[6-chloro-2-(1H-tetrazol-5-yl)phenoxy]-1'H-spiro[cyclopentane-1,4'-quinazolin]-2'(3'H)-one,

5 8'-chloro-5'-[2-(1H-tetrazol-5-yl)phenoxy]-1'H-spiro[cyclopentane-1,4'-quinazolin]-2'(3'H)-one,

8'-chloro-5'-[2-(1H-tetrazol-5-yl)phenoxy]-1'H-spiro[cyclohexane-1,4'-quinazolin]-2'(3'H)-one,

10 8'-chloro-5'-[2-fluoro-6-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)phenoxy]-1'H-spiro[cyclohexane-1,4'-quinazolin]-2'(3'H)-one,

8'-chloro-5'-[2-fluoro-6-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)phenoxy]-1'H-spiro[cyclohexane-1,4'-quinazolin]-2'(3'H)-one,

2-[(8'-chloro-2'-oxo-2',3'-dihydro-1'H-spiro[cyclohexane-1,4'-quinazolin]-5'-yl)oxy]-3-fluoro-N-(methylsulfonyl)benzamide,

15 N-{2-[(8'-chloro-2'-oxo-2',3'-dihydro-1'H-spiro[cyclohexane-1,4'-quinazolin]-5'-yl)oxy]-3-fluorophenyl}-1,1,1-trifluoromethanesulfonamide,

{2-[(8'-chloro-2'-oxo-2',3'-dihydro-1'H-spiro[cyclohexane-1,4'-quinazolin]-5'-yl)oxy]-3-fluorophenyl}acetic acid,

20 {2-[(8'-chloro-2'-oxo-2',3'-dihydro-1'H-spiro[cyclohexane-1,4'-quinazolin]-5'-yl)oxy]phenoxy}acetic acid,

{4-[(8'-chloro-2'-oxo-2',3'-dihydro-1'H-spiro[cyclohexane-1,4'-quinazoline-5'-yl)oxy]phenoxy}acetic acid,

methyl 2-[(8'-chloro-2'-oxo-2',3'-dihydro-1'H-spiro[cyclohexane-1,4'-quinazolin]-5'-yl)oxy]-3-fluorobenzoate,

25 and pharmaceutically acceptable salts, solvates and prodrugs thereof.

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In another related embodiment, the following PDE7 inhibitors are useful in the methods of the invention:

8'-chloro-5'-[2-fluoro-6-(2H-tetrazol-5-yl)phenoxy]-1'H-spirocyclohexane-1,4'-quinazolin]-2'(3'H)-one,

5 8'-chloro-5'-[4-fluoro-2-(1H-tetrazol-5-yl)phenoxy]-1'H-spiro[cyclohexane-1,4'-quinazolin]-2'(3'H)-one,

8'-chloro-5'-[6-fluoro-2-(1H-tetrazol-5-yl)phenoxy]-1'H-spiro[cyclohexane-1,4'-quinazolin]-2'(3'H)-one,

10 8'-chloro-5'-[4-fluoro-2-(1H-tetrazol-5-yl)phenoxy]-1'H-spiro[cyclopentane-1,4'-quinazolin]-2'(3'H)-one,

8'-chloro-5'-[6-fluoro-2-(1H-tetrazol-5-yl)phenoxy]-1'H-spiro[cyclopentane-1,4'-quinazolin]-2'(3'H)-one,

8'-chloro-5'-[6-chloro-2-(1H-tetrazol-5-yl)phenoxy]-1'H-spiro[cyclopentane-1,4'-quinazolin]-2'(3'H)-one,

15 8'-chloro-5'-[2-(1H-tetrazol-5-yl)phenoxy]-1'H-spiro[cyclopentane-1,4'-quinazolin]-2'(3'H)-one,

8'-chloro-5'-[2-(1H-tetrazol-5-yl)phenoxy]-1'H-spiro[cyclohexane-1,4'-quinazolin]-2'(3'H)-one,

and pharmaceutically acceptable salts, solvates and prodrugs thereof.

20 The following compounds are most preferred:

8'-chloro-5'-[2-fluoro-6-(2H-tetrazol-5-yl)phenoxy]-1'H-spiro[cyclohexane-1,4'-quinazolin]-2'(3'H)-one,

8'-chloro-5'-[4-fluoro-2-(1H-tetrazol-5-yl)phenoxy]-1'H-spiro[cyclohexane-1,4'-quinazolin]-2'(3'H)-one,

25 8'-chloro-5'-[6-fluoro-2-(1H-tetrazol-5-yl)phenoxy]-1'H-spiro[cyclopentane-1,4'-quinazolin]-2'(3'H)-one,

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8'-chloro-5'-[2-(1H-tetrazol-5-yl)phenoxy]-1'H-spiro[cyclohexane-1,4'-quinazolin]-2'(3'H)-one,

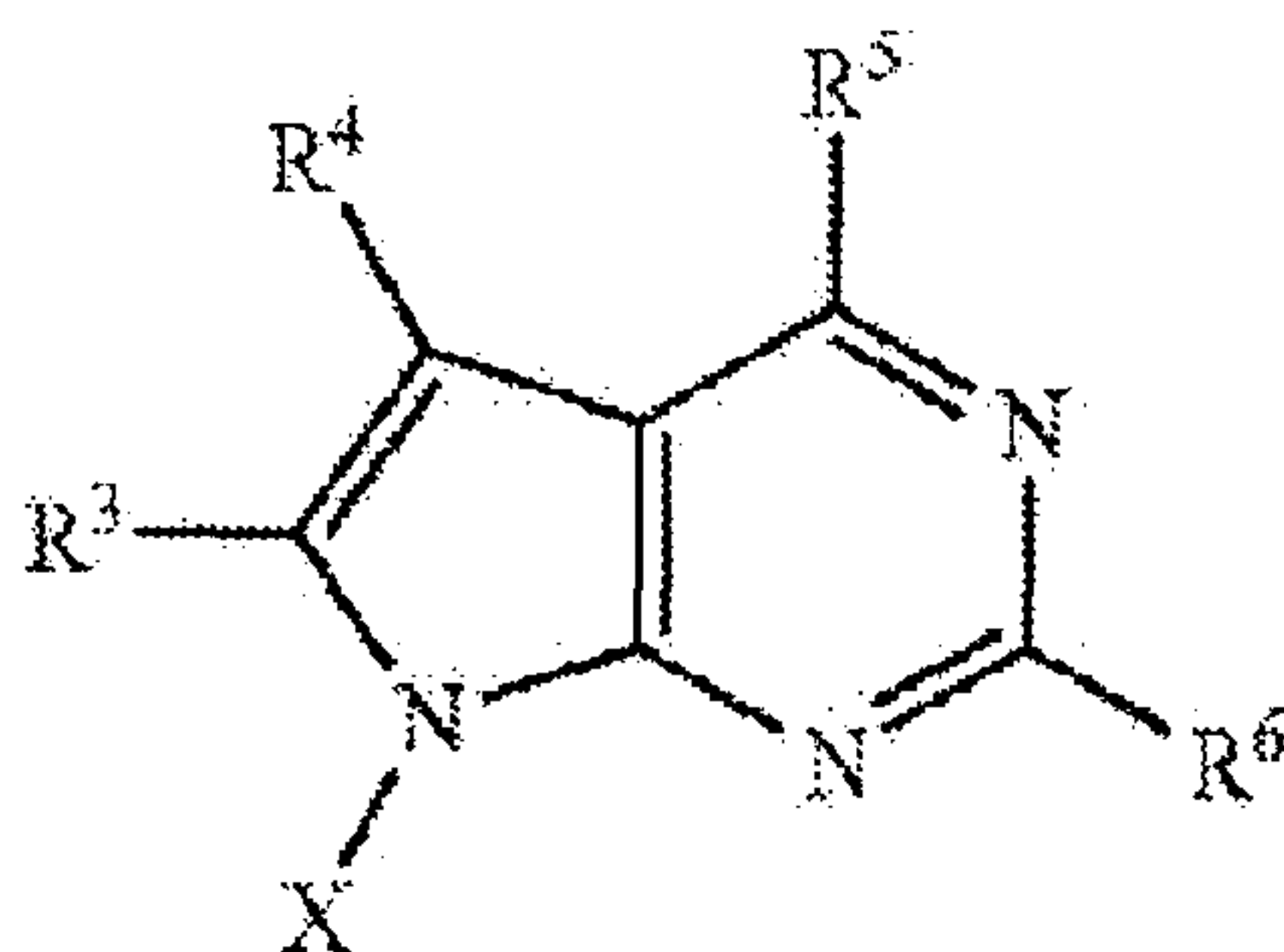
and pharmaceutically acceptable salts, solvates and prodrugs thereof.

The preparation of these compounds is described in WO 2008/142550.

5

In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in US 7498334, US 2005/0059686 and WO 2003/055882.

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



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The substituents for the above compounds are defined as follows:

X is phenyl or Het, each of which is unsubstituted or monosubstituted or polysubstituted by R1 and/or R2, R1 and R2 are each, independently of one another, A, OH, OA, SA, SOA, SO2A, SO2NH2, SO2NHA, SO2AA', CN, NO2, NH2, NHA, NAA', NHCOA, NHCOOA, COOH, COOA, CONH2, CONHA, CONAA' or Hal, R' and R2 together are alternatively —OCH2O— or —OCH2CH2O—, R3 is A, OH, OA, SA, SOA, SO2A, SO2NH2, SO2NHA, SO2AA', CN, NO2, NH2, NHA, NHB, NAA', NHCOA, NHCOOA, NHCOB, NHCOOB, COOH, COOA, COOB, CONH2, CONHA,

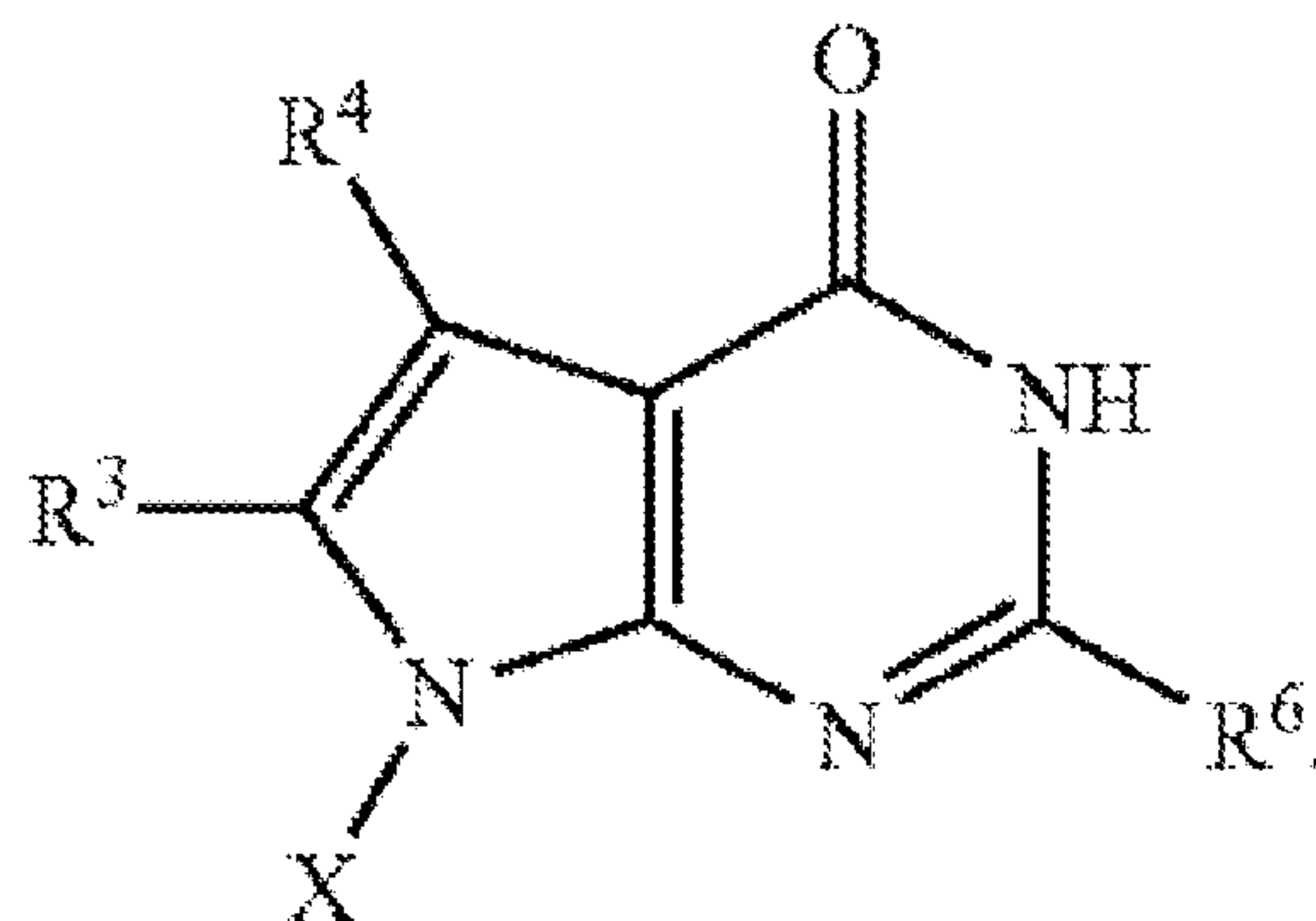
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CONHB, CONAA' or Hal, R4 is branched or unbranched alkyl or alkenyl having up to 10 carbon atoms, which may be substituted by from 1 to 5 F and/or Cl atoms and/or in which one or more CH2 groups may be replaced by O, S, SO, SO2, NH, NA, NHCO, NACO, NHCOO or NACOO, or cycloalkyl or cycloalkenyl having from 3 to 7 carbon
5 atoms, in which one or two CH2 groups may be replaced by O, S, SO, SO2, SO2NH, SO2NA, NH, NHA, NHCONH, NACONH, NACONA, NHCO, NACO, NHCOO or NACOO, R5 is OH, OA, SA, SOA, SO2A, SO2NH2, SO2NHA, SO2AA', CN, NO2, NH2, NHA, NAA', NHCOA, NHCOOA, COOH, COOA, CONH2, CONHA, CONAA' or Hal, R6 is H, OH, OA, SA, SOA, SO2A, SO2NH2, SO2NHA, SO2AA', CN, NO2,
10 NH2, NHA, NAA', NHCOA, NHCOOA, COOH, COOA, CONH2, CONHA, CONAA' or Hal, A and A' are each, independently of one another, branched or unbranched alkyl or alkenyl having up to 10 carbon atoms, which may be substituted by from 1 to 5 F and/or Cl atoms and/or in which one or more CH2 groups may be replaced by O, S, SO, SO2, NH, NR7, NHCO, NR7CO, NHCOO or NR7COO. A and A' together are alternatively
15 alkylene having from 3 to 7 carbon atoms, in which one or two CH2 groups may be replaced by CHR7, CHR7R8, O, S, SO, SO2, NH, NR7, NHCO, NR7CO, NHCOO or NR7COO. B is phenyl or Het, each of which is unsubstituted or monosubstituted or polysubstituted by R1 and/or R2, Het is an aromatic 5- or 6-membered heterocyclic ring having 1-3 N, O and/or S atoms which is unsubstituted or monosubstituted, disubstituted
20 or trisubstituted by A'', Hal or CF3, R7 and R8 are each, independently of one another, branched or unbranched alkyl or alkenyl having up to 5 carbon atoms, which may be substituted by from 1 to 5 F and/or Cl atoms and/or in which one or more CH2 groups may be replaced by O, S, SO, SO2 or NH, A'' is alkyl having from 1 to 6 carbon atoms, and Hal is F, Cl, Br or I, and pharmaceutically usable derivatives, solvates and
25 stereoisomers thereof, including mixtures thereof in all ratios.

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In a related embodiment, PDE7 inhibitors useful in the methods of the invention include compounds of the above formula in which R⁵ is OH may also be in the form of their tautomers of the formula:



5 In regard to the above compounds, PDE7 inhibitors useful in methods of the invention include the optically active forms (stereo-isomers), the enantiomers, the racemates, the diastereomers and the hydrates and solvates of these compounds. The term solvates of the compounds is taken to mean adductions of inert solvent molecules onto the compounds which form owing to their mutual attractive force. Solvates are, for
 10 example, monohydrates, dihydrates or alcoholates.

In regards to the above compounds, the term pharmaceutically usable derivatives is taken to mean, for example, the salts of the above compounds and so-called prodrug compounds. The term prodrug derivatives is taken to mean, for example, the above compounds which have been modified, for example, with alkyl or acyl groups, sugars or
 15 oligopeptides and which are rapidly cleaved in the organism and thus release the active compounds. These also include biodegradable polymer derivatives of the above compounds, as described, for example, in *Int. J. Pharm.* 115, 61-67 (1995).

In regard to the above compounds, the meanings of all radicals which occur more than once are in each case independent of one another.

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A and A' are preferably alkyl, furthermore preferably alkyl which is substituted by from 1 to 5 fluorine and/or chlorine atoms, furthermore preferably alkenyl.

In the above formulae, alkyl is preferably unbranched and has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms, preferably 1, 2, 3, 4, 5 or 6 carbon atoms, and is preferably methyl, ethyl, trifluoromethyl, pentafluoroethyl or propyl, furthermore preferably isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, but also n-pentyl, neopentyl, isopentyl or n-hexyl. Particular preference is given to methyl, ethyl, trifluoromethyl, propyl, isopropyl, butyl, n-pentyl, n-hexyl or n-decyl.

A'' is preferably alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, for example methyl, ethyl or propyl, furthermore preferably isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, but also n-pentyl, neopentyl, isopentyl or n-hexyl. Particular preference is given to methyl, ethyl, propyl, isopropyl or butyl.

Cycloalkyl preferably has 3-7 carbon atoms and is preferably cyclopropyl or cyclobutyl, furthermore preferably cyclopentyl or cyclohexyl, furthermore also cycloheptyl; particular preference is given to cyclopentyl.

Alkenyl is preferably vinyl, allyl, 2- or 3-butenyl, isobutenyl or sec-butenyl; preference is furthermore given to 4-pentenyl, isopentenyl or 5-hexenyl.

Alkylene is preferably unbranched and is preferably methylene or ethylene, furthermore preferably propylene or butylene.

Hal is preferably F, Cl or Br, furthermore also I.

The radicals R1 and R2 may be identical or different and are preferably in the 2- or 4-position of the phenyl ring. They are, for example, independently of one another, A or Hal, or together are methylenedioxy.

However, they are preferably each methyl, ethyl, propyl, methoxy, ethoxy, propoxy, isopropoxy, benzyloxy, but also fluoro-, difluoro- or trifluoro-methoxy, or

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1-fluoro-, 2-fluoro-, 1,2-difluoro-, 2,2-difluoro-, 1,2,2-trifluoro- or 2,2,2-trifluoroethoxy, furthermore fluorine or chlorine.

R1 is particularly preferably fluorine, chlorine, methyl, ethyl or propyl.

R2 is particularly preferably fluorine, chlorine, methyl, ethyl or propyl.

5 X is preferably a phenyl radical which is monosubstituted by R1 or is unsubstituted Het.

X is particularly preferably 2-chlorophenyl, 2-fluorophenyl, 4-methyl-phenyl, 3-chlorophenyl or 4-chlorophenyl.

Het is preferably, for example, unsubstituted 2- or 3-furyl, 2- or 3-thienyl, 1-, 2-
10 or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, or 1,2,3-thia-diazol-4- or -5-yl.

R3 is preferably, for example, COOA" or COOH.

15 R4 is preferably, for example, unbranched or branched alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, which may be substituted by 1-5 F or Cl atoms, preferably methyl, ethyl, trifluoromethyl, pentafluoroethyl or propyl, furthermore preferably isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, but also n-pentyl, neopentyl, isopentyl or n-hexyl. Particular preference is given to methyl, ethyl, trifluoromethyl, propyl, isopropyl, butyl,
20 n-pentyl, n-hexyl or n-decyl.

R5 is preferably Cl or OH.

R6 is preferably H.

In regard to the above compounds, at least one of the said radicals has one of the preferred meanings indicated above.

25 In a related embodiment, PDE7 inhibitors useful in the methods of the invention include the following compounds, wherein X is a phenyl radical which is

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monosubstituted by R1, or is unsubstituted Het; R1 is A or Hal; R3 is COOA" or COOH; R4 is unbranched or branched alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, which may be substituted by 1-5 F or Cl atoms; R5 is Cl or OH; and R6 is H;

In other related embodiments, PDE7 inhibitors useful in the methods of the invention include the following compounds, wherein X is a phenyl radical which is monosubstituted by R1, or is unsubstituted Het, R1 is A or Hal, R3 is COOA" or COOH, R4 is unbranched or branched alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, which may be substituted by 1-5 F or Cl atoms, R5 is Cl or OH, R6 is H, Het is furyl, thienyl, pyrrolyl, imidazolyl, pyridyl or pyrimidinyl, A and A" are each, independently of one another, unbranched or branched alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms, which may be substituted by 1-5 F or Cl atoms, Hal is F, Cl or Br, and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

The preparation of the above compounds and also the starting materials for their preparation are described in the literature (for example in the standard works, such as Houben-Weyl, *Methoden der organischen Chemie* [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions. Use can also be made here of variants which are known per se, but are not mentioned here in greater detail.

In another related embodiment, PDE7 inhibitors useful in the methods of the invention include:

ethyl 5-isopropyl-4-oxo-7-p-tolyl-4,7-dihydro-3H-pyrrolo[2,3-d]-pyrimidine-6-carboxylate, ethyl 5-methyl-4-oxo-7-(3-chlorophenyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidine-6-carboxylate, ethyl 5-methyl-4-oxo-7-(2-chlorophenyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidine-6-carboxylate, ethyl 5-methyl-4-oxo-7-(2-fluorophenyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidine-6-carboxylate, ethyl 5-propyl-4-oxo-7-(2-chlorophenyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidine-6-carboxylate, ethyl 5-methyl-4-

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oxo-7-(4-chlorophenyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidine-6-carboxylate, ethyl 5-methyl-4-oxo-7-p-tolyl-4,7-dihydro-3H-pyrrolo[2,3-d]-pyrimidine-6-carboxylate, methyl 5-methyl-4-oxo-7-(2-chlorophenyl)-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidine-6-carboxylate, methyl 5-methyl-4-oxo-7-phenyl-4,7-dihydro-3H-pyrrolo[2,3-d]-pyrimidine-6-carboxylate, methyl 5-methyl-4-oxo-7-(2-thienyl)-4,7-dihydro-3H-pyrrolo[2,3-d]-pyrimidine-6-carboxylate, and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

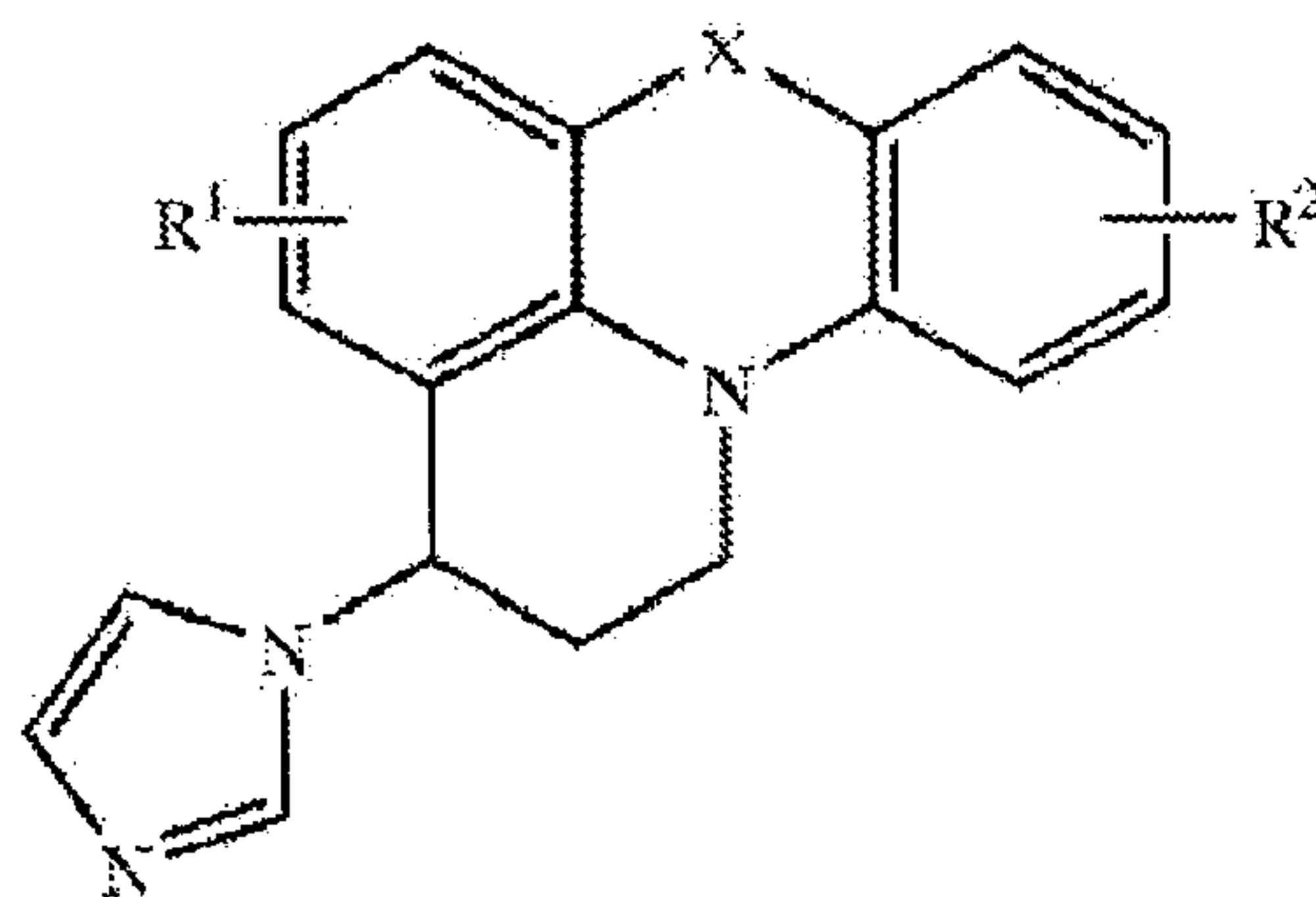
The preparation of the above compounds is described in US 7498334 and WO 2003/055882.

10

In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in U.S. Pat. No. 6884800 and WO 01/36425.

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:

15



(37)

The substituents for the above compounds are defined as follows:

R1 and R2, independently of one another, each denote A1, OA1, SA1 or Hal, A1 denotes H, A, alkenyl, cycloalkyl or alkylencycloalkyl, A denotes alkyl having 1-10

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carbon atoms, Hal denotes F, Cl, Br or I, and x denotes O, S, SO or SO₂, and their physiologically acceptable salts and/or solvates.

In regards to the above compounds, A denotes alkyl having 1-10 carbon atoms and has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms and preferably denotes methyl, ethyl or propyl, furthermore preferably isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, but also n-pentyl, neopentyl, isopentyl or hexyl. In these radicals, 1-7 H atoms may also be replaced by F and/or Cl. A therefore also denotes, for example, trifluoromethyl or pentafluoroethyl. Cycloalkyl has 3-9 carbon atoms and preferably denotes, for example, cyclopentyl or cyclohexyl. Alkenyl has 2-10 carbon atoms, is linear or branched and preferably denotes vinyl, propenyl or butenyl. Alkylencycloalkyl has 4-10 carbon atoms and denotes, for example, methylenecyclopentyl, ethylenecyclopentyl, methylenecyclohexyl or ethylenecyclohexyl. R1 and R2 preferably denote, in each case independently of one another, H, fluorine, chlorine, methyl, ethyl, propyl, methoxy, ethoxy, propoxy, methylthio, cyclopentyl or cyclohexyl.

In a related embodiment, PDE7 inhibitors useful in the methods of the invention include the following compounds, wherein

X is S;

X is S, R1 is H;

X is S, R1 is F or Cl;

X is S, R2 is H;

X is S, R2 is F or Cl;

X is S, R1 is H, R2 is F or Cl;

X is S, R1 is F or Cl, R2 is H;

X is S; A1 is H or A, A is alkyl having 1, 2, 3 or 4 carbon atoms;

X is S, R1 and R2, independently of one another, each denote A1 or Hal, A1 is H or A, A is alkyl having 1, 2, 3 or 4 carbon atoms, Hal is F or Cl;

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and their physiologically acceptable salts and solvates.

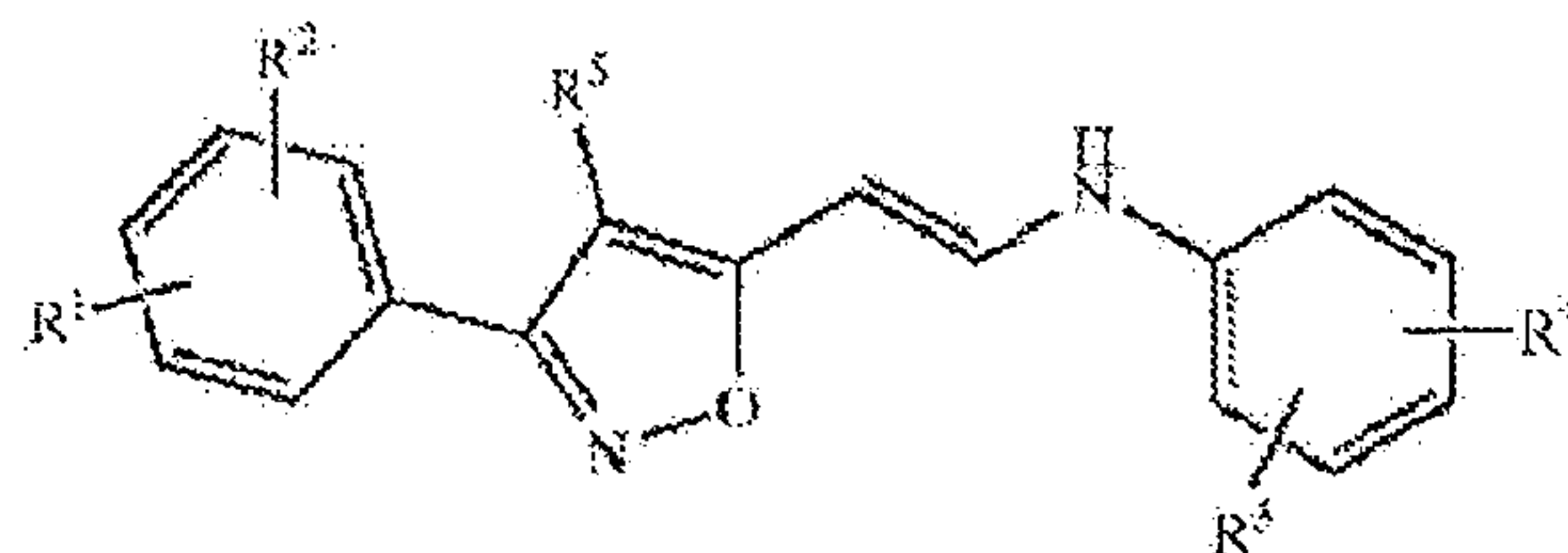
In another related embodiment, PDE7 inhibitors useful in the methods of the invention include the following compounds:

10-Chloro-3-imidazol-1-yl-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine, 4-
 5 chloro-3-imidazol-1-yl-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine, 10-methoxy-3-
 imidazol-1-yl-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine, 10-propoxy-3-imidazol-1-
 yl-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine, 10-methylthio-3-imidazol-1-yl-2,3-
 dihydro-1H-pyrido[3,2,1-kl]phenothiazine, 10-fluoro-3-imidazol-1-yl-2,3-dihydro-1H-
 pyrido[3,2,1-kl]phenothiazine, 4,10-dichloro-3-imidazol-1-yl-2,3-dihydro-1H-
 10 pyrido[3,2,1-kl]phenothiazine, 10-trifluoromethyl-3-imidazol-1-yl-2,3-dihydro-1H-
 pyrido[3,2,1-kl]phenothiazine, 4-cyclopentoxy-3-imidazol-1-yl-2,3-dihydro-1H-
 pyrido[3,2,1-kl]phenothiazine, 10-chloro-3-imidazol-1-yl-2,3-dihydro-1H-7-oxa-11b-
 azabenz[de]anthracene, and 10-chloro-3-imidazol-1-yl-2,3-dihydro-1H-pyrido[3,2,1-
 kl]phenothiazine 7,7-dioxide.

15 The preparation of these compounds is described in U.S. Pat. No. 6,884,800 and
 WO 01/36425.

In another embodiment, PDE7 inhibitors useful in the methods of the invention
 are selected from those compounds generally or specifically disclosed in U.S. Pat.
 20 No. 6,531,498 and WO 01/32175.

In one embodiment, PDE7 inhibitors useful in the methods of the invention
 have the formula:



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(38)

The substituents of the above compounds are defined as follows:

R1, R2, R3, R4 are each, independently of one another, Hal, OA1, SA1, A, H, COOA1, CN or CONA1A2,

5 R5 is COOA1, CN or CONA1A2,

A1, A2 are each, independently of one another, H, A, alkenyl, cycloalkyl or alkylenecycloalkyl,

A is alkyl having 1 to 10 C atoms,

Hal is F, Cl, Br or I,

10 and their physiologically acceptable salts and/or solvates.

In regard to the above compounds, A is alkyl having 1-10 C atoms and has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 C atoms and is preferably methyl, ethyl or propyl, also preferably isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, but is also n-pentyl, neopentyl, isopentyl or hexyl. It is also possible for 1-7 H atoms in the radicals to be replaced by F and/or Cl.

15 A is therefore also, for example, trifluoromethyl or pentafluoroethyl.

Cycloalkyl has 3-9 C atoms and is preferably, for example, cyclopentyl or cyclohexyl. Alkenyl has 2-10 C atoms, is linear or branched and is preferably vinyl, propenyl or butenyl.

20 Alkylenecycloalkyl has 4-10 C atoms and is, for example methylenecyclopentyl, ethylenecyclopentyl, methylenecyclohexyl or ethylenecyclohexyl.

In a related embodiment, PDE7 inhibitors useful in the methods of the invention include the compounds wherein

R1 is H;

R1 and R2 are H;

25 R1 is H and R2 is F or Cl;

R1, R2 are each, independently of one another, H or Hal;

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R1, R2 are each, independently of one another, H or Hal, A1, A2 are each, independently of one another, H or A;

A1, A2 are each, independently of one another, H or A;

R1, R2 are each, independently of one another, H or Hal, A1, A2 are each,
 5 independently of one another, H or A, A is alkyl having 1, 2, 3 or 4 C atoms, Hal is F or Cl.

In another related embodiment, PDE7 inhibitors useful in the methods of the invention include the compounds:

5-[2-(2-Fluoro-4-hydroxyphenylamino)vinyl]-4-cyano-3-phenylisoxazole,
 10 5-[2-(2,4-Difluorophenylamino)vinyl]-4-cyano-3-phenylisoxazole,
 5-[2-(3-Methylthiophenylamino)vinyl]-4-cyano-3-phenylisoxazole,
 5-[2-(2,4-Dimethoxyphenylamino)vinyl]-4-cyano-3-(2-chlorophenyl)isoxazole,
 5-(2-Amino-2-phenylvinyl)-4-methylaminocarbonyl-3-phenylisoxazole,
 5-(2-Phenylaminovinyl)-4-methoxycarbonyl-3-phenylisoxazole,
 15 5-[2-(4-Carboxyphenylamino)vinyl]-4-cyano-3-phenylisoxazole,
 5-[2-(4-Carboxyphenylamino)vinyl]-4-methoxycarbonyl-3-phenylisoxazole,
 5-[2-(5-Chloro-2-hydroxyphenylamino)vinyl]-4-cyano-3-phenylisoxazole,
 5-[2-(3,4-Dimethylphenylamino)vinyl]-4-cyano-3-(2-chlorophenyl)isoxazole,
 5-[2-(4-Chlorophenylamino)vinyl]-4-cyano-3-(2-chlorophenyl)isoxazole,
 20 5-(2-Phenylaminovinyl)-4-cyano-3-(2-chlorophenyl)isoxazole,
 5-[2-(4-Methoxyphenylamino)vinyl]-4-cyano-3-(2-chlorophenyl)isoxazole,
 5-[2-(4-Carboxyphenylamino)vinyl]-4-cyano-3-(2-chlorophenyl)isoxazole,
 5-[2-(2-Fluoro-4-hydroxyphenylamino)vinyl]-4-cyano-3-(2-
 chlorophenyl)isoxazole,
 25 5-[2-(4-Fluorophenylamino)vinyl]-4-cyano-3-(2-chlorophenyl)isoxazole,
 5-[2-(3,5-Dichlorophenylamino)vinyl]-4-cyano-3-(2-chlorophenyl)isoxazole,

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- 5-[2-(3-Chlorophenylamino)vinyl]-4-cyano-3-(2-chlorophenyl)isoxazole,
 5-(2-Phenylaminovinyl)-4-cyano-3-(2,6-dichlorophenyl)isoxazole,
 5-[2-(4-Chlorophenylamino)vinyl]-4-cyano-3-(2,6-dichlorophenyl)isoxazole,
 5-(2-Phenylaminovinyl)-4-methoxycarbonyl-3-(2,6-dichlorophenyl)isoxazole,
 5 5-[2-(4-Chlorophenylamino)vinyl]-4-methoxycarbonyl-3-(2,6-dichlorophenyl)isoxazole,
 5-[2-(4-Carboxyphenylamino)vinyl]-4-methoxycarbonyl-3-(2,6-dichlorophenyl)isoxazole,
 5-[2-(2,4-Difluorophenylamino)vinyl]-4-cyano-3-(2,6-dichlorophenyl)isoxazole,
 10 5-[2-(2,4-Dichlorophenylamino)vinyl]-4-cyano-3-(2,6-dichlorophenyl)isoxazole,
 5-[2-(4-Carboxyphenylamino)vinyl]-4-cyano-3-(2,6-dichlorophenyl)isoxazole,
 5-[2-(3,5-Dichlorophenylamino)vinyl]-4-cyano-3-(2,6-dichlorophenyl)isoxazole,
 5-[2-(4-Methoxyphenylamino)vinyl]-4-cyano-3-(2,6-dichlorophenyl)isoxazole,
 5-[2-(2,4-Dimethoxyphenylamino)vinyl]-4-cyano-3-(2,6-dichlorophenyl)isoxazole,
 15 5-[2-(2-Phenylphenylamino)vinyl]-4-cyano-3-(2,6-dichlorophenyl)isoxazole,
 5-[2-(4-Methylphenylamino)vinyl]-4-cyano-3-(2,6-dichlorophenyl)isoxazole,
 5-(2-Phenylaminovinyl)-4-cyano-3-(2-chloro-6-fluorophenyl)isoxazole,
 5-[2-(4-Carboxyphenylamino)vinyl]-4-cyano-3-(2-chloro-6-fluorophenyl)isoxazole,
 20 5-[2-(4-Chlorophenylamino)vinyl]-4-cyano-3-(2-chloro-6-fluorophenyl)isoxazole,
 5-[2-(3-Methoxyphenylamino)vinyl]-4-cyano-3-(2-chloro-6-fluorophenyl)isoxazole,
 5-[2-(4-Chlorophenylamino)vinyl]-4-methoxycarbonyl-3-(2-chloro-6-fluorophenyl)isoxazole,
 25 5-[2-(4-Chlorophenylamino)vinyl]-4-methoxycarbonyl-3-(2-chloro-6-fluorophenyl)isoxazole,

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5-(2-Phenylaminovinyl)-4-methoxycarbonyl-3-(2-chloro-6-fluorophenyl)isoxazole,

5-[2-(2,4-Dichlorophenylamino)vinyl]-4-methoxycarbonyl-3-(2-chloro-6-fluorophenyl)isoxazole,

5 5-(2-Phenylaminovinyl)-4-cyano-3-phenylisoxazole,

5-[2-(3-Trifluoromethoxyphenylamino)vinyl]-4-cyano-3-phenylisoxazole,

5-[2-(4-Methoxyphenylamino)vinyl]-4-cyano-3-phenylisoxazole,

5-[2-(4-Methoxyphenylamino)vinyl]-4-methoxycarbonyl-3-(2-chloro-6-fluorophenyl)isoxazole,

10 5-[2-(3-Methylthiophenylamino)vinyl]-4-cyano-3-phenylisoxazole,

5-[2-(2,4-Difluorophenylamino)vinyl]-4-cyano-3-phenylisoxazole,

5-[2-(2-Fluoro-4-hydroxyphenylamino)vinyl]-4-cyano-3-phenylisoxazole.

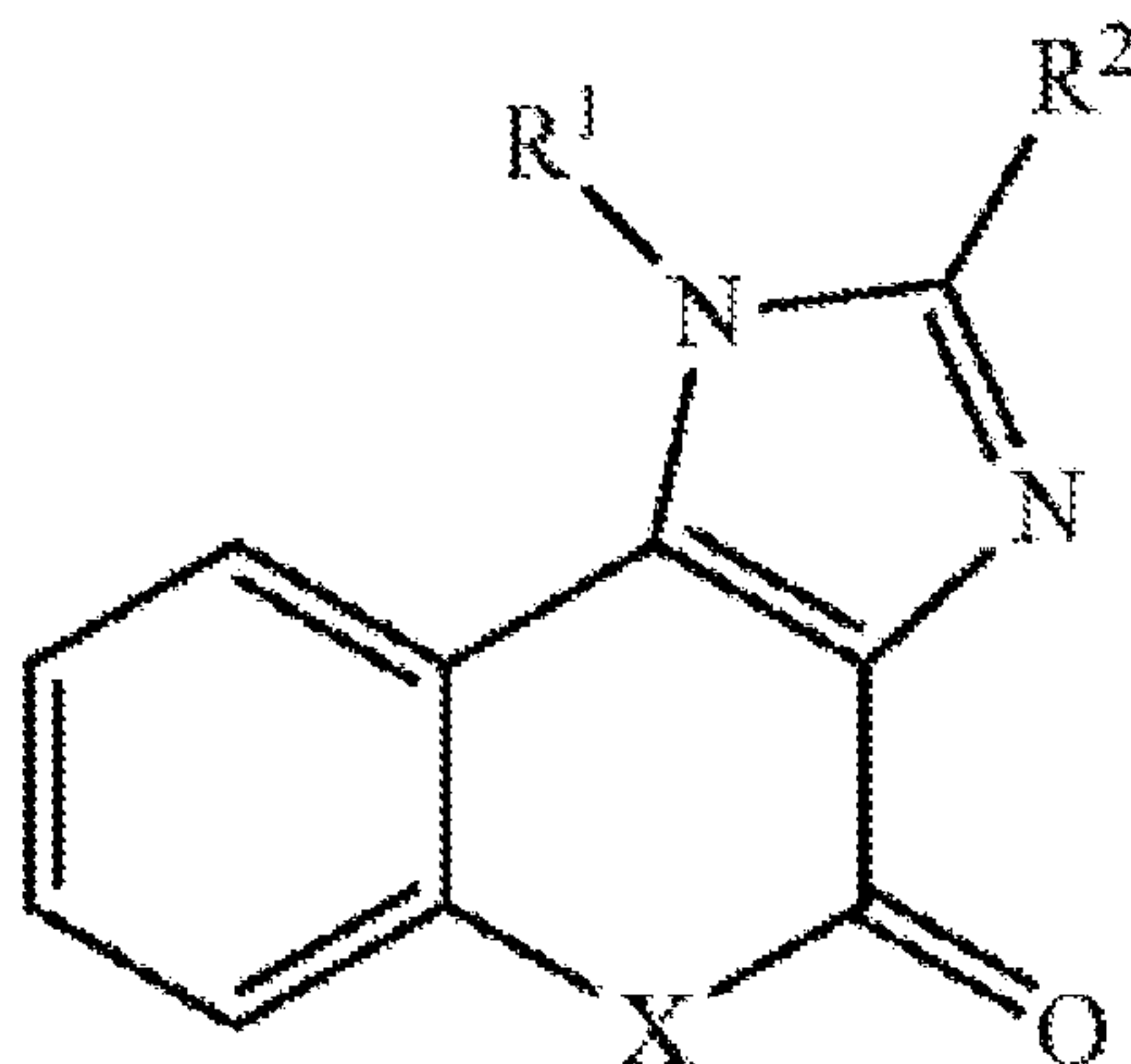
The preparation of these compounds is described in U.S. Pat. No. 6531498 and WO 01/32175.

15

In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in US 7491742 and WO 2001/29049.

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:

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(39)

The substituents of the above compounds are defined as follows:

R₁ is H, A, benzyl, indan-5-yl, 1,2,3,4-tetrahydronaphthalen-5-yl, dibenzothien-2-yl, or phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal, A, A—CO—NH, benzyloxy, alkoxy, COOH or COOA, R₂ is H or A, X is O or S, Hal is F, Cl, Br or I, A is alkyl with 1 to 6 C atoms, and the physiologically acceptable salts and/or solvates thereof.

In regard to the above compounds, A is alkyl with 1-6 C atoms and has 1, 2, 3, 4, 5 or 6 C atoms and is preferably methyl, ethyl or propyl, also preferably isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, but also n-pentyl, neopentyl, isopentyl or hexyl. A is also cycloalkyl such as, for example, cyclohexyl. Alkoxy is preferably methoxy, ethoxy, propoxy or butoxy. Hal is preferably F or Cl. A-CO--NH is preferably acetamido.

In a related embodiment, PDE7 inhibitors useful in the methods of the invention are selected from the following compounds:

1-Phenyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one, 1-Benzyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one, 1-Cyclohexyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one, 1-Cyclopentyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one, 1-Butyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one, 1-Isopropyl-[1]benzopyrano[3,4-

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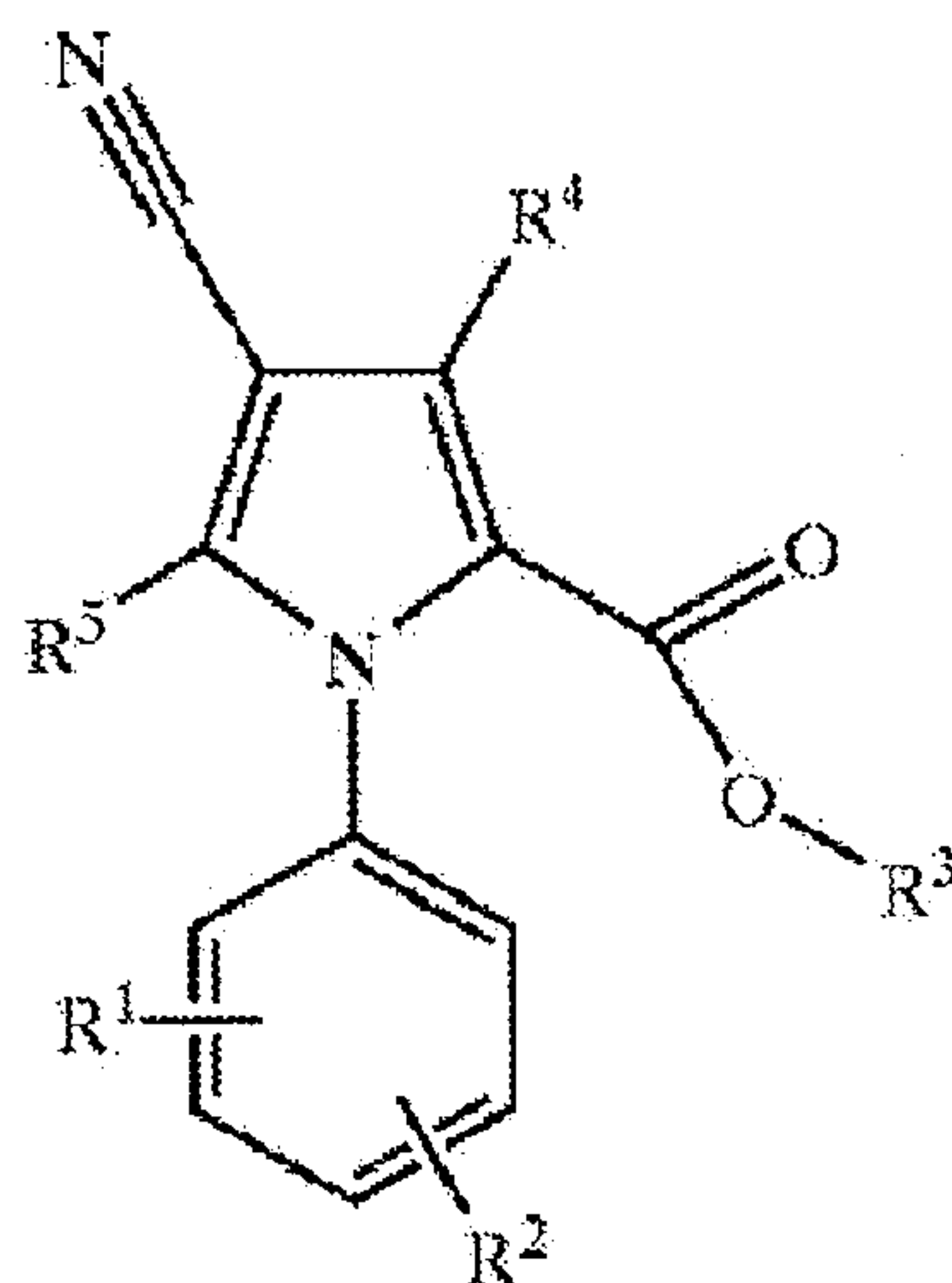
d]imidazol-4-(1H)-one, 1-Propyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one, 1-Ethyl-
 [1]benzopyrano[3,4-d]imidazol-4-(1H)-one, 1-Methyl-[1]benzopyrano[3,4-d]imidazol-4-
 (1H)-one, [1]Benzopyrano[3,4-d]imidazol-4-(1H)-one, 2-Methyl-[1]benzopyrano[3,4-
 d]imidazol-4-(1H)-one, 1-Phenyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one, 1-
 5 Benzyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one, 1-Cyclohexyl-
 [1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one, 1-Cyclopentyl-[1]benzothiopyrano[3,4-
 d]imidazol-4-(1H)-one, 1-Butyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one, 1-
 Isopropyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one, 1-Propyl-
 [1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one, 1-Ethyl-[1]benzothiopyrano[3,4-
 10 d]imidazol-4-(1H)-one, 1-Methyl-[1]benzothiopyrano[3,4-d]imidazol-4-(1H)-one,
 [1]Benzothiopyrano[3,4-d]imidazol-4-(1H)-one, 2-Methyl-[1]benzothiopyrano[3,4-
 d]imidazol-4-(1H)-one, 1-(2-Chlorophenyl-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one,
 1-(4-Methyl-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one, 1-(4-Fluorophenyl)-
 [1]benzopyrano[3,4-d]imidazol-4-(1H)-one, 1-(2,4-Dimethyl-phenyl)-
 15 [1]benzopyrano[3,4-d]imidazol-4-(1H)-one, 1-(3-Chlorophenyl)-[1]benzopyrano[3,4-
 d]imidazol-4-(1H)-one, 1-(2,4-Dichlorophenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-
 one, 1-(2,5-Dichlorophenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one, 1-(4-
 Acetamido-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one, 1-(2-Fluorophenyl)-
 [1]benzopyrano[3,4-d]imidazol-4-(1H)-one, 1-(3-Fluorophenyl)-[1]benzopyrano[3,4-
 20 d]imidazol-4-(1H)-one, 1-(2-Benzyloxy-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-
 one, 1-(2,6-Dimethyl-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one, 1-(Indan-5-
 yl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one, 1-(2-Methoxy-phenyl)-
 [1]benzopyrano[3,4-d]imidazol-4-(1H)-one, 1-(2,3-Dimethyl-phenyl)-
 [1]benzopyrano[3,4-d]imidazol-4-(1H)-one, 1-(2,3-Dichlorophenyl)-[1]benzopyrano[3,4-
 25 d]imidazol-4-(1H)-one, 1-(3-Chloro-4-methyl-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-
 (1H)-one, 1-(2,5-Dimethyl-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one, 1-(4-

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Chlorophenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one, 1-(1,2,3,4-Tetrahydronaphthalen-5-yl)-[1]benzopyrano-[3,4-d]imidazol-4-(1H)-one, 1-(Dibenzothien-2-yl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one, 1-(3-Methoxy-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one, 1-(4-Carboxy-2-methyl-phenyl)-[1]benzopyrano[3,4-d]imidazol-4-(1H)-one, and their physiologically acceptable salts and/or solvates thereof.

In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in U.S. Pat. No. 6,737,436 and WO 01/32618.

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



(40)

The substituents for the above compounds are defined as follows:

R1 and R2, independently of one another, each denote H, A, OA, SA or Hal,

R3 denotes H or A,

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R4 denotes A or NH₂,

R5 denotes H, NH₂, NHA or NA₂,

A denotes alkyl having 1 to 10 carbon atoms, alkenyl, cycloalkyl or alkylenecycloalkyl,

5 Hal denotes F, Cl, Br or I,

and their physiologically acceptable salts and/or solvates.

In regard to the above compounds, A denotes alkyl having 1-10 carbon atoms and has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms and preferably denotes methyl, ethyl or propyl, furthermore preferably isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, but also
10 n-pentyl, neopentyl, isopentyl or hexyl. In these radicals, 1-7 H atoms may also be replaced by F and/or Cl. A therefore also denotes, for example, trifluoromethyl or pentafluoroethyl.

A also denotes cycloalkyl having 3-8 carbon atoms and preferably denotes, for example, cyclopentyl or cyclohexyl.

15 A also denotes alkenyl. Alkenyl has 2-10 carbon atoms, is linear or branched and denotes, for example, vinyl, propenyl or butenyl. A furthermore denotes alkylenecycloalkyl. Alkylenecycloalkyl has 4-10 carbon atoms and preferably denotes, for example, methylenecyclopentyl, ethylenecyclopentyl, methylenecyclohexyl or ethylenecyclohexyl.

20 R1 and R2 preferably each denote, independently of one another, H, methyl, ethyl, propyl, butyl, isopropyl, tert-butyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, S-methyl, S-ethyl, F or Cl.

R3 preferably denotes H, methyl or ethyl.

R4 preferably denotes methyl, ethyl, propyl, butyl or NH₂.

25 R5 preferably denotes H, amino, methylamino, ethylamino, dimethylamino or diethylamino.

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In a related embodiment, PDE7 inhibitors useful in the methods of the invention include compounds of the above formula wherein R1 and R2 are not both H and wherein when one of R1 or R2 is H, the other cannot be CH₃, OCH₃ or Cl.

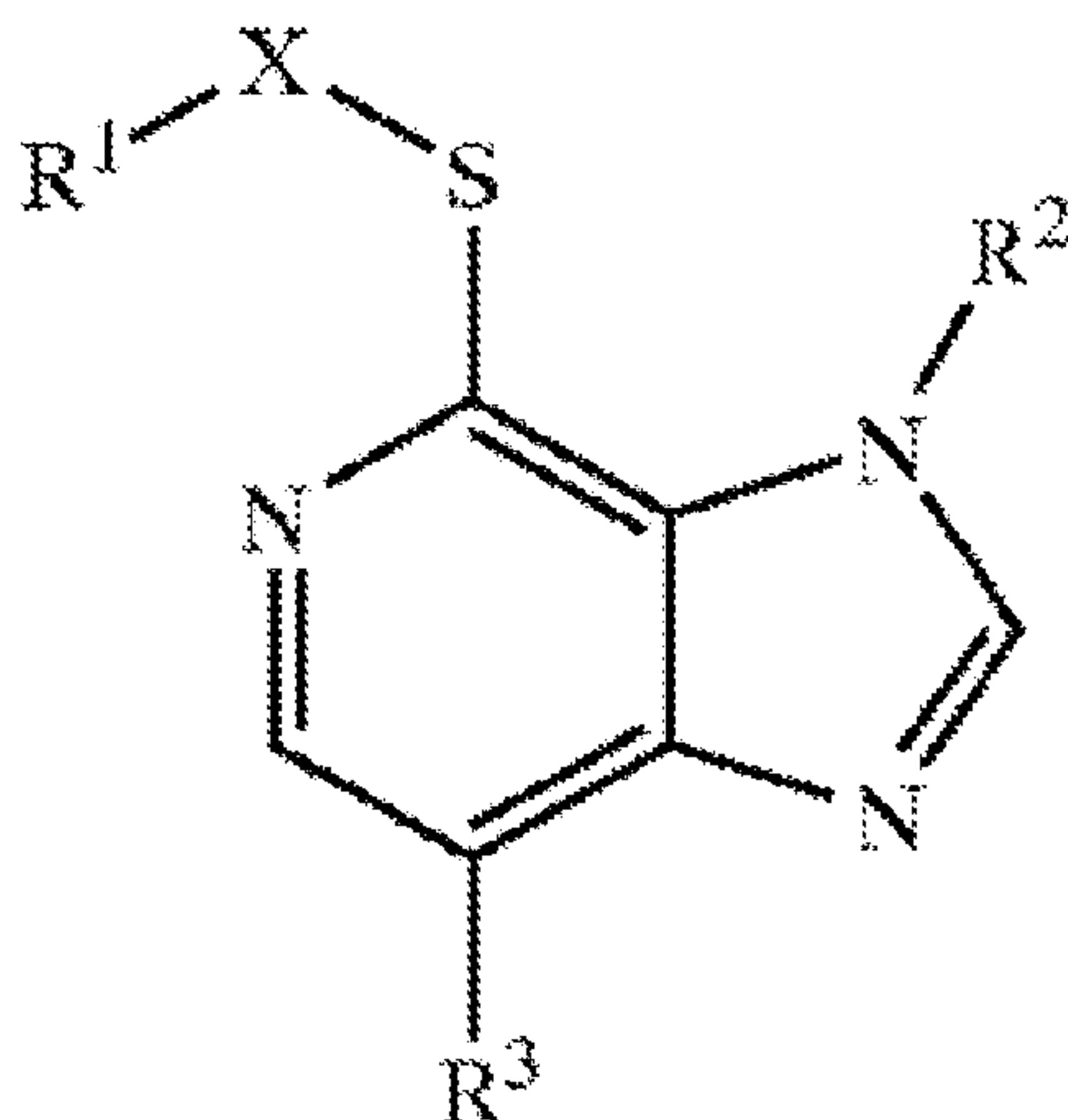
In another related embodiment, PDE7 inhibitors useful in the methods of the invention include compounds wherein

- R1, R2, R3 and R5 are H and R4 is methyl;
- R1 is 4-Cl, R2 is H, R3 is ethyl, R4 is amino and R5 is H;
- R1 and R2 are H, R3 is ethyl, R4 is methyl and R5 is amino;
- R1 and R2 are H, R3 is ethyl, R4 is amino and R5 is H;
- 10 R1 and R2 are H, R3 is ethyl, R4 is H and R5 is amino;
- R1 is 3-Cl, R2 is 4-O-methyl, R3 is ethyl, R4 is amino and R5 is H;
- R1 is 3-Cl, R2 is 4-O-methyl, R3 is ethyl, R4 is methyl and R5 is amino;
- R1 is 4-OCF₃, R2 is H, R3 is ethyl, R4 is amino and R5 is H;
- R1 is 3-Cl, R2 is 4-O-methyl, R3 is ethyl, R4 is amino and R5 is H;
- 15 R1 is 3-Cl, R2 is 4-O-methyl, R3 is ethyl, R4 is methyl and R5 is amino;
- R1 is 4-OCF₃, R2 is H, R3 is ethyl, and R4 is amino and R5 is H.

In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in U.S. Pat. No. 6,613,778 and WO 01/34601.

20 In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:

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(41)

The substituents for the above compounds are defined as follows:

R¹ denotes CONR⁴R⁵,

5 R² denotes H or A,

R⁴ and R⁵, independently of one another, each denote H or A¹,

R³ denotes Hal,

Hal denotes F, Cl, Br or I,

A denotes alkyl having 1-4 carbon atoms,

10 A¹ denotes alkyl having 1-10 carbon atoms,

X denotes alkylene having 1-4 carbon atoms, in which an ethylene group may also be replaced by a double or triple bond,

and their physiologically acceptable salts and/or solvates.

In regard to the above compounds, A denotes alkyl having 1-4 carbon atoms and
 15 has 1, 2, 3 or 4 carbon atoms and preferably denotes methyl, ethyl or propyl, furthermore preferably isopropyl, butyl, isobutyl, sec-butyl or tert-butyl. 1-7 H atoms in the radicals may also be replaced by F and/or Cl. A therefore also denotes, for example, trifluoromethyl or pentafluoroethyl.

A¹ denotes alkyl having 1-10 carbon atoms and has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10
 20 carbon atoms and preferably denotes methyl, ethyl or propyl, furthermore preferably

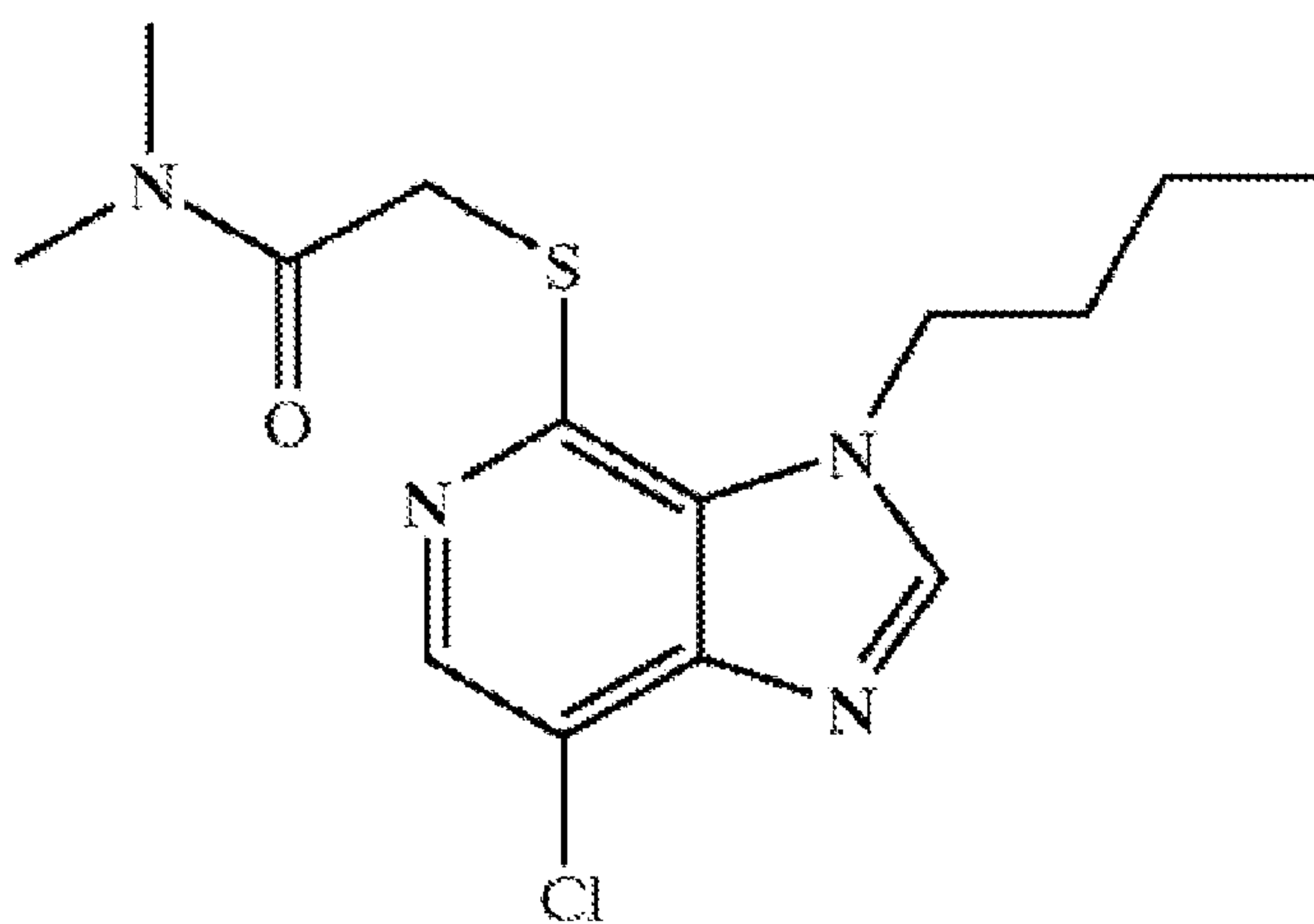
-191-

isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, but also n-pentyl, neopentyl, isopentyl or hexyl. 1-7 H atoms in the radicals may also be replaced by F and/or Cl. A1 therefore also denotes, for example, trifluoromethyl or pentafluoroethyl.

X denotes alkylene having 1-4 carbon atoms, preferably methylene, ethylene, propylene or butylene, in which one ethylene group may also be replaced by a double or triple bond. X therefore also denotes, for example, —CH₂—CH=CH—H₂— or —C≡—C—.

In a related embodiment, PDE7 inhibitors useful in the methods of the invention include the following compounds:

10 2-(3-Butyl-7-chloro-3H-imidazo[4,5-c]pyridin-4-ylsulfanyl)-N,N-dimethylacetamide



2-(3-butyl-7-chloro-3H-imidazo[4,5-c]pyridin-4-ylsulfanyl)acetamide,
 2-(3-butyl-7-chloro-3H-imidazo[4,5-c]pyridin-4-ylsulfanyl)propionamide,
 15 2-(3-butyl-7-chloro-3H-imidazo[4,5-c]pyridin-4-ylsulfanyl)butyramide,
 2-(3-butyl-7-chloro-3H-imidazo[4,5-c]pyridin-4-ylsulfanyl)-N-hexylacetamide,
 2-(3-butyl-7-chloro-3H-imidazo[4,5-c]pyridin-4-ylsulfanyl)-N-octylacetamide,
 4-(3-butyl-7-chloro-3H-imidazo[4,5-c]pyridin-4-ylsulfanyl)-but-2-enoic acid
 dimethylamide.

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In another related embodiment, PDE7 inhibitors useful in the methods of the invention include the following compounds, wherein

R3 is Cl;

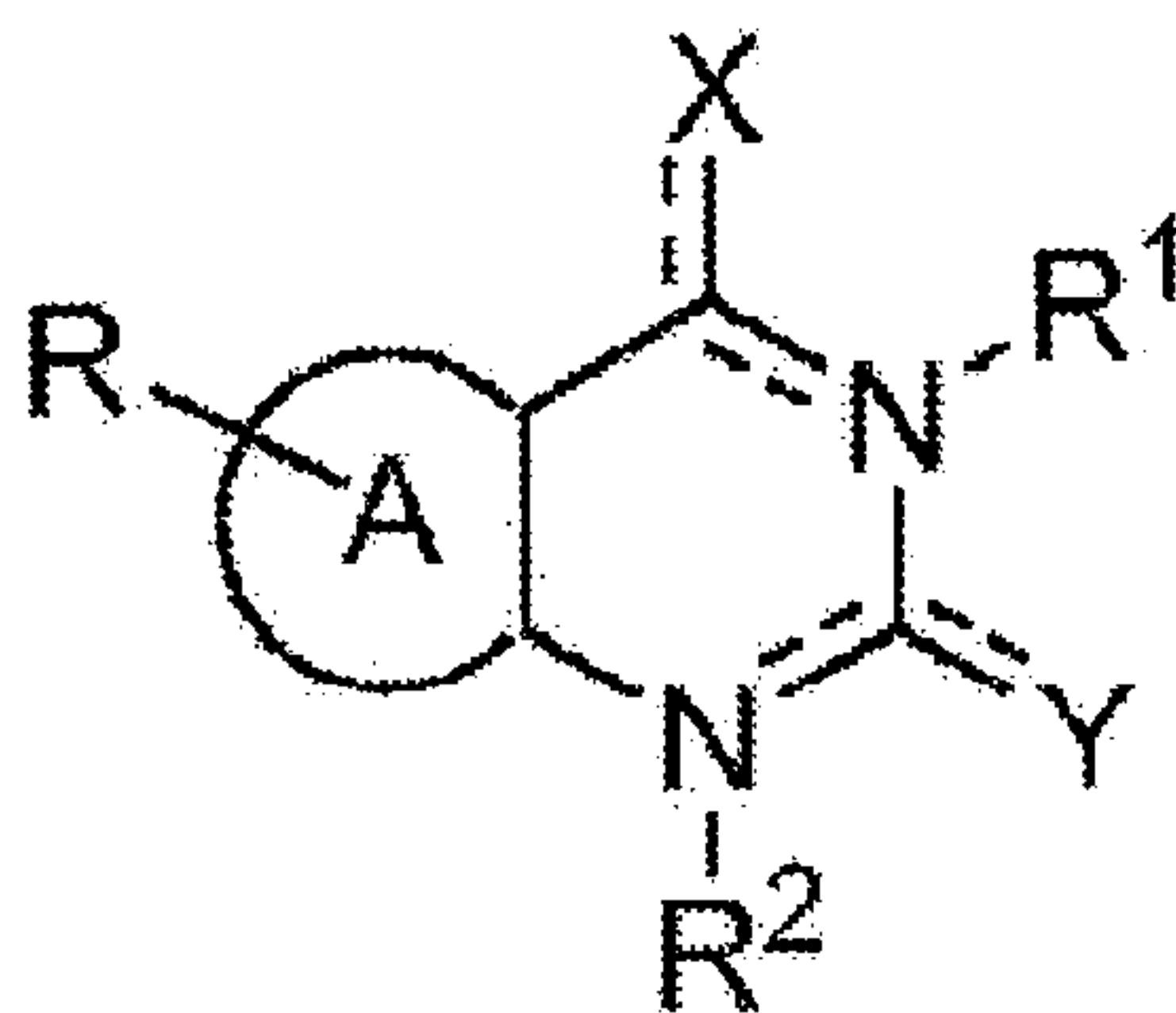
R3 is Cl, and X is alkylene having 1-4 carbon atoms;

5 R3 is Cl, X is alkylene having 1, 2, 3 or 4 carbon atoms, and A1 is alkyl having 1, 2, 3 or 4 carbon atoms.

The preparation of these compounds is described in U.S. Pat. No. 6,613,778 and WO 01/34601.

10 In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in WO 2008/113881 and ES P 200700762.

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



15 (42)

The substituents for the above compounds are defined as follows:

A is fused carbocycle or heterocycle of 5, 6 or 7 members and may be saturated or unsaturated; the dashed lines represent, independently, a single or double bond; X and
 20 Y are chosen independently from the group consisting of alkyl, hydrogen, =O, =S, -N(alkyl), -N(aryl), aryl, O-alkyl, O-aryl, alkyl-S and -S-aryl; and R1 and R2 are chosen

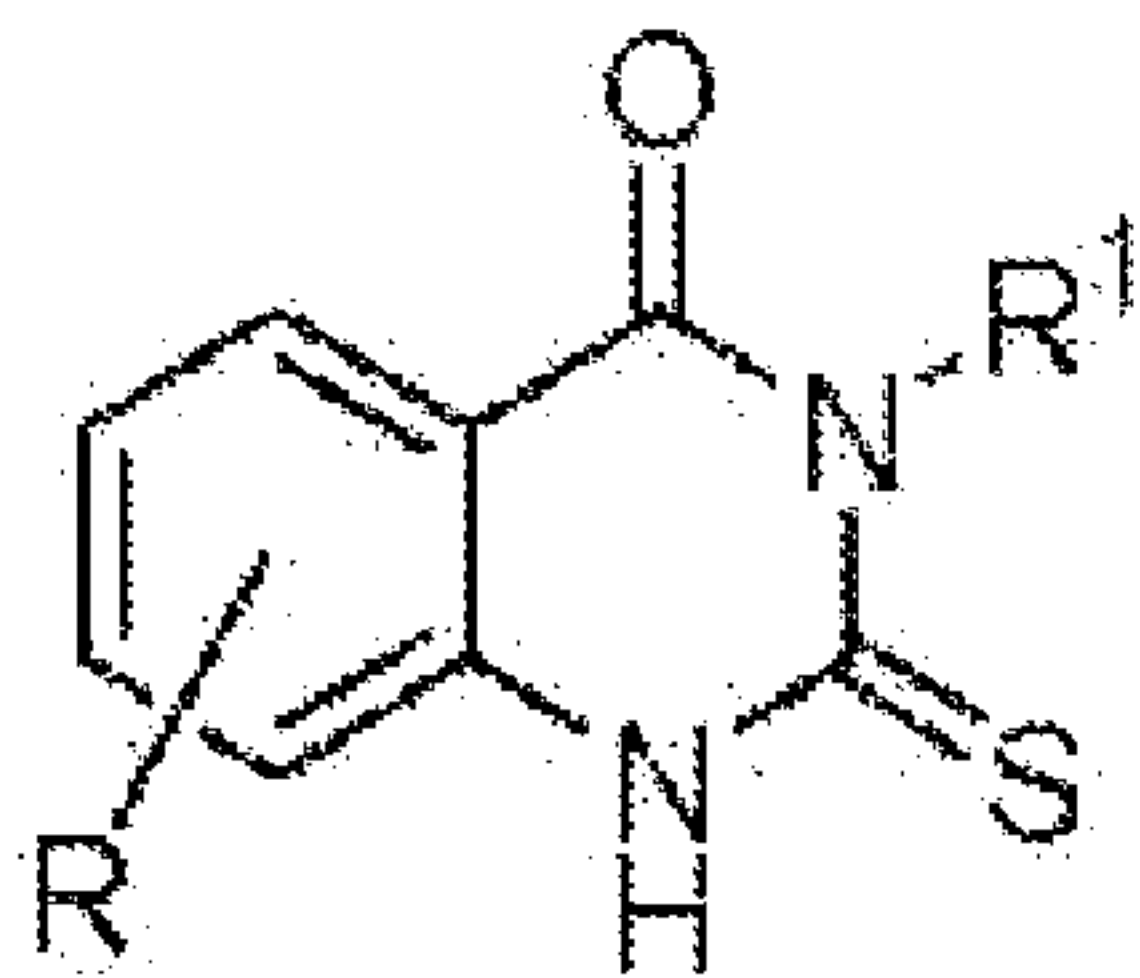
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independently from the group consisting of hydrogen, halogen, alkyl, haloalkyl, aryl, cycloalkyl, (Z)_n-aryl, heteroaryl, -OR₃; -C(O)OR₃, -(Z)_n-C(O)OR₃ and -S(O), or a pharmaceutically acceptable salt, derivative, prodrug, solvate or stereoisomer of the same.

Exception: when A is unsubstituted benzene, X=O, Y=S, when A is unsubstituted benzene, X=O, Y=O, when A is unsubstituted benzene, X=O, Y=S-Me, when A is unsubstituted thiophene, X=O, Y=S, and when A is unsubstituted benzothiophene, X=O, Y=S.

In related embodiments, the above compounds constitute a useful pharmaceutical composition that includes a therapeutically effective amount of the above compounds, or mixtures of the same, a salt, derivative, prodrug, solvate or pharmaceutically acceptable stereoisomer of the same along with a carrier, adjuvant or pharmaceutically acceptable vehicle, for IV administration to patient.

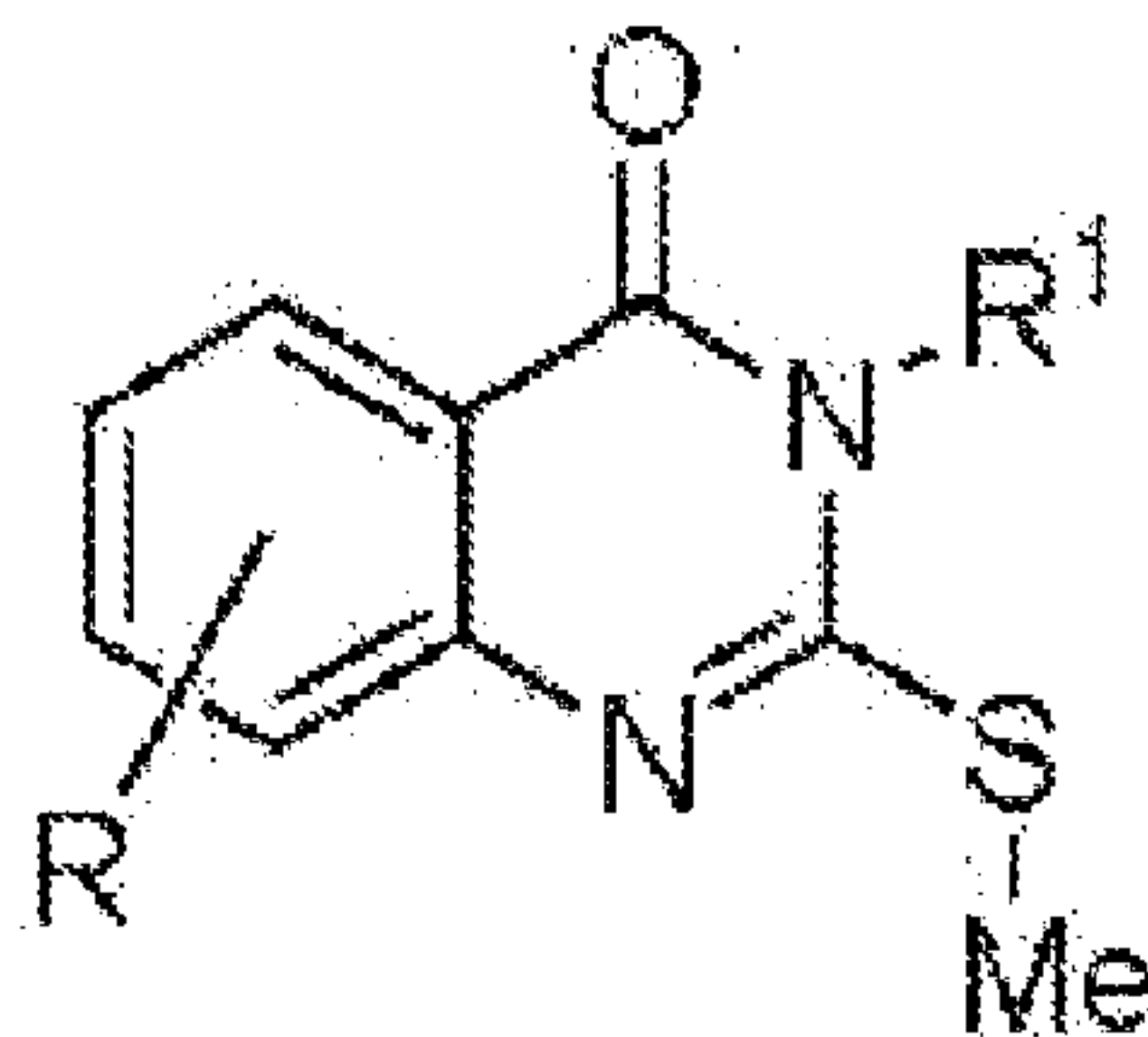
In other related embodiments, the PDE7 inhibitors useful in the methods of the present invention include the following compound: 4-oxo-2-dioxo-1,2,3,4-tetrahydroquinazoline, and derivatives thereof selected from the following group:



6-Bromo-2,3,4-tetrahydroquinazoline, 6-Bromo-(2,6-difluorophenyl)-4-oxo-2-dioxo-1,2,3,4-tetrahydroquinazoline, 6-Bromo-(2,3,4-trifluorophenyl)-4-oxo-2-dioxo-1,2,3,4-tetrahydroquinazoline, 6-Bromo-(2-bromophenyl)-4-oxo-2-dioxo-1,2,3,4-tetrahydroquinazoline, 3-(2,6-Difluorophenyl)-8-methyl-4-oxo-2-dioxo-1,2,3,4-tetrahydroquinazoline, 3-(2,3,4-Trifluorophenyl)-8-methyl-4-oxo-2-dioxo-1,2,3,4-tetrahydroquinazoline, and 3-(2-Bromophenyl)-8-methyl-4-oxo-2-dioxo-1,2,3,4-tetrahydroquinazoline.

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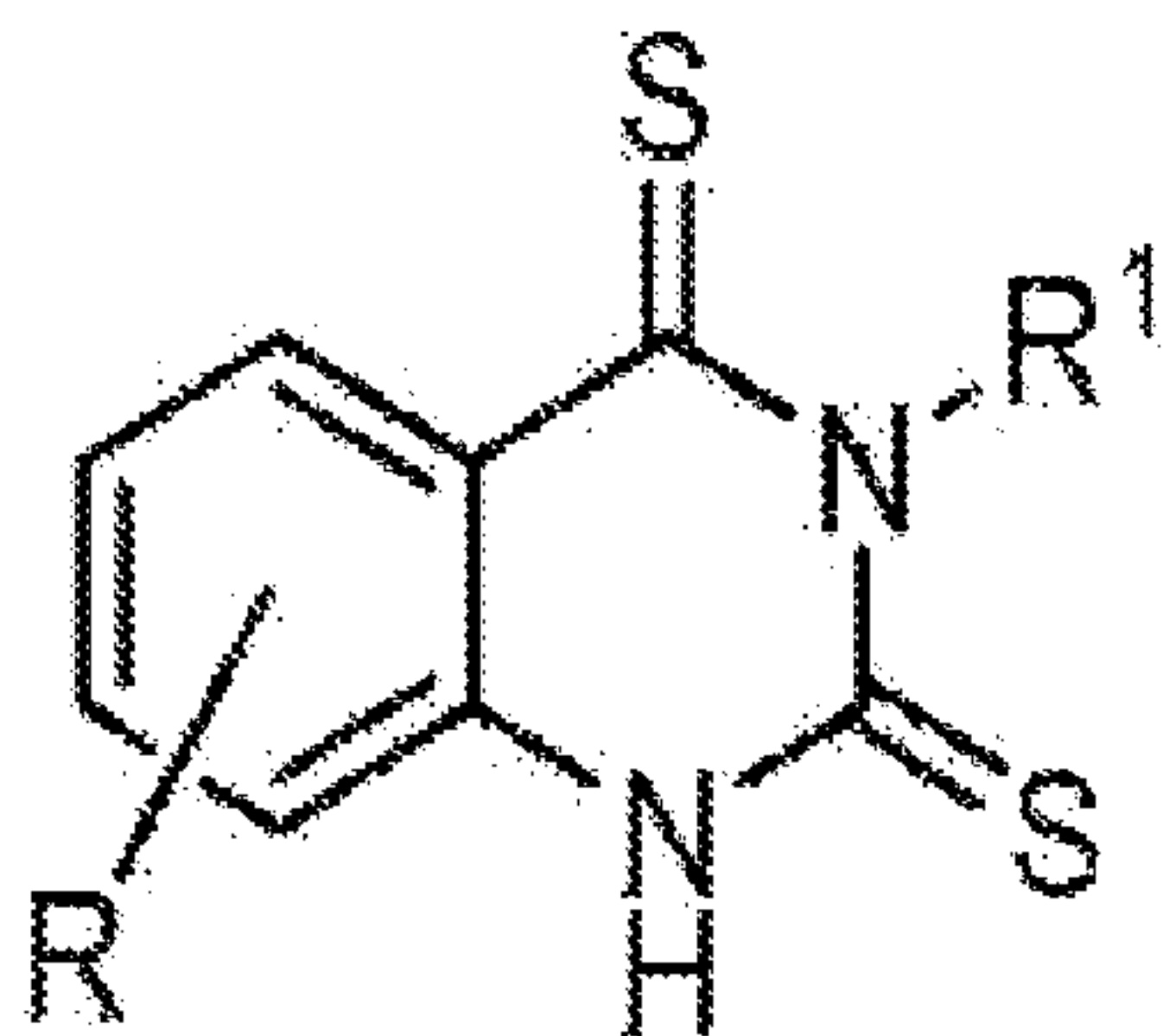
In a further related embodiment, the PDE7 inhibitors useful in the methods of the present invention include the following compound: 2-methylthio-4-oxo-3,4-dihydroquinazoline and derivatives thereof selected from the following group:



5

6-Bromo-(2,6-difluorophenyl)-2-methylthio-4-oxo-3,4-dihydroquinazoline, 6-Bromo- (2,3,4-trifluorophenyl)-2-methylthio-4-oxo-3,4-dihydroquinazoline, 6-Bromo-(2-bromophenyl)-2-methylthio-4-oxo-3,4-dihydroquinazoline, 3-Phenyl-8-methyl-2-methylthio-4-oxo-3,4-dihydroquinazoline, 3-(2,6-Difluorophenyl)-8-methyl-2-methylthio-4-oxo-3,4-dihydroquinazoline, 3-(2,3,4-Trifluorophenyl)-8-methyl-2-methylthio-4-oxo-3,4-dihydroquinazoline, and 3-(2-Bromophenyl)-8-methyl-2-methylthio-4-oxo-3,4-dihydroquinazoline.

In another related embodiment, the PDE7 inhibitors useful in the methods of the present invention include the following compound: 2,4-dithioxo-1,2,3,4-tetrahydroquinazoline, and derivatives thereof selected from the following group:

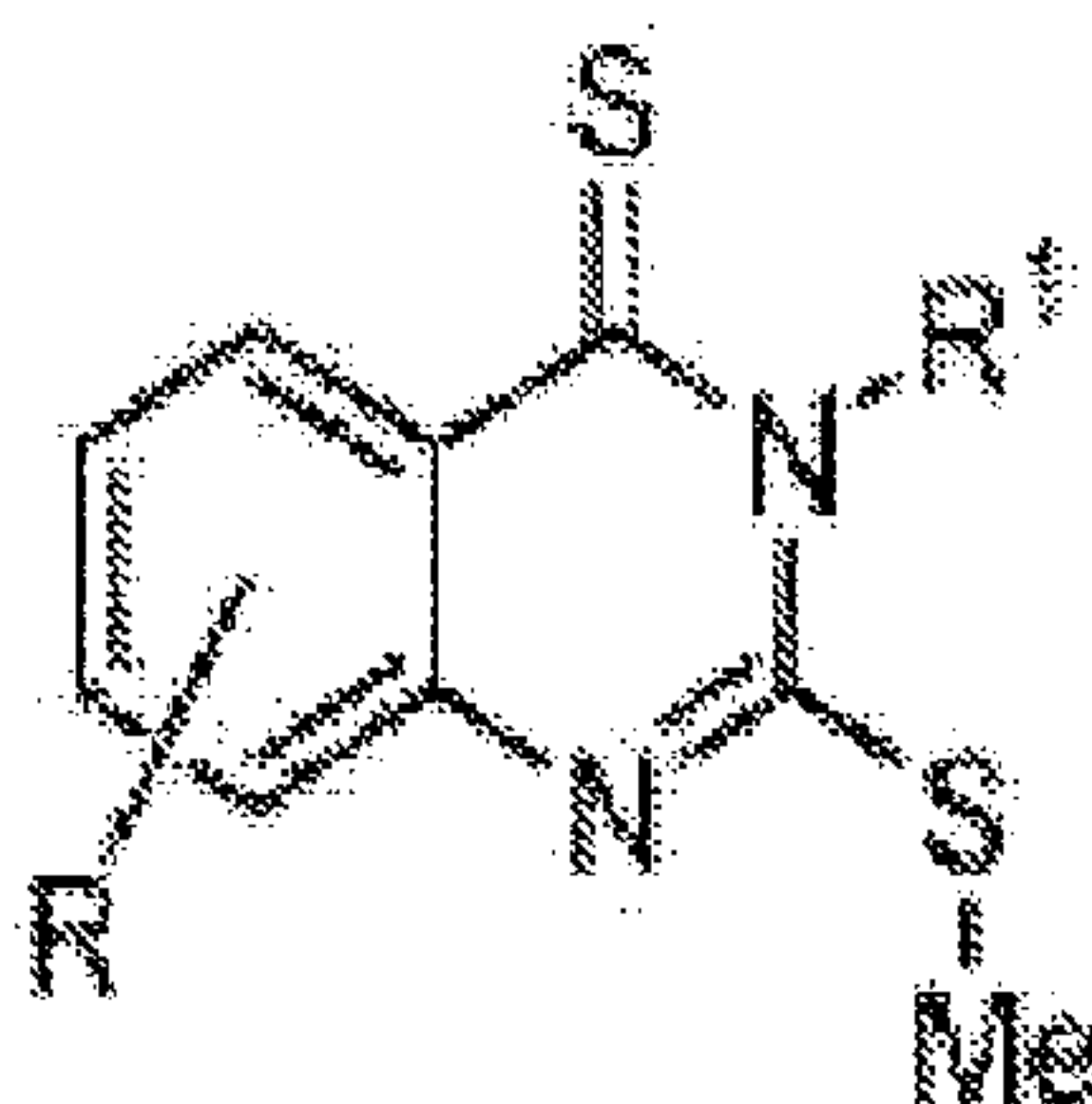


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3-Phenyl-2,4-dithioxo-1,2,3,4-tetrahydroquinazoline, 3-(2,6-Difluorophenyl)-2,4-dithioxo-1,2,3,4-tetrahydroquinazoline, and 3-(2,3,4-Trifluorophenyl)-2,4-dithioxo-1,2,3,4-tetrahydroquinazoline.

In another related embodiment, PDE7 inhibitors useful in the methods of the present invention include the following compound: (2-methylthio-4-thioxo-3,4-dihydroquinazoline) and derivatives thereof selected from the following group:



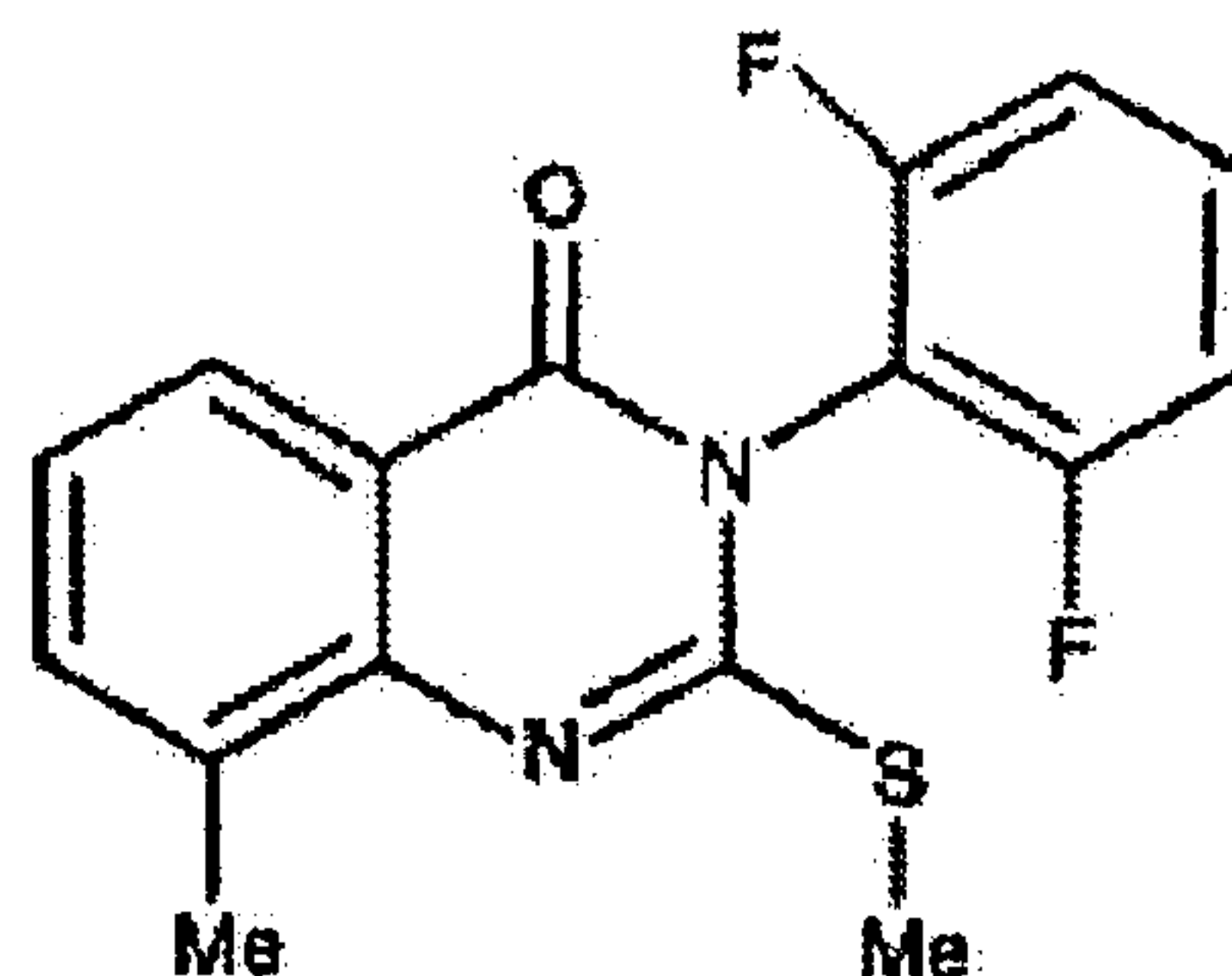
3-Phenyl-2-methylthio-4-thioxo-3,4-dihydroquinazoline, 3-(2,6-Difluorophenyl)-2-methylthio-4-thioxo-3,4-dihydroquinazoline, 3-(2,3,4-Trifluorophenyl)-2-methylthio-4-thioxo-3,4-dihydroquinazoline, and 3-(2-Bromophenyl)-2-methylthio-4-thioxo-3,4-dihydroquinazoline.

The preparation of the above compounds is described in WO 2008/113881.

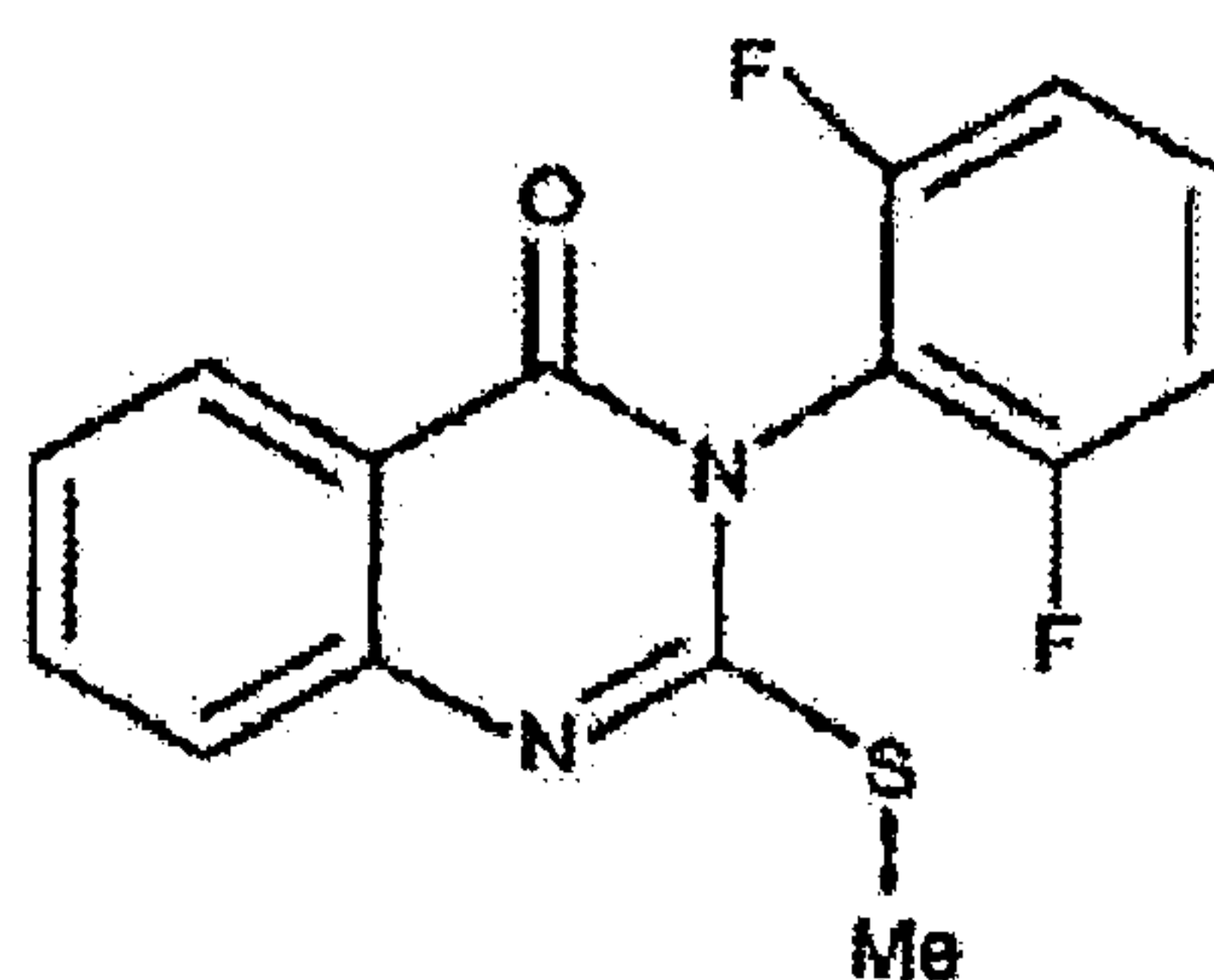
In a related embodiment, PDE7 inhibitors useful in the methods of the invention are described in ES P 200700762.

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formulas:

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(43A)



(43B)

5 In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in U.S. Pat. No. 7,214,676, and U.S. 2007/0049558.

 In one embodiment, PDE7 inhibitors useful in the methods of the invention include the following compounds:

10	Spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,	6'-
	Methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,	
	Spiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,	7'-
	Methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,	6'-
	Phenylspiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,	8'-
15	Methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,	8'-
	Chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,	7'-

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- chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 5'-
- chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-
- methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 6'-
- chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-
- 5 bromospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-
- fluorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 6'-
- methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 5',8'-
- dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 6',7'-
- dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 5',6'-
- 10 dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 6'-
- phenylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-
- iodospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-
- Bromospiro[cyclobutane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-
- Bromospiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Bromo-4-
- 15 methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-
- Bromospiro[bicyclo[3,2,1]octane-2-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 6',8'-
- dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-chloro-6'-
- iodospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-chloro-6'-
- methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-chloro-6'-
- 20 phenylspiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-chloro-6'-
- phenylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-chloro-6'-
- methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-chloro-6'-(3-
- pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-chloro-6'-(4-
- pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 6'-(4-
- 25 carboxyphenyl)-8'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 6'-(3-carboxyphenyl)-8'-chlorospiro(cyclohexane-1-4'-(3',4'-dihydro)-quinazolin]-

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2'(1H)-one, 8'-chloro-6'-(1H-indol-5yl)spiro[cyclohexane-1-4'-(3',4'-
 dihydro)quinazolin]-2'(1H)-one, 8'-chloro-6'-(2-pyridyl)spiro[cyclohexane-1-4'-(3',4'-
 dihydro)quinazolin]-2'(1H)-one, 8'-chloro-6'-(3-dimethylamino-prop-1-
 ynyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)-quinazolin]-2'(1H)-one, 8'-chloro-6'-(3-
 5 methylamino-prop-1-ynyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1H)-one,
 8'-chloro-6'-[4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-
 dihydro)quinazolin]-2'(1H)-one, 8'-chloro-6'-[4-(3-N-dimethylamino-
 propylcarboxamide)phenyl]-spiro-[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1H)-
 one, 8'-chloro-6'-[4-(2-N-dimethylamino-ethylcarboxamide)phenyl]-spiro-[cyclohexane-
 10 1-4'-(3',4'-dihydro)quinazolin]-2'(1H)-one, 8'-chloro-6'-[3-(3-N-dimethylamino-
 propylcarboxamide)phenyl]-spiro-[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1H)-
 one, 8'-chloro-6'-[3-(4-methyl-piperazine-1-carbonyl)-phenyl]spiro-[cyclohexane-1-4'-
 (3',4'-dihydro)quinazolin]-2'(1H)-one, 8'-chloro-6'-[3-(2-N-dimethylamino-
 ethylcarboxamide)phenyl]spiro-[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1H)-one,
 15 8'-Chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1H)-thione, 8'-Chloro-2'-
 cyanoiminospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline, 8'-chloro-6'-[4-(4-
 pyrimidin-2-yl-piperazine-1-carbonyl)phenyl]spiro[-cyclohexane-1-4'-(3',4'-
 dihydro)quinazolin]-2'(1H)-one, 8'-chloro-6'-[4-(4-(2-morpholin-4-yl-ethyl)-piperazine-
 1-carbonyl)-phenyl]spiro[-cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1H)-one, 8'-
 20 chloro-6'-[4-(4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[-
 cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1H)-one, 8'-chloro-6'-[4-(4-(2-hydroxy-
 ethoxy)-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[-cyclohexane-1-4'-(3',4'-
 dihydro)quinazolin]-2'(1H)-one, Spiro[cyclohexane-1-9'-(8',9'-dihydro)-pyrazolo[4',3'-
 f]quinazolin]-7'(6H)-one, 8'-Chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-
 25 dihydro)quinazolin]-2'(1H)-one, 5',8'-difluorospiro[cyclohexane-1-4'-(3',4'-
 dihydro)quinazolin]-2'(1H)-one, 8'-Chloro-5'-methylspiro[cyclohexane-1-4'-(3',4'-

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dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-6'-(morpholin-4-yl)methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-5'-hydroxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-5'-hydroxy-6'-iodo-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-6'-iodo-5'-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-6'-cyano-5'-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-5'-[2-(4-morpholino)ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-5'-[2-dimethylaminoethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-5'-(2-aminoethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-5'-[2-(methylamino)ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-5'-[2-(2-aminoethoxy)ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-5'-[3-dimethylaminopropoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-5'-ethoxycarbonylmethoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 5'-carboxymethoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 5'-carboxypropoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-chloro-5'-(3-sulphopropoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-5'-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-5'-(2-hydroxy-ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-5'-(5-ethoxycarbonyl-furan-2-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-5'-(5-carboxy-furan-2-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-5'-cyanomethoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-5'-(1H-tetrazol-5-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-5'-(5-hydroxy-[1,2,4]oxadiazol-3-

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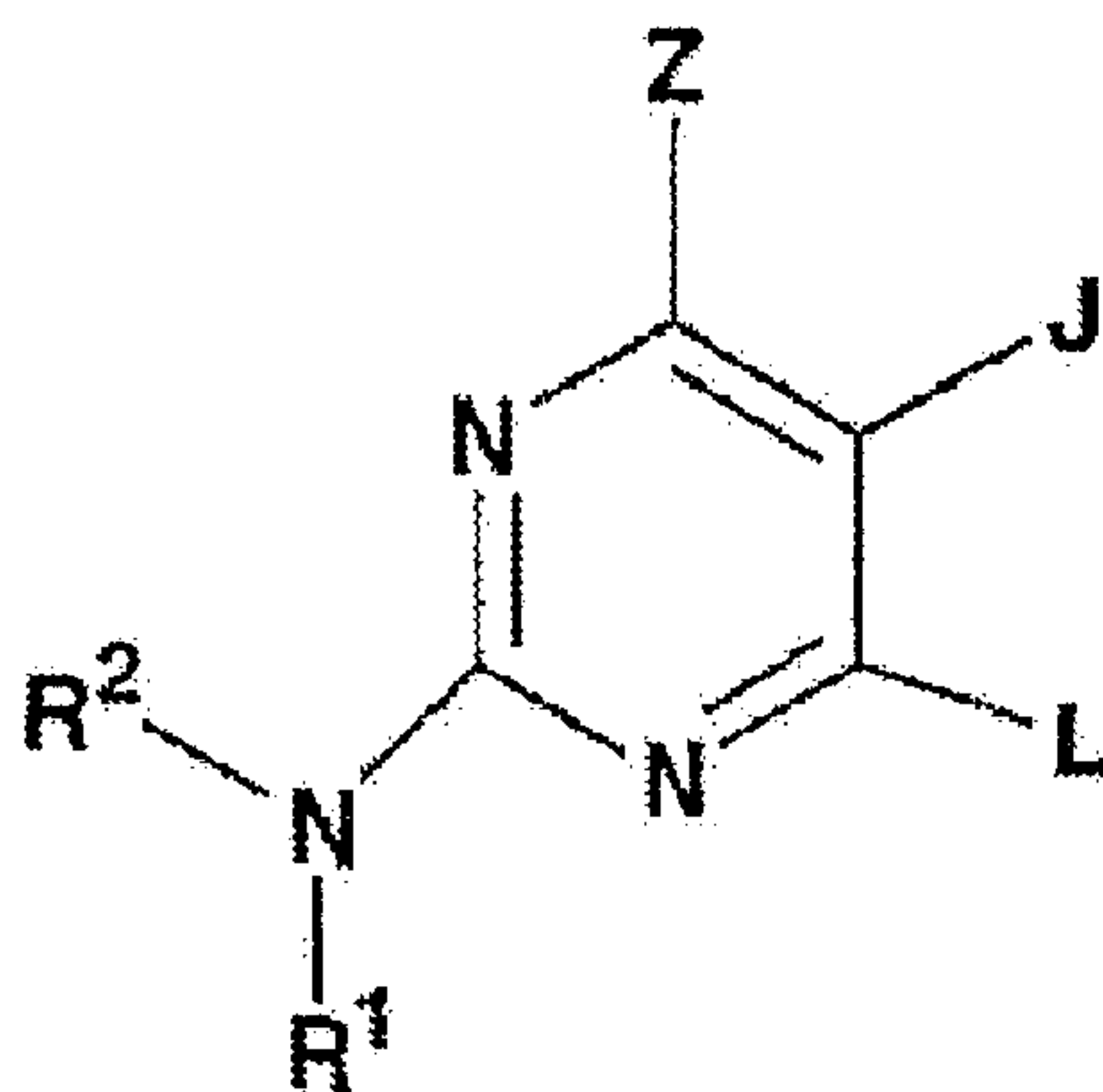
ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-6'-iodo-5'-[2-dimethylamino-ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 6'-(4-carboxyphenyl)-8'-chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 6'-(3-carboxyphenyl)-8'-chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-chloro-6'-[2-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-chloro-6'-[2-methyl-4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-chloro-6'-[4-(piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-chloro-6'-[4-carbamoyl-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-chloro-6'-[4-((1-methyl-piperidin-4-yl)-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-chloro-5'-methoxy-6-[4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Trifluoromethylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-6'-cyanomethylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-5'-(3-dimethylamino-2-hydroxy-propoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-5'-(3-methylamino-2-hydroxy-propoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-5'-[2-(ethoxycarbonylmethyl-amino)-ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-5'-[2-(carboxymethyl-amino)-ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one hydrochloride, 8'-Chloro-5'-(2-methanesulfonylamino-2-oxo-ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one, 8'-Chloro-5'-(2-[(5-methyl-isoxazol-3-ylmethyl)-amino]ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one.

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Preparation of these compounds is described in U.S. Pat. No. 7,087,614, U.S. 2007/0049558 and WO 2002/074754.

In another embodiment, PDE7 inhibitors and dual PDE4/7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in US 7,087,614, US 2003/0162802 and WO 2002/102313 .

In one embodiment, PDE7 inhibitors useful in the methods of the invention have the formula:



(54)

The PDE7 inhibitors useful in the methods of the invention include enantiomers, diastereomers, tautomers, and pharmaceutically acceptable salts, prodrugs, and solvates of the compounds of the above formula.

The substituents for the above compounds are defined as follows:

R₁ is H or alkyl;

R₂ is (a) heteroaryl, or heterocyclo, either of which may be optionally substituted with one to three groups T₁, T₂, T₃; (b) aryl substituted with one to three groups T₁, T₂, T₃ provided that at least one of T₁, T₂, T₃ is other than H; or (c) aryl fused to a heteroaryl or heterocyclo ring wherein the combined ring system may be optionally substituted with one to three groups T₁, T₂, T₃;

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Z is (a) -OR₄, -C(O)R₄, -C(O)OR₄, -SR₄, -NR₃R₄, -C(O)NR₃R₄, -NR₃SO₂R_{4c}, halogen, nitro, haloalkyl; or (b) alkyl, aryl, heteroaryl, heterocyclo, or cycloalkyl any of which may be optionally substituted with one to three groups T1a, T2a T3a;

J is (a) hydrogen, halo, -OR_{4a}, or (b) alkyl, alkenyl, or alkynyl any of which may
5 be optionally substituted with one to three groups T1b, T2b or T3b;

L is (a) hydrogen, -OR_{4b}, -C(O)R_{4b}, -C(O)OR_{4b}, -SR_{4b}, -NR₅R₆, -C(O)NR₅R₆, -NR₅SO₂R_{4d}, halogen, haloalkyl, nitro, or (b) alkyl, aryl, heteroaryl, heterocyclo, or cycloalkyl any of which may be optionally substituted with one to three groups T1c, T2c or T3c;

10 R₃ and R₄ are independently H, alkyl, alkenyl, aryl, (aryl)alkyl, heteroaryl, (heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclo or (heterocyclo)alkyl any of which may be optionally substituted with one to three groups T1a, T2a or T3a;

or R₃ and R₄ together with the nitrogen atom to which they are attached may combine to form a 4 to 8 membered heterocyclo ring optionally substituted with one to
15 three groups T1a, T2a or T3a;

R_{4a} is hydrogen, alkyl, alkenyl, aryl, heteroaryl, (aryl)alkyl, (heteroaryl)alkyl, heterocyclo, (heterocyclo)alkyl, cycloalkyl or (cycloalkyl)alkyl any of which may be optionally substituted with one to three groups T1b, T2b or T3b;

R_{4b} is hydrogen, alkyl, alkenyl, aryl, heteroaryl, (aryl)alkyl, (heteroaryl)alkyl,
20 heterocyclo, (heterocyclo)alkyl, cycloalkyl or (cycloalkyl)alkyl any of which may be optionally substituted with one to three groups T1c, T2c or T3c;

R_{4c} and R_{4d} are independently alkyl, alkenyl, aryl, (aryl)alkyl, heteroaryl, (heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclo or (heterocyclo)alkyl any of which may be optionally substituted with one to three groups T1a, T2a or T3a;

25 R₅ and R₆ are independently H, alkyl, alkenyl, aryl, (aryl)alkyl, heteroaryl, (heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclo or (heterocyclo)alkyl any of

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which may be optionally independently substituted where valance allows with one to three groups T1c, T2c or T3c;

or R5 and R6 together with the nitrogen atom to which they are attached may combine to form a 4 to 8-membered heterocyclo ring optionally substituted with one to
5 three groups T1c, T2c or T3c;

T1-1c T2-2c, and T3-3c are each independently (1) hydrogen or T6, where T6 is (i) alkyl, (hydroxy)alkyl, (alkoxy)alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, cycloalkenyl, (cycloalkenyl)alkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, hcteroaryl, or (hcteroaryl)alkyl; (ii) a group (i) which is itself substituted by one or more
10 of the same or different groups (i); or (iii) a group (i) or (ii) which is independently substituted by one or more (preferably 1 to 3) of the following groups (2) to (13) of the definition of T1-1c, T2-2c and T3-3c (2) -OH or -OT6, (3) -SH or -ST6, (4) -C(O)tH, -C(O)tT6, or -O-C(O)T6, where t is 1 or 2; (5) -SO3H, -S(O)T6, or S(O)tN(T9)T6, (6) halo, (7) cyano, (8) nitro, (9) -T4-NT7T8, (10) -T4-N(T9)-T5-NT7T8, (11) -T4-N(T10)-
15 T5-T6, (12) -T4-N(T10)-T5-H, (13) oxo,

T4 and T5 are each independently (1) a single bond, (2) -T11-S(O)t-T12-, (3) -T11-C(O)-T12-, (4) -T11-C(S)-T12-, (5) -T11-O-T12-, (6) -T11-S-T12-, (7) -T11-O-C(O)-T12-, (8) -T11-C(O)-O-T12-, (9) -T11-C(=NT9a)-T12-, or (10) -T11-C(O)-C(O)-T12,

20 T7, T8, T9, T9a and T10 (1) are each independently hydrogen or a group provided in the definition of T6, or (2) T7 and T8 may together be alkylene or alkenylene, completing a 3-to 8- membered saturated or unsaturated ring together with the atoms to which they are attached, which ring is unsubstituted or substituted with one or more groups listed in the description of T1-1c, T2-2c and T3-3c, or (3) T7 or T8, together with
25 T9, may be alkylene or alkenylene completing a 3-to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring

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is unsubstituted or substituted with one or more groups listed in the description of T1-1c, T2-2c and T3-3c, or (4) T7 and T8 or T9 and T10 together with the nitrogen atom to which they are attached may combine to form a group-N=CT13T14 where T13 and T14 are each independently H or a group provided in the definition of T6;

5 and T11 and T12 are each independently (1) a single bond, (2) alkylene, (3) alkenylene, or (4) alkynylene.

In a related embodiment, PDE7 inhibitors useful in the methods of the present invention include the above compounds, wherein:

Z is (a) halogen, alkoxy, haloalkyl, -NR3R4, -C(O)OR4, -C(O)NR3R4; (b) aryl or
10 heteroaryl either of which may be optionally substituted with one or more T1a, T2a, T3a (especially cyano, optionally substituted alkyl, (hydroxy)alkyl, -OH, -OT6, -ST6, -SOT6, -COtH, -COtT6, -T4NT7T8, or -T4N(T10)-T5-T6); (c) optionally substituted alkyl (especially substituted with one or more -OH, -COtH, -COtT6, -T4-NT7T8, -T4-N(T10)-T5-H, or -T4-N(T10)-T5-T6);

15 J is (a) H, or (b) alkyl or alkenyl either of which may be optionally substituted (especially with one or more -OH, -OT6, -COtH, or -COtT6);

L is (a) H; (b) halogen, alkoxy, haloalkyl, -NR5R6, -C(O)OR4b, -C(O)NR5R6; (c) aryl or heteroaryl either of which may be optionally substituted with one or more T1c, T2c, T3c (especially cyano, optionally substituted alkyl, (hydroxy)alkyl, -OH, -OT6, -
20 ST6, -SOT6, -COtH, -COtT6, -T4NT7T8, or -T4N(T10)-T5-T6); or (d) optionally substituted alkyl (especially substituted with one or more -OH, -COtH, -COtT6, -T4-NT7T8, -T4-N(T10)-T5-H, or; -T4-N(T10)-T5-T6);

R1 is H or alkyl;

R2 is (a) heteroaryl (more preferably thiazolyl or oxazolyl) optionally substituted
25 with one to three groups T1, T2, T3, preferably including H, alkyl, haloalkyl, halo, heteroaryl, cyano, C(O)tT6, OT6, -T4NT7T8; (b) aryl substituted with one to three

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groups T1, T2, T3 (preferably including heteroaryl (preferably, imidazolyl, oxazolyl, or thiazolyl any of which may be further optionally substituted), cyano, C(O)tT6, S(O)tN(T9)T6, halo alkyl, and haloalkyl); or (c) aryl fused to a heterocyclo ring (e.g., 2, 3-dihydro-1H-indole bound through the aryl ring, quinolyl bound through the aryl ring
 5 (especially quinol-6-yl), quinazolinyl bound through the aryl ring (especially quinazolin-7-yl), cinnolinyl bound through the aryl ring (especially cinnolin-6-yl), isoquinolinyl bound through the aryl ring (especially isoquinol-6-yl), and phthalazinyl bound through the aryl ring (especially phthalazin-6-yl)) wherein the combined ring system may be optionally substituted with one to three groups T1, T2, T3 (especially halo, OH, OT6,
 10 alkyl, -COtH, -COtT6, or -C(O)NT7T8);

R3 is H or optionally substituted alkyl (especially substituted with one or more -OH, or -OT6);

R4 is (a) hydrogen; (b) (aryl)alkyl where the aryl group is optionally independently substituted with one or more groups T1a, T2a, T3a (especially optionally
 15 substituted alkyl, halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT6, -ST6, -COtH, -COtT6, -SO3H, -SOtT6, -SOtN(T9)(T6), -T4NT7T8, -T4-N(T10)-T5-T6, heterocyclo, or heteroaryl); (c) (heteroaryl)alkyl where the heteroaryl group is optionally independently substituted with one or more groups T1a, T2a, T3a (especially optionally substituted
 20 alkyl, halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT6, -ST6, -COtH, -COtT6, -SO3H, -SOtT6, -SOtN(T9)(T6), -T4NT7T8, -T4-N(T10)-T5-T6, heterocyclo, or heteroaryl); (d) (heterocyclo)alkyl where the heterocyclo group is optionally independently substituted with one or more groups T1a, T2a, T3a (especially optionally substituted alkyl, halo, cyano, nitro, oxo, (hydroxy)alkyl, -OH, -OT6, -ST6, -COtH, -COtT6, -SO3H, -SOtT6, -
 25 SOtN(T9)(T6), -T4NT7T8, -T4-N(T10)-T5-T6, heterocyclo, or heteroaryl); (e) alkyl optionally independently substituted with one or more groups T1a, T2a, T3a (especially -OH, -OT6, -COtH, -COtT6, -T4NTT8 or -T4-N(T10)-T5-T6); (f) heterocyclo optionally

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independently substituted with one or more groups T1a, T2a, T3a (especially optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl, optionally substituted heterocyclo, cyano, -OH, -OT6, -COtH, -COtT6, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T4-N(T10)-T5-T6, or -T4-NT2T8);

5 or R3 and R4 together with the nitrogen atom to which they are attached combine to form a 4 to 8-membered heterocyclo ring (especially pyrrolidinyl, piperadinyl, piperazinyl, morpholinyl, diazapanyl or 1,4-dioxa-8-azaspiro[4.5]decan-8-yl) optionally substituted with one to three groups T1a, T2a, T3a (especially optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted
10 aralkyl, optionally substituted heterocyclo, cyano, -OH, -OT6, -COtH, -COtT6, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T4-N(T10)-T5-T6, or -T4-NT7T8);

R5 is hydrogen or alkyl;

R6 is (a) hydrogen; (b) (aryl)alkyl where the aryl group is optionally independently substituted with one or more groups T1c, T2c, T3c (especially optionally
15 substituted alkyl, halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT6, -ST6, -COtH, -COtT6, -SO3H, -SOtT6, -SOtN(T9)(T6), -T4-N(T10)-T5-T6, heterocyclo, or heteroaryl); (c) (heteroaryl)alkyl where the heteroaryl group is optionally independently substituted with one or more groups T1c, T2c, T3c (especially optionally substituted alkyl, halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT6, -ST6, -COtH, -COtT6, -SO3H, -SOtT6,
20 -SOtN(T9)(T6), -T4-N(T10)-T5-T6, heterocyclo, or heteroaryl); (d) (heterocyclo)alkyl where the heterocyclo group is optionally independently substituted with one or more groups T1c, T2c, T3c (especially optionally substituted alkyl, halo, cyano, nitro, oxo, (hydroxy)alkyl, -OH, -OT6, -ST6, -COtH, -COtT6, -SO3H, -SOtT6, -SOtN(T9)(T6), -T4-N(T10)-T5-T6, heterocyclo, or heteroaryl); (e) alkyl optionally independently substituted
25 with one or more groups T1c, T2c, T3c (especially -OH, -OT6, -COtH, -COtT6, -T4NT7T8 or -T4-N(T10)-T5-T6); (f) heterocyclo optionally independently substituted

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with one or more groups T1c, T2c, T3c (especially optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl, optionally substituted heterocyclo, cyano, -OH, -OT6, -COtH, -COtT6, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T4-N(T10)-T5-T6, or -T4-NT7T8);

5 or R5 and R6 together with the nitrogen atom to which they are attached combine to form a 4 to 8-membered heterocyclo ring (especially pyrrolidinyl, piperadinyl, piperazinyl, morpholinyl, diazapanyl or 1,4-dioxo-8-azaspiro[4.5]decan-8-yl) optionally substituted with one to three groups T1c, T2c, T3c (especially optionally substituted alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted
10 aralkyl, optionally substituted heterocyclo, cyano, -OH, -OT6, -COtH, -COtT6, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T4-N(T10)-T5-T6, or -T4-NT7T8).

In another related embodiment, PDE7 inhibitors useful in the methods of the present invention include the above compounds, wherein:

Z is (a) halogen, alkoxy, haloalkyl, -NR₃R₄, -C(O)OR₄, -C(O)NR₃R₄; (b) aryl or
15 heteroaryl either of which may be optionally substituted with one or more T1a, T2a, T3a selected from cyano, optionally substituted alkyl, (hydroxy)alkyl, -OH, -OT6, -ST6, -SOT6, -COtH, -COtT6, -T4NT7T8, or -T4N(T10)-T5-T6, where T4 is a bond or -C(O)-; T5 is -C(O)-, or -C(O)O-; T6 is alkyl or haloalkyl; T7 and T8 are independently H; alkyl optionally substituted with cycloalkyl, heteroaryl, hydroxy or -NT7T8 cycloalkyl; or aryl
20 optionally substituted with halogen; or T7 and T8 together with the nitrogen atom to which they are attached combine to form a heterocyclo ring optionally substituted with (hydroxy)alkyl, COtH or COtT6, T10 is hydrogen; (c) alkyl optionally substituted with one or more -OH, -COtH, -COtT6, -T4-NT7T8, -T4-N(T10)-T5-H, or -T4-N(T10)-T5-T6 where T4 is -C(O)-; T5 is -alkylene-O-; T6 is alkyl; T7 and T8 are independently H,
25 alkyl, cycloalkyl, aryl, (aryl)alkyl (optionally substituted as described in the definition of

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R4), or heterocyclo (optionally substituted as described in the definition of R3 and R4 combining to form a heterocyclo ring); and T10 is H;

J is (a) H, or (b) alkyl or alkenyl either of which may be optionally substituted with one or more -OH, -OT6, -COtH, or -COtT6, where T6 is alkyl;

5 L is (a) H; (b) halogen, alkoxy, haloalkyl, -NR5R6, -C(O)OR4b, -C(O)NR5R6; (c) aryl or heteroaryl either of which may be optionally substituted with one or more T1c, T2c, T3c selected from cyano, optionally substituted alkyl (especially substituted with COtH or COtT6), (hydroxy)alkyl, -OH, -OT6, -ST6, -SOtT6, -COtH, -COtT6, -T4NT7T8, or -T4N(T10)-T5-T6, where T4 is a bond or -C(O)-; T5 is -C(O)-, or -C(O)O-; 10 T6 is alkyl or haloalkyl; T7 and T8 are independently H; alkyl optionally substituted with cycloalkyl, heteroaryl, hydroxy or -NT7T8; cycloalkyl; or aryl optionally substituted with halogen; or T7 and T8 together with the nitrogen atom to which they are attached combine to form a heterocyclo ring optionally substituted with (hydroxy)alkyl, COtH or COtT6; T10 is hydrogen; (d) alkyl optionally substituted with one or more -OH, -COtH, -COtT6, -T4-NT7T8, -T4-N(T10)-T5-H, or -T4-N(T10)-T5-T6 where T4 is -C(O)-; T5 is 15 -alkylene-O-; T6 is alkyl; T7 and T8 are independently H, alkyl, cycloalkyl, aryl, (aryl)alkyl (optionally substituted as described in the definition of R4), or heterocyclo (optionally substituted as described in the definition of R3 and R4 combining to form a heterocyclo ring); and T10 is H;

20 R1 is H or alkyl;

R2 is (a) heteroaryl (more preferably thiazolyl or oxazolyl) optionally substituted with one to three groups T1, T2, T3, preferably including H, alkyl, haloalkyl, halo, heteroaryl, cyano, C(O)tT6, OT6, -T4NT7T8; (b) aryl substituted with one to three groups T1, T2, T3 (preferably including heteroaryl (preferably, imidazolyl, oxazolyl, or 25 thiazolyl any of which may be further optionally substituted), cyano, C(O)tT6, S(O)tN(T9)T6, halo alkyl, and haloalkyl); or (c) aryl fused to a heterocyclo ring (e.g., 2,

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3-dihydro-1H-indole bound through the aryl ring) wherein the combined ring system may be optionally substituted with one to three groups T1, T2, T3 (especially halo, -OH, -OT6, alkyl, -COtH, -COtT6, or -C(O)NT7T8);

R3 is H or optionally substituted alkyl (especially substituted with one or more -
5 OH, or -OT6);

R4 is (a) hydrogen; (b) (aryl)alkyl where the aryl group is optionally independently substituted with one or more groups T1a, T2a, T3a selected from optionally substituted alkyl, halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT6, -ST6, -COtH, -COtT6, -SO3H, -SOtT6, -SOtN(T9)(T6), -T4NT7T8, -T4N(T10)-T5-T6, heterocyclo, or
10 heteroaryl) where T4 is a bond, -SO2-, or -C(O)-; T5 is -SO2-, or -alkylene-O-; T6 is alkyl, or cycloalkyl; T7 and T8 are independently H or alkyl; and T9 and T10 are hydrogen; (c) (heteroaryl)alkyl where the heteroaryl group is optionally independently substituted with one or more groups T1a, T2a, T3a selected from optionally substituted alkyl, halo, cyano, nitro, oxo, (hydroxy)alkyl, -OH, -OT6, -ST6, -COtH, -COtT6, -SO3H,
15 -SOtT6, -SOtN(T9)(T6), -T4NT7T8, -T4-N(T10)-T5-T6, heterocyclo, or heteroaryl) where T4 is a bond, -SO2-, or -C(O)-; T5 is -SO2-, or -alkylene-O-; T6 is alkyl, or cycloalkyl; T7 and T8 are independently H or alkyl; and T9 and T10 are hydrogen; (d) (heterocyclo)alkyl where the heterocyclo group is optionally independently substituted with one or more groups T1a, T2a, T3a selected from optionally substituted alkyl, halo,
20 cyano, nitro, (hydroxy)alkyl, -OH, -OT6, -ST6, -COtH, -COtT6, -SO3H, -SOtT6, -T4NT7T8, -T4-N(T10)-T5-T6, heterocyclo, or heteroaryl) where T4 is a bond, -SO2-, or -C(O)-; T5 is -SO2-, or -alkylene-O-; T6 is alkyl, or cycloalkyl; T7 and T8 are independently H or alkyl; and T9 and T10 are hydrogen; (e) alkyl optionally independently substituted with one or more groups T1a, T2a, T3a selected from -OH, -
25 OT6, -COtH, -COtT6, -T4NT7T8 or -T4-N(T10)-T5-T6) where T4 is a bond; T5 is -C(O)-; T6 is alkyl; T7 and T8 are independently H or alkyl; and T10 is hydrogen;

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heterocyclo optionally independently substituted with one or more groups T1a, T2a, T3a selected from optionally substituted alkyl (especially substituted with -T4NT7T8), optionally substituted aryl (especially substituted with halogen or haloalkyl), cyano, -OH, -OT6, -COtH, -COtT6, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T4-N(T10)-T5-T6, or -T4-NT7T8) where T4 is a bond or -C(O)-; T5 is -C(O)-, -SO₂-, or -alkylene-C(O)O-; T6 is
 5 alkyl, alkoxy, or heteroaryl; T7 and T8 are independently H, alkyl, or cycloalkyl; or T7 and T8 together with the nitrogen atom to which they are attached combine to form an optionally substituted heterocyclo ring;

or R3 and R4 together with the nitrogen atom to which they are attached combine
 10 to form a heterocyclo ring selected from pyrrolidinyl, piperadinyl, piperazinyl, morpholinyl, diazapanyl or 1,4-dioxo-8-azaspiro[4.5]decan-8-yl), any of which are optionally independently substituted with one to three groups T1a, T2a, T3a selected from optionally substituted alkyl (especially substituted with -T4NT7T8), optionally substituted aryl (especially substituted with halogen or haloalkyl), cyano, -OH, -OT6, -
 15 COtH, -COtT6, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T4-N(T10)-T5-T6, or -T4-NT7T8) where T4 is a bond or -C(O)-; T5 is -C(O)-, -SO₂-, or -alkylene-C(O)O-; T6 is alkyl, alkoxy, or heteroaryl; T7 and T8 are independently H, alkyl, or cycloalkyl; or T7 and T8 together with the nitrogen atom to which they are attached combine to form an optionally substituted heterocyclo ring;

20 R5 is hydrogen or alkyl;

R6 is (a) hydrogen; (b) (aryl)alkyl where the aryl group is optionally independently substituted with one or more groups T1c, T2c, T3c selected from optionally substituted alkyl, halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT6, -ST6, -COtH, -COtT6, -SO₃H, -SOtT6, -SOtN(T9)(T6), -TNT7T8, -T4-N(T10)-T5-T6, heterocyclo, or
 25 heteroaryl) where T4 is a bond, -SO₂-, or -C(O)-; T5 is -SO₂-, or -alkylene-O-; T6 is alkyl, or cycloalkyl; T7 and T8 are independently H or alkyl; and T9 and T10 are

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hydrogen; (c) (heteroaryl)alkyl where the heteroaryl group is optionally independently substituted with one or more groups T1c, T2c, T3c selected from optionally substituted alkyl, halo, cyano, nitro, oxo, (hydroxy)alkyl, -OH, -OT6, -ST6, -COtH, -COtT6, -SO3H, -SOtT6, -SOtN(T9)(T6), -T4NT7T8, -T4-N(T10)-T5-T6, heterocyclo, or heteroaryl) where T4 is a bond, -SO2-, or -C(O)-; T5 is -SO2-, or -alkylene-O-; T6 is alkyl, or cycloalkyl; T7 and T8 are independently H or alkyl; and T9 and T10 are hydrogen; (d) (heterocyclo)alkyl where the heterocyclo group is optionally independently substituted with one or more groups T1c, T2c, T3c selected from optionally substituted alkyl, halo, cyano, nitro, (hydroxy)alkyl, -OH, -OT6, -ST6, -COtH, -COtT6, -SO3H, -SOtT6, -T4NT7T8, -T4-N(T10)-T5-T6, heterocyclo, or heteroaryl) where T4 is a bond, -SO2-, or -C(O)-; T5 is -SO2-, or -alkylene-O-; T6 is alkyl, or cycloalkyl; T7 and T8 are independently H or alkyl; and T9 and T10 are hydrogen; (e) alkyl optionally independently substituted with one or more groups T1c, T2c, T3c selected from -OH, -OT6, -OCtH, -COtT6, -T4NT7T8 or -T4-N(T10)-T5-T6) where T4 is a bond; T5 is -C(O)-; T6 is alkyl; T7 and T8 are independently H or alkyl; and T10 is hydrogen; heterocyclo optionally independently substituted with one or more groups T1c, T2c, T3c selected from optionally substituted alkyl (especially substituted with -T4NT7T8), optionally substituted aryl (especially substituted with halogen or haloalkyl), cyano, -OH, -OT6, -COtH, -COtT6, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T4-N(T10)-T5-T6, or -T4-NT7T8, where T4 is a bond or -C(O)-; T5 is -C(O)-, -SO2-, or -alkylene-C(O)O-; T6 is alkyl, alkoxy, or heteroaryl; T7 and T8 are independently H, alkyl, or cycloalkyl; or T7 and T8 together with the nitrogen atom to which they are attached combine to form an optionally substituted heterocyclo ring;

or R5 and R6 together with the nitrogen atom to which they are attached combine to form a heterocyclo ring selected from pyrrolidinyl, piperadinyl, piperazinyl, morpholinyl, diazapanyl or 1,4-dioxo-8-azaspiro[4.5]decan-8-yl), any of which are

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optionally independently substituted with one to three groups T1a, T2a, T3a selected from optionally substituted alkyl (especially substituted with -T4NT7T8), optionally substituted aryl (especially substituted with halogen or haloalkyl), cyano, -OH, -OT6, -COtH, -COtT6, oxo, hydroxy(alkyl), (alkoxy)alkyl, -T4-N(T10)-T5-T6, or -T4-NT7T8
 5 where T4 is a bond or -C (O)-; 5 is -C (O)-, -SO2-, or -alkylene-C(O)O-; T6 is alkyl, alkoxy, or heteroaryl; T7 and T8 are independently H, alkyl, or cycloalkyl; or T7 and T8 together with the nitrogen atom to which they are attached combine to form a an optionally substituted heterocyclo ring.

In a futher related embodiment, PDE7 inhibitors useful in the methods of the
 10 present invention include the following compounds:

2-[[4-[[[4-(Aminosulfonyl)phenyl]methyl]amino]-6-(4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[[[3,4-Dimethoxyphenyl]methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester trifluoroacetate salt; 2-[[4-[[[4-(Aminosulfonyl)phenyl]methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 4-Methyl-2-[[4-[[[4-(methylsulfonyl)phenyl]methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[[[4-Methoxyphenyl]methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[[[3-Methoxyphenyl]methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[[[2-Methoxyphenyl]methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 4-Methyl-2-[[4-(1-piperazinyl)-6-[[[3,4,5-trimethoxyphenyl]methyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[[[2-Ethoxyphenyl]methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[[[2,5-Dimethoxyphenyl]methyl]amino]-6-(1-

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piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-
 [[(3,5-Dimethoxyphenyl)methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-
 methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[[2,6-
 Dimethylphenyl)methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-
 5 thiazolecarboxylic acid ethyl ester; 2-[[4-[[4-(Methoxycarbonyl)phenyl]methyl]amino]-
 6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-
 [[4-[[3-Bromophenyl)methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-
 5-thiazolecarboxylic acid ethyl ester; 2-[[4-[(1,3-Benzodioxol-5-yl)methyl]amino]-6-(1-
 piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 4-
 10 Methyl-2-[[4-[methyl(3-pyridinylmethyl)amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-
 5-thiazolecarboxylic acid ethyl ester; 4-Methyl-2-[[4-(1-piperazinyl)-6-[[4-(1,2,3-
 thiadiazol-4-yl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid
 ethyl ester; 2-[[4-[[3-(Cyclopentyloxy)-4-methoxyphenyl]methyl]amino]-6-(1-
 piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 4-
 15 Methyl-2-[[4-[(phenylmethyl)amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-5-
 thiazolecarboxylic acid ethyl ester; 4-Methyl-2-[[4-(4-methyl-1-piperazinyl)-6-[[3,4,5-
 trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl
 ester; 2-[[4-(4-Hydroxy-1-piperidinyl)-6-[[4-(methylsulfonyl)phenyl]methyl]amino]-2-
 pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 4-Methyl-2-[[4-[[2-
 20 (1-methylethoxy)ethyl]amino]-6-[[4-(methylsulfonyl)phenyl]methyl]amino]-2-
 pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[3-(Aminocarbonyl)-1-
 piperidinyl]-6-[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-
 methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-
 6-[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-
 25 thiazolecarboxylic acid ethyl ester; 4-Methyl-2-[[4-[[4-
 (methylsulfonyl)phenyl]methyl]amino]-6-[[3-(4-morpholinyl)propyl]amino]-2-

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- pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[(2-Methoxy-1-methylethyl)amino]-6-[[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 4-Methyl-2-[[4-[[[4-(methylsulfonyl)phenyl]methyl]amino]-6-[[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[4-(2-Hydroxyethyl)-1-piperazinyl]-6-[[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[2-(Aminocarbonyl)-1-pyrrolidinyl]-6-[[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 4-Methyl-2-[[4-[methyl(3-pyridinylmethyl)amino]-6-[[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[4-(Hydroxymethyl)-1-piperidinyl]-6-[[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[[2-(Diethylamino)ethyl]methylamino]-6-[[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 4-Methyl-2-[[4-[[[4-(methylsulfonyl)phenyl]methyl]amino]-6-[[3-(2-oxo-1-pyrrolidinyl)propyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[3-(Hydroxymethyl)-1-piperidinyl]-6-[[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 4-Methyl-2-[[4-(4-methyl-1-piperazinyl)-6-[[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[[2-[(Acetylamino)ethyl]amino]-6-[[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-(4-Ethyl-1-piperazinyl)-6-[[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-(4-Acetyl-1-piperazinyl)-6-[[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-

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- thiazolecarboxylic acid ethyl ester; 2-[[4-[[2-(Dimethylamino)ethyl]amino]-[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-
- thiazolecarboxylic acid ethyl ester; 2-[[4-[3-(Aminocarbonyl)-1-piperazinyl]-6-[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-
- 5 thiazolecarboxylic acid ethyl ester; 2-[[4-(3-Hydroxy-1-pyrrolidinyl)-6-[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-
- thiazolecarboxylic acid ethyl ester; 2-[[4-[(4-Hydroxybutyl)amino]-6-[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-
- thiazolecarboxylic acid ethyl ester; 2-[[4-[(2,3-Dihydroxypropyl)amino]-6-[[4-
- 10 (methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-
- thiazolecarboxylic acid ethyl ester; 2-[[4-[(4-Amino-1-piperidinyl)-6-[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-
- thiazolecarboxylic acid ethyl ester; 2-[[4-[4-Hydroxy-3-(hydroxymethyl)-1-piperidinyl]-6-[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-
- 15 thiazolecarboxylic acid ethyl ester; 2-[[4-(4-Dimethylamino-1-piperidinyl)-6-[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-
- thiazolecarboxylic acid ethyl ester; 2-[[4-[[4-(Aminosulfonyl)phenyl]methyl]amino]-6-(methylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-
- [4,6-Bis-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic
- 20 acid ethyl ester; 2-[4-(4-Hydroxy-piperidin-1-yl)-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[4-(3-Hydroxymethyl-piperidin-1-yl)-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-
- carboxylic acid ethyl ester; 4-Methyl-2-[4-(4-methyl-piperazin-1-yl)-6-morpholin-4-yl-pyrimidin-2-ylamino]-thiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Amino-piperidin-1-
- 25 yl)-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[4,6-Bis-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-

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thiazole-5-carboxylic acid ethyl ester; 2-[4-(4-oxo-piperidin-1-yl)-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[4-(4-methyl-4-hydroxy-piperidin-1-yl)-6-(4-methyl-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[4-(4-hydroxy-piperidin-1-yl)-6-(4-dimethylmethyl-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[4-(4-hydroxymethyl-piperidin-1-yl)-6-(4-dimethylmethyl-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[4-(3-hydroxymethyl-piperidin-1-yl)-6-(4-dimethylmethyl-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[4-(4-hydroxymethyl-piperidin-1-yl)-6-(4-hydroxy-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 4-Methyl-2-[4-(4-hydroxy-piperazin-1-yl)-6-morpholin-4-yl-pyrimidin-2-ylamino]-thiazole-5-carboxylic acid ethyl ester; 2-[[4-[[[4-(Methylsulfonyl)phenyl]methyl]amino]-6-chloro-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[[[4-(Aminosulfonyl)phenyl]methyl]amino]-6-chloro-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[[4-(Dimethylamino)-1-piperidinyl]-6-[(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[[1-piperizinyl]-6-methyl-6-[(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[[4-(4-Amino-1-piperidinyl)-6-[[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[[4-hydroxy-1-piperidinyl]-6-methyl-6-[(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[[4-(Hydroxymethyl)-1-piperidinyl]-6-methyl-6-[(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[4-(4-Hydroxypiperidin-1-yl)-6-(3-oxo-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[[4-[[3-(Aminocarbonyl)-1-

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piperiziny]-6-methyl-6-[[3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-
 4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[1-morpholinyl]-6-methyl-6-
 [[3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-
 thiazolecarboxylic acid, ethyl ester; 2-[[4-[3-Oxo-1-piperiziny]-6-[(1,1-dioxido-3-oxo-
 5 1,2-benzisothiazol-2-(3H)-yl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-
 thiazolecarboxylic acid, ethyl ester; 2-[[4-[3-Oxo-1-piperiziny]-6-[(4-
 (ethylsulfonylamino)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-
 thiazolecarboxylic acid, ethyl ester; 2-[[4-[3-Oxo-1-piperiziny]-6-[(4-
 (hydroxysulfonyl)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-
 10 thiazolecarboxylic acid, ethyl ester; 2-[4-(4-Hydroxypiperidin-1-yl)-6-(4-methyl-3-oxo-
 piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-
 [4-(4-(Dimethylamino)-piperizin-1-yl)-6-(4-((1-pyrrolidinyl)carbonylmethyl)piperazin-1-
 yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[[4-[3-
 (Aminocarbonyl)-1-piperazinyl]-6-[[3,4,5-trimethoxyphenyl)methyl]amino]-2-
 15 pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-(4-Amino-1-
 piperidinyl)-6-[[3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-
 5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-(Hydroxymethyl)-1-piperidinyl]-6-[4-
 [tetrazol-5-yl]-4-hydroxypiperidin-1-yl]2-pyrimidinyl]amino]-4-methyl-5-
 thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-methyl-1-piperazinyl]-6-[N-methyl-N-
 20 [[3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-
 thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-Hydroxy-1-piperidinyl]-6-[(4-
 (hydroxysulfonyl)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-
 thiazolecarboxylic acid, ethyl ester; 2-[[4-[[4-(Cyanophenyl)methyl]amino]-6-(1-
 piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester;
 25 trifluoroacetate (1:1); 2-[[4-[[4-(Aminosulfonyl)phenyl)methyl]amino]-6-(4-
 morpholinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-

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[[4-[4-Hydroxy-1-piperidiny]l]-6-[(1-oxa-3,8-diazaspiro[4.5]decan-2,4,dion-8-yl)-2-
 pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[4-(2-
 (Dimethylamino)ethyl)-piperazin-1-yl]-6-(4-methylpiperazin-1-yl)-pyrimidin-2-
 ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[[4-(4-Hydroxy-1-
 5 piperidiny]l)-6-[methyl(3-pyridinylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-
 thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-Hydroxy-3-hydroxymethylpiperidin-1-yl]-6-
 [(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-
 thiazolecarboxylic acid, ethyl ester; 2-[[4-(3,4-Dihydro-6,7-dihydroxy-2(1H)-
 isoquinolinyl)-6-(4-methyl-1-piprazinyl)-2-pyrimidinyl]amino]-4-methyl-5-
 10 thiazolecarboxylic acid, ethyl ester, trifluoroacetate 1:1); 2-[[4-[4-
 [(Methoxyacetyl)amino]-1-piperidiny]l]-6-[[4-(methylsulfonyl)phenyl]methyl]amino]-2-
 pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[(3,4-
 Dimethoxyphenyl)methyl]amino]-6-[4-(dimethylamino)-1-piperidiny]l]-2-
 pyrimidinyl]amino]-4-methyl-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-
 15 (Hydroxyethyl)piperidin-1-yl]-6-[4-(dimethylamino)-1-piperidiny]l]-2-
 pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-
 (Dimethylamino)-1-piperidiny]l]-6-[methyl(3-pyridinylmethyl)amino]-2-
 pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-
 (Hydroxy)piperidin-1-yl]-6-[4-(methoxycarbonyl)-1-piperidiny]l]-2-pyrimidinyl]amino]-
 20 4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-(Hydroxy)piperidin-1-yl]-6-[4-
 (methyl)-4-(hydroxy)-1-piperidiny]l]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic
 acid, ethyl ester; 2-[4-(3-oxopiprazin-1-yl)-6-(4-methylpiperazin-1-yl)-pyrimidin-2-
 ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[[4-[[4-
 Cyanophenyl)methyl]amino]-6-[4-dimethylamino)-1-piperidiny]l]-2-pyrimidinyl]amino]-
 25 4-methyl-5-thiazolecarboxylic acid, ethyl ester; 4-Methyl-2-[[4-[[4-(3-
 nitrophenyl)methyl]amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-5-thiazolecarboxylic

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acid, ethyl ester, trifluoroacetate (1:1); 2-[[4-(4-Hydroxy-1-piperidiny)]-6-[[3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[4-(Dimethylamino)-piperazin-1-yl]-6-(4-methyl piperazin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[4-

5 (Dimethylamino)-piperidin-1-yl]-6-(3-(aminocarbonyl)-1-piperazinyl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[4-(2-Hydroxyethyl)-piperazin-1-yl]-6-(4-methyl-1-piperazinyl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[[4-[4-(Aminocarbonyl)-1-piperidiny)]-6-[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-

10 thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-(Hydroxymethyl)-1-piperidiny)]-6-[N-methyl-N-(3-pyridinylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-Methylpiperazin-1-yl]-6-[[3,4-dimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[piperazin-1-yl]-6-[[4-carboxyphenyl)methyl]amino]-2-

15 pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[3-Hydroxymethylpiperidin-1-yl]-6-[N-[(3,4,5-trimethoxyphenyl)methyl]]-N-(methyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[4-(4-Hydroxypiperidin-1-yl)-6-(4-carboxypiperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[[4-[Piperazin-1-yl]-6-[[3,4-

20 dimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-(4-Formyl-1-piperazinyl)-6-[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[4-(4-Hydroxypiperidin-1-yl)-6-(4-(hydroxy)-4-(4-chlorophenyl)piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid

25 ethyl ester; 4-Methyl-2-[[4-[4-dimethylamino-1-piperidiny)]-6-[[tetrahydro-2-furanyl)methyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester; 2-[[4-

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[Piperazin-1-yl]-6-[[N-methyl-N-(5-tetrazolylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-Morpholinyl]-6-[4-[tetrazol-5-yl]-4-hydroxypiperidin-1-yl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-Hydroxy-1-piperidinyl]-6-[(1,1-dioxido-3-oxo-1,2-benzisothiazol-2-(3H)-yl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester;

5 2-[4-(4-Hydroxypiperidin-1-yl)-6-(4-(1-methyl-1-hydroxyethyl)piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[[4-[3-(Aminocarbonyl)-1-piperidinyl]-6-[[N-methyl-N-(3-pyridinylmethyl)]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-Hydroxymethyl-1-piperidinyl]-6-[(4-(ethylsulfonylamino)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-Hydroxy-1-piperidinyl]-6-[4-[tetrazol-5-yl]-4-hydroxypiperidin-1-yl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-tertButyloxycarbonylamino-1-piperidinyl]-6-[[N-[(3,4,5-trimethoxyphenyl)methyl]]-N-(methyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[(4-Cyanophenyl)methyl]amino]-6-(4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester, trifluoroacetate (1:1); 2-[[4-[4-[(2-Ethoxy-2-oxoethyl)amino]carbonyl]-1-piperazinyl]-6-[methyl(3-pyridinylmethy)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester, trifluoroacetate (1:1);

10 2-[4-(4-Hydroxypiperidin-1-yl)-6-(3-hydroxypiperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Hydroxypiperidin-1-yl)-6-(4-hydroxy-4-phenyl-1-piperidinyl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 4-Methyl-2-[[4-[4-morpholinyl]-6-[(tetrahydro-2-furanyl)methyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[(Tetrahydro-2-furanyl)methyl]amino]-6-[[N-[(3,4,5-trimethoxyphenyl)methyl]]-N-(methyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-

15 2-[[4-[(4-Cyanophenyl)methyl]amino]-6-(4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester, trifluoroacetate (1:1); 2-[[4-[4-[(2-Ethoxy-2-oxoethyl)amino]carbonyl]-1-piperazinyl]-6-[methyl(3-pyridinylmethy)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester, trifluoroacetate (1:1);

20 2-[4-(4-Hydroxypiperidin-1-yl)-6-(3-hydroxypiperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Hydroxypiperidin-1-yl)-6-(4-hydroxy-4-phenyl-1-piperidinyl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 4-Methyl-2-[[4-[4-morpholinyl]-6-[(tetrahydro-2-furanyl)methyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[(Tetrahydro-2-furanyl)methyl]amino]-6-[[N-[(3,4,5-trimethoxyphenyl)methyl]]-N-(methyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-

25 2-[[4-[(4-Cyanophenyl)methyl]amino]-6-(4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester, trifluoroacetate (1:1); 2-[[4-[4-[(2-Ethoxy-2-oxoethyl)amino]carbonyl]-1-piperazinyl]-6-[methyl(3-pyridinylmethy)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester, trifluoroacetate (1:1);

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[[4-[4-Morpholinyl]-6-[[4-(hydroxysulfonyl)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[Bis-4,6-(4-Cyano-1-piperidinyl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[[4-[4-(Cyclopentylaminocarbonyl)-1-piperazinyl]-6-[N-methyl-N-(3-
 5 pyridinylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[4-(2-Methoxyethyl)-piperazin-1-yl]-6-(4-methyl-1-piperziny)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Hydroxypiperidin-1-yl)-6-(3-carboxypiperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[[4-[4-Methylpiperazin-1-yl]-6-[3-(acetyl-amino)-1-pyrrolidinyl]-2-
 10 pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[3-(Aminocarbonyl)-1-piperazinyl]-6-[N-methyl-N-(3-pyridinylmethyl)]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[2-Methyl-3-oxol-piperiziny]-6-[4-methyl-1-piperazinyl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[3-(Aminocarbonyl)-1-piperazinyl]-6-(4-
 15 methyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[3-(Aminocarbonyl)-1-piperidinyl]-6-(4-dimethylamino-1-piperidinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[1-piperazinyl]-6-[N-methyl-N-(2-furylmethyl)]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[[4-(Methoxycarbonylphenyl)methyl]amino]-6-
 20 (4-dimethyl-1-piperidinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester, trifluoroacetate (1:1); 2-[[4-[3-Oxo-1-piperazinyl]-6-[[4-(methylsulfonylamino)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[3-Oxo-1-piperazinyl]-6-[[4-(propylsulfonylamino)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-
 25 thiazolecarboxylic acid, ethyl ester; 2-[[4-[3-(Aminocarbonyl)-1-piperidinyl]-6-[[3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic

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acid, ethyl ester; 2-[Bis-4,6-(4-Hydroxy-4-methyl-1-piperidiny)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 4-Methyl-2-[[4-[4-dimethylamino-1-piperidiny]-6-[(2-oxo-1-pyrrolidiny)propyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[3-Oxo-1-piperaziny]-6-[(4-(isopropylsulfonylamino)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[4-(4-Hydroxypiperidin-1-yl)-6-(3-hydroxymethyl-1-piperidiny)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 4-Methyl-2-[[4-[4-hydroxy-1-piperidiny]-6-[(2-(4-morpholinyl)ethyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[[4-(Ethylaminosulfonyl)phenyl]methyl]amino]-6-methoxy-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, methyl ester, trifluoroacetate (1:1); 2-[[4-[4-Morpholinyl]-6-[(1-oxa-3,8-diazaspiro[4.5]decan-2,4, dion-8-yl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-Hydroxy-1-piperidiny]-6-[(4-(ethylsulfonylamino)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[tertButyloxycarbonyl-1-piperaziny]-6-[(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[3-(Aminocarbonyl)-1-piperidiny]-6-[(3,4-dimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-ethoxycarbonyl-1-piperaziny]-6-[[N-methyl-N-(5-tetrazolyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[3-Oxo-1-piperiziny]-6-[(4-(cyclopropylsulfonylamino)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-Hydroxymethyl-1-piperidiny]-6-[(4-(methylsulfonylamino)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[4-(4-Dimethylamino-1-piperaziny)-6-(4-tertbutyloxycarbonylamino-1-piperidiny)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-

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carboxylic acid ethyl ester; 2-[4-(4-Hydroxypiperidin-1-yl)-6-(4-methoxymethyl-1-piperidinyl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Hydroxypiperidin-1-yl)-6-(4-hydroxyethyl-1-piperidinyl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Hydroxypiperidin-1-yl)-6-(4-(hydroxy)-4-(3-trifluoromethylphenyl)piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[[4-[4-morpholinyl]-6-[4-[1-methyl-1-hydroxyethyl]-1-piperidinyl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-(3-Oxo-1-piperiziny)]-6-[[3-pyridyl]oxy]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-Methyl-1-piperazinyl]-6-[(1,4-dioxaspiro[4.5]decan-8-yl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-Morpholinyl]-6-[[4-(methylsulfonylamino)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[3-Oxo-1-piperazinyl]-6-[(1-oxa-3,8-diazospiro[4.5]decan-2,4, dion-8-yl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-Hydroxy-1-piperidinyl]-6-[[4-(carboxy)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[4-(4-Hydroxypiperidin-1-yl)-6-(4-(hydroxy)-4-(4-bromophenyl)piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[[4-[4-Morpholinyl]-6-[[4-(ethylsulfonylamino)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[3-(Aminocarbonyl)-1-piperazinyl]-6-[[3,4-dimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-Formyl-1-piperazinyl]-6-[[3-(5-(1H)tetrazolyl)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-(Hydroxymethyl)-1-Piperidinyl]-6-[[N-methyl-N-(5-tetrazolylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-Methyl-1-piperazinyl]-6-[[2,5-dimethyl)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic

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acid, ethyl ester; 2-[[4-[3-(2-oxo-1-pyrrolidinyl)propyl]amino]-6-[N-methyl-N-(3-pyridinylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[(1-Morpholinyl)]-6-[[N-methyl-N-(5-tetrazolylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-methyl-1-piperazinyl]-6-[4-[methylsulfonylamino]-1-piperidinyl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-hydroxy-1-piperidinyl]-6-[(2,5-dimethyl)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 4-Methyl-2-[[4-(4-morpholinyl)-6-[(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid, ethyl ester; 2-[4-(4-Hydroxypiperidin-1-yl)-6-(3-hydroxy-1-piperidinyl)-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 4-Methyl-2-[[4-(4-methyl-1-piperazinyl)-6-[methyl(3-pyridinylmethyl)amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[3-Oxo-1-piperazinyl]-6-[(2-(5-(1H)tetrazolyl)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-4-thiazolecarboxylic acid, ethyl ester; 2-[[4-[(2-Furanylmethyl)amino]-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester, trifluoroacetate (1:1); 2-[[4-[(3,4-Dimethoxyphenyl)methyl]amino]-6-(4-morpholinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 4-Methyl-2-[[4-[methyl(3-pyridinylmethyl)amino]-6-[[tetrahydro-2-furanyl)methyl]amino]-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[(4-hydroxy-1-piperidinyl)]-6-[[N-methyl-N-(5-tetrazolylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[4-(4-Hydroxypiperidin-1-yl)-6-[(4-(hydroxy)-4-(phenylmethyl)piperidin-1-yl)]-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Dimethylamino-1-piperazinyl)-6-[[2-(1-morpholinyl)ethyl]amino]pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[[4-[4-hydroxy-1-piperidinyl]-6-[(3-pyridinylmethyl)]oxy]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl

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ester; 2-[[4-[3-(Aminocarbonyl)-1-piperidinyl]-6-[[2,6-dimethylphenyl)methyl]amino]-
 2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-hydroxy-
 1-piperidinyl]-6-[[4-(methylsulfonylamino)phenyl)methyl]amino]-2-
 pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-hydroxy-1-
 5 piperidinyl]-6-[[4-(propylsulfonylamino)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-
 methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[3-(Aminocarbonyl)-1-piperidinyl]-6-
 (4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl
 ester; 2-[[4-(3,4-Dihydro-6,7-dimethoxy-2(1H)-isoquinoliny)-6-(4-methyl-1-
 piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-
 10 [4-Formyl-1-piperazinyl]-6-[[N-methyl-N-(5-tetrazolylmethyl)amino]-2-
 pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[[4-
 Carboxyphenyl)methyl]amino]-6-[4-(hydroxymethyl)-1-piperidinyl]-2-
 pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[[4-
 Carboxyphenyl)methyl]amino]-6-(4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-
 15 methyl-5-thiazolecarboxylic acid, ethyl ester, monohydrochloride; 4-Methyl-2-[[4-(4-
 methyl-1-piperazinyl)-6-[[4-(tetrahydro-2-furanyl)methyl]amino]-2-pyrimidinyl]amino]-5-
 thiazolecarboxylic acid, ethyl ester; 2-[[4-[[4-(4-Carboxyphenyl)methyl]amino]-6-[3-
 (hydroxymethyl)-1-piperidinyl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic
 acid, ethyl ester; 2-[[4-[[4-[[4-[(2-Methoxyethyl)amino]carbonyl]phenyl)methyl]amino]-6-
 20 (4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl
 ester, trifluoroacetate (1:1); 2-[4,6-Bis-(1-morpholinyl)-pyrimidin-2-ylamino]-4-methyl-
 thiazole-5-carboxylic acid ethyl ester; 2-[[4-[3-(Aminocarbonyl)-1-piperazinyl]-6-[[N-
 methyl-N-(5-tetrazolylmethyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-
 thiazolecarboxylic acid ethyl ester; 4-Methyl-2-[[4-[-methyl(3-pyridinylmethyl)amino]-6-
 25 [4-morpholinyl]-2-pyridinylmethyl]amino]-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-
 [3-(Aminocarbonyl)-1-piperazinyl]-6-[[4-(methoxycarbonyl)phenyl)methyl]amino]-2-

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pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-Chloro-6-[(1-oxa-3,8-diazaspiro[4.5]decan-2,4-dion-8-yl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-(Hydroxymethyl)-1-piperidinyl]-6-[(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[3-(Hydroxymethyl)-1-Piperidinyl]-6-[[N-methyl-N-(5-tetrazolyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[3-(Hydroxymethyl)-1-pyrrolidinyl]-6-[[N-methyl-N-(5-tetrazolyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 4-Methyl-2-[[4-[methyl(phenylmethyl)amino]-6-(4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-(Dimethylamino)-6-[[4-(methylsulfonyl)phenyl]methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-Hydroxy-1-piperidinyl]-6-[(3-(5-(1H)tetrazolyl)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-hydroxymethyl-1-piperidinyl]-6-[(4-(propylsulfonylamino)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-hydroxymethyl-1-piperidinyl]-6-[(4-(cyclopropylsulfonylamino)phenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[3-(Hydroxymethyl)-1-piperidinyl]-6-[(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-tetrahydropyranyl]oxy-6-[[N-[(3,4,5-trimethoxyphenyl)methyl]]-N-(methyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-Methyl-1-piperazinyl]-6-[(4-methoxyphenyl)oxy]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 4-Methyl-2-[4-(4-methyl-piperazin-1-yl)-6-[[4-(aminosulfonyl)phenyl]methyl]amino]pyrimidin-2-ylamino]-thiazole-5-carboxylic acid ethyl ester; 2-[4-Isopropyl-6-(4-sulfamoyl-benzylamino)-pyrimidin-2-ylamino]-4-methyl-

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thiazole-5-carboxylic acid ethyl ester; 4-Methyl-2-[4-(4-sulfamoyl-benzylamino)-6-methyl-pyrimidin-2-ylamino]-thiazole-5-carboxylic acid ethyl ester; 4-Methyl-2-[4-(4-sulfamoyl-benzylamino)-6-hydroxymethyl-pyrimidin-2-ylamino]-thiazole-5-carboxylic acid ethyl ester; 4-Methyl-2-[4-(4-methyl-piperazin-1-yl)-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino]-thiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Hydroxy-piperidin-1-yl)-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 4-Methyl-2-[4-[(tetrahydro-furan-2-ylmethyl)-amino]-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino]-thiazole-5-carboxylic acid ethyl ester; 4-Methyl-2-[4-morpholin-4-yl-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino]-thiazole-5-carboxylic acid ethyl ester; 2-[4-(3-Carbamoyl-piperidin-1-yl)-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Hydroxymethylpiperidin-1-yl)-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[4-(2-Hydroxymethyl-1-pyrrolidinyl)-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[4-(3-N,N-Diethylcarbamoyl-1-piperidinyl)-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[4-(3-Hydroxy-1-pyrrolidinyl)-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 4-Methyl-2-[[[2-[4-morpholin-4-yl]ethyl]amino]-6-[4-(1H-tetrazol-5-yl)-benzylamino]pyrimidin-2-ylamino]-thiazole-5-carboxylic acid ethyl ester; 4-Methyl-2-[[[4-hydroxyl]butyl]amino]-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino]-thiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Formyl-1-piperazinyl)-6-[4-(1H-tetrazol-5-yl)-benzylamino]-pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl ester; 2-[4-[[4-(4-Chlorophenyl)methyl]amino]-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[4-[[4-(4-Aminosulfonylphenyl)methyl]amino]-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-

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methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-Morpholino-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[(3,4-Dimethoxyphenyl)methyl]amino]-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-(1,4-Dioxo-8-aza-spiro[4.5]dec-8-yl)-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[4-Hydroxy-4-phenyl-piperidinyl]-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[(4-Methylsulfonylphenyl)methyl]amino]-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[4-Hydroxy-piperidinyl]-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[4-Ethoxycarbonyl-piperidinyl]-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-Piperidinyl-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[N-Methylpiperazinyl-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[N-(2-Furylcarbonyl)piperazinyl-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[N-Acetyl-1,4-diazepyl]-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[N-Methyl-N-(N-methyl-4-piperidinyl)-amino]-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[N-Methyl-1,4-diazepyl]-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-N,N-Dimethoxyethylamino-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[(1',4)-Bipiperidinyl]-6-(5-oxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[4-(4-Hydroxy-piperidin-1-yl)-6-(3,4,5-trimethoxy-phenyl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[(4-(4-Hydroxy-piperidin-1-yl)-6-[4-(1H-tetrazol-5-yl)-phenyl]-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Hydroxy-piperidin-1-yl)-6-pyridin-3-yl-pyrimidin-2-ylamino]-4-methylthiazole-5-

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carboxylic acid ethyl ester; 2-[4-(4-Methanesulfonyl-benzylamino)-6-pyridin-3-yl-
 pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Hydroxy-
 piperidin-1-yl)-6-pyrimidin-4-yl-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic
 acid ethyl ester; 2-[4-(4-Cyano-phenyl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-
 5 ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Acetyl-phenyl)-6-(4-
 hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl
 ester; 2-[4-(4-Hydroxymethyl-phenyl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-
 ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Hydroxy-phenyl)-6-(4-
 hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl
 10 ester; 2-[4-(4-Methanesulfonyl-benzylamino)-6-(3,4,5-trimethoxy-phenyl)-pyrimidin-2-
 ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Methanesulfinylphenyl)-
 6-(4-hydroxypiperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid
 ethyl ester; 2-[4-(4-(Amino)phenyl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-
 4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Carboxymethyl-phenyl)-6-(4-
 15 hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl
 ester; 2-[4-(4-(Trifluoromethylcarbonylamino)phenyl)-6-(4-hydroxy-piperidin-1-yl)-
 pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-
 (Ethoxycarbonylmethyl)phenyl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-
 methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(1,2,3,6-Tetrahydropyridin-4-yl)-6-(4-
 20 hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl
 ester; 2-[4-(3-(cyano)phenyl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-
 methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-(Methoxycarbonyl)phenyl)-6-(4-
 hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl
 ester; 2-[4-(2-(Methoxy)-5-pyridinyl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-
 25 ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-tertButyloxycarbonyl-
 1,2,3,6-Tetrahydropyridin-4-yl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-

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methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(1,4-Dioxaspiro[4.5]dec-7-en-8-yl)-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Methyl-1-piperazin-yl)-6-(3,4,5-trimethoxy-phenyl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Morpholinyl)-6-(3,4,5-trimethoxy-phenyl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Morpholinyl)-6-(3-pyridinyl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[[4-[4-Hydroxypiperidinyl]-6-(3,5-dimethyl-4-isoxazolyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[4-(4-tert-Butoxycarbonylamino-phenyl)-6-(4-hydroxypiperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[4-(4-Cyano-phenyl)-6-(4-methanesulfonyl-benzylamino)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[4-(4-Methanesulfonylphenyl)-6-(4-hydroxypiperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Methanesulfanylphenyl)-6-(4-hydroxypiperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Carboxy-phenyl)-6-(4-hydroxypiperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Carboxy-phenyl)-6-(3-oxo-piperazin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Carboxy-phenyl)-6-(4-methylpiperazin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Carboxy-phenyl)-6-morpholin-4-yl-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Carboxy-phenyl)-6-(4-methyl-[1,4]diazepan-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Carboxy-phenyl)-6-(3-R-hydroxypiperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Carboxy-phenyl)-6-(3-hydroxymethyl-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Acetyl-

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[1,4]diazepan-1-yl)-6-(4-carboxy-phenyl)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Carboxy-phenyl)-6-[N-methyl-N-(1-N-methyl-piperidin-4-yl)-amino]-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Carboxy-phenyl)-6-piperazin-1-yl-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[4-(4-Carboxy-phenyl)-6-(4-sulfamoyl-benzylamino)-pyrimidin-2-ylamino]-4-methylthiazole-5-carboxylic acid ethyl ester; 2-[[4-[[5-Allyl[4-(aminosulfonyl)phenyl]methyl]amino]-6-chloro-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[[[4-(Aminosulfonyl)phenyl]methyl]amino]-5-methyl-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester, trifluoroacetate (1:3); 2-[[4-[[[4-(Aminosulfonyl)phenyl]methyl]amino]-5-methyl-6-(4-morpholinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[[5-Allyl[4-(aminosulfonyl)phenyl]methyl]amino]-6-(4-methylpiperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[[5-[2-[2-Methylprop-3-en]]-4-[4-(aminosulfonyl)phenyl]methyl]amino]-6-(4-methylpiperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[[[3,4,5-(Trimethoxy)phenyl]methyl]amino]-5-methyl-6-(1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester, trifluoroacetate; 2-[[4-[[5-[2,3-propandiol][4-(aminosulfonyl)phenyl]methyl]amino]-6-(4-methylpiperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[[[3,4,5-(Trimethoxy)phenyl]methyl]amino]-5-methyl-6-(4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester, trifluoroacetate; 2-[[4-[[5-[2-[2-Methylprop-3-en]]-4-[4-(aminosulfonyl)phenyl]methyl]amino]-6-chloro-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[[[4-(Aminosulfonyl)phenyl]methyl]amino]-5-methyl-6-(4-tertbutyloxycarbonyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-[[4-[N-[[3,4,5-(Trimethoxy)phenyl]methyl]-N-methylamino]-5-methyl-6-(4-methyl-1-

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piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-
 [4,6-Bis-(4-hydroxy-piperidin-1-yl)-5-methylpyrimidin-2-ylamino]-4-methyl-thiazole-5-
 carboxylic acid ethyl ester; 2-[4,6-Bis-(3-oxo-piperazin-1-yl)-5-
 [ethoxycarbonylmethyl]pyrimidin-2-ylamino]-4-methyl-thiazole-5-carboxylic acid ethyl
 5 ester; 2-[4,6-Bis-(4-hydroxy-piperidin-1-yl)-5-methoxypyrimidin-2-ylamino]-4-methyl-
 thiazole-5-carboxylic acid ethyl ester; 2-[[4-[N-[[3,4,5-(Trimethoxy)phenyl]methyl]-N-
 methylamino]-5-methoxy-6-(4-methyl-1-piperazinyl)-2-pyrimidinyl]amino]-4-methyl-5-
 thiazolecarboxylic acid, ethyl ester; 2-[[4-[[3-pyridyl]methyloxy]-5-(2-propenyl-6-(4-
 morpholinyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, ethyl ester; 2-
 10 [(4-Ethoxycarbonylmethyl-6-morpholin-4-yl-pyrimidin-2-yl)-amino]-4-methyl-5-
 thiazolecarboxylic acid ethyl ester; 2-[(4-Ethoxycarbonylmethyl-6-[3-oxo-1-piperazinyl]-
 pyrimidin-2-yl)-amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[(4-
 Carboxymethyl-6-morpholin-4-yl-pyrimidin-2-yl)-amino]-4-methyl-5-thiazolecarboxylic
 acid; 2-[4-Morpholin-4-yl-6-[(3,4,5-trimethoxy-phenylcarbamoyl)-methyl]-pyrimidin-2-
 15 ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[2-oxo-2-(3-oxo-
 piperazin-1-yl)-ethyl]-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-
 thiazolecarboxylic acid ethyl ester; 2-[[4-(4-sulfamoyl-benzylamino)-6-[(4-sulfamoyl-
 benzylcarbamoyl)-methyl]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid
 ethyl ester; 2-[4-[2-(1,4-Dioxo-8-aza-spiro[4.5]dec-8-yl)-2-oxo-ethyl]-6-(4-sulfamoyl-
 20 benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-
 [[4-[[4-(4-Chloro-phenyl)-methyl-carbamoyl]-methyl]-6-(4-sulfamoyl-benzylamino)-2-
 pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[2-(4-Hydroxy-
 piperidin-1-yl)-2-oxo-ethyl]-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-
 methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[2-(4-Ethoxycarbonyl-piperidin-1-yl)-
 25 2-oxo-ethyl]-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-
 thiazolecarboxylic acid ethyl ester; 2-[[4-(2-oxo-2-piperidin-1-yl-ethyl)-6-(4-sulfamoyl-

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benzylamino)2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[2-[4-(Furan-2-carbonyl)-piperazin-1-yl]-2-oxo-ethyl]-6-(4-sulfamoyl-benzylamino)2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[(Cyclohexyl-methyl-carbamoyl)-methyl]-6-(4-sulfamoyl-benzylamino)2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[2-(4-Acetyl-[1,4]diazepan-1-yl)-2-oxo-ethyl]-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[[Methyl-(1-methyl-piperidin-4-yl)-carbamoyl]-methyl]-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[2-(4-methyl-[1,4]diazepan-1-yl)-2-oxo-ethyl]-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[[Bis-(2-methoxy-ethyl)-carbamoyl]-methyl]-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[[4-(2-[1,4']Bipiperidinyl-1'-yl)-2-oxo-ethyl]-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[2-(4-Hydroxy-4-phenyl-piperidin-1-yl)-2-oxo-ethyl]-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-Ethoxycarbonyl-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-Carboxyl-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-(Carboxymethyl-carbamoyl)-6-(4-sulfamoyl-benzylamino)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[4-(4-Hydroxy-piperidin-1-yl)-6-(4-methylsulfanyl-benzyl)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[4-(4-Hydroxy-piperidin-1-yl)-6-(4-methanesulfonyl-benzyl)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-(4-Hydroxy-piperidin-1-yl)-6-(4-methanesulfonyl-benzyl)-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[[4-[4-methyl-1-piperazinyl]-6-[N-methyl-N-[(3,4,5-

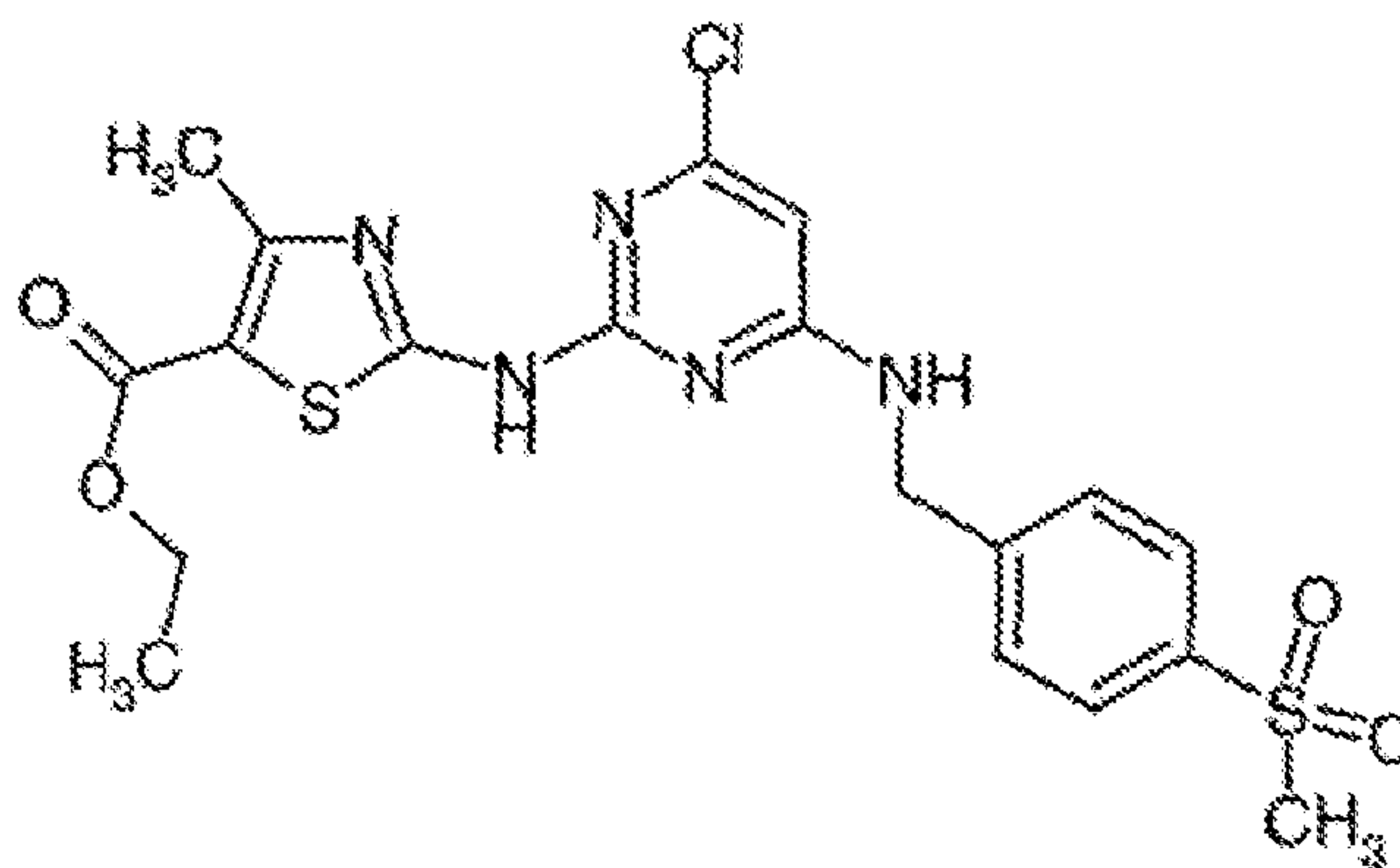
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trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-trifluoromethyl-5-
 thiazolecarboxylic acid, ethyl ester; 2-[[4-[4-Methylpiperazin-1-yl]-6-(N-methyl-N-
 [[(3,4,5-trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-
 cyanothiazole; 2-[[4-[4-Methylpiperazin-1-yl]-6-methyl-6-[[3,4,5-
 5 trimethoxyphenyl)methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic
 acid, 2-methoxyethyl ester; 2-[[4-[4-Hydroxy-piperidin-1-yl]-6-[N-methyl[[N-[(3,4,5-
 trimethoxyphenyl)methyl]]-N-methyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-
 thiazolecarboxylic acid, butyl ester; 2-[[4-[1-morpholinyl]-6-[[2-[1-
 morpholinyl]ethyl]amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid,
 10 butyl ester; 2-[[4-[4-methyl-1-piperazinyl]-6-[[N-[(3,4,5-trimethoxyphenyl)methyl]]-N-
 (methyl)amino]-2-pyrimidinyl]amino]-4-isopropyl-5-thiazolecarboxylic acid, ethyl ester;
 2-[[4-[4-methyl-1-piperazinyl]-6-[[N-[(3,4,5-trimethoxyphenyl)methyl]]-N-
 (methyl)amino]-2-pyrimidinyl]amino]-4-methyl-5-thiazolecarboxylic acid, methyl amide;
 2-[4-[4-(2-Diisopropylamino-ethylcarbamoyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-
 15 pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[4-[4-(3-
 Dimethylamino-propylcarbamoyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-
 ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[4-[4-
 (Cyclohexylmethylcarbamoyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-
 ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[4-[4-(Pyridin-4-
 20 ylmethylcarbamoyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-
 methyl-5-thiazolecarboxylic acid ethyl ester; 2-[4-[4-(Isobutylcarbomoyl)-phenyl]-6-(4-
 hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl
 ester; 2-[4-[4-(N-Cyclohexyl-N-methylcarbamoyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-
 pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[4-[4-(N-
 25 Cyclopropylmethyl-N-propylcarbamoyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-
 pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[4-[4-(4-

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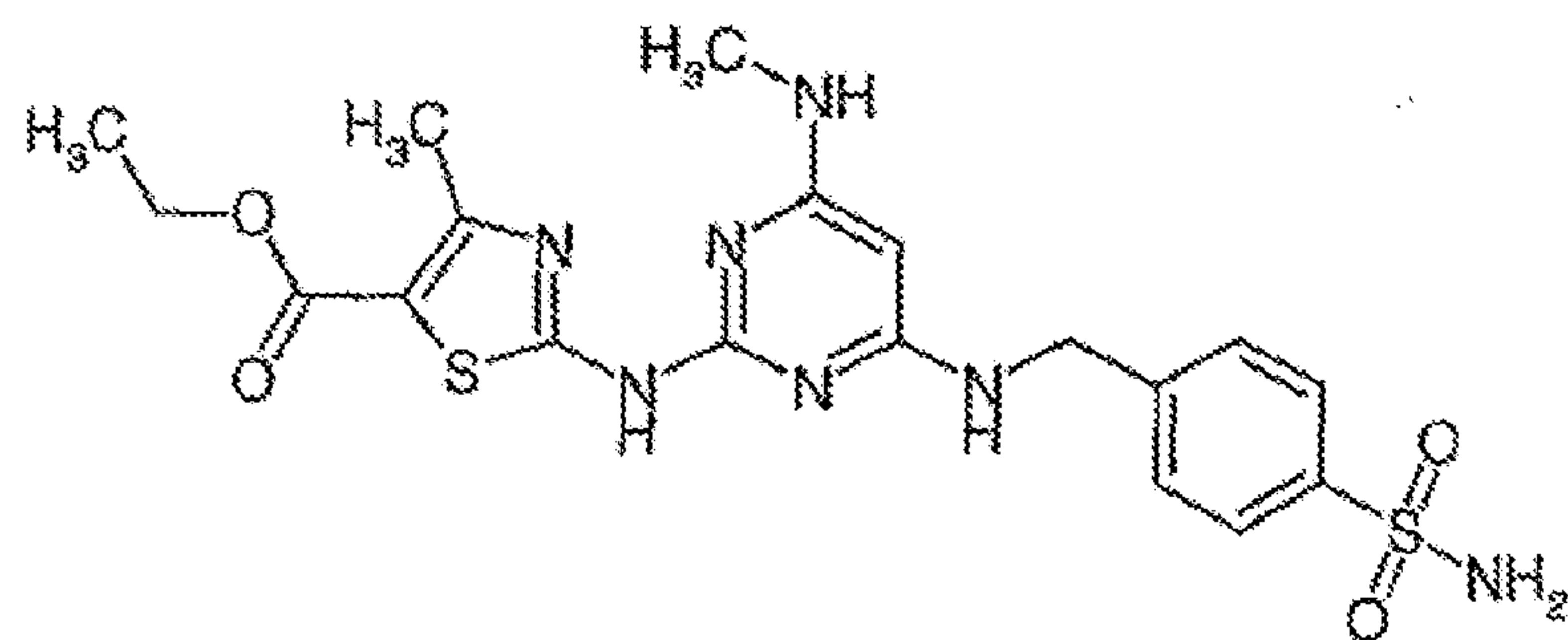
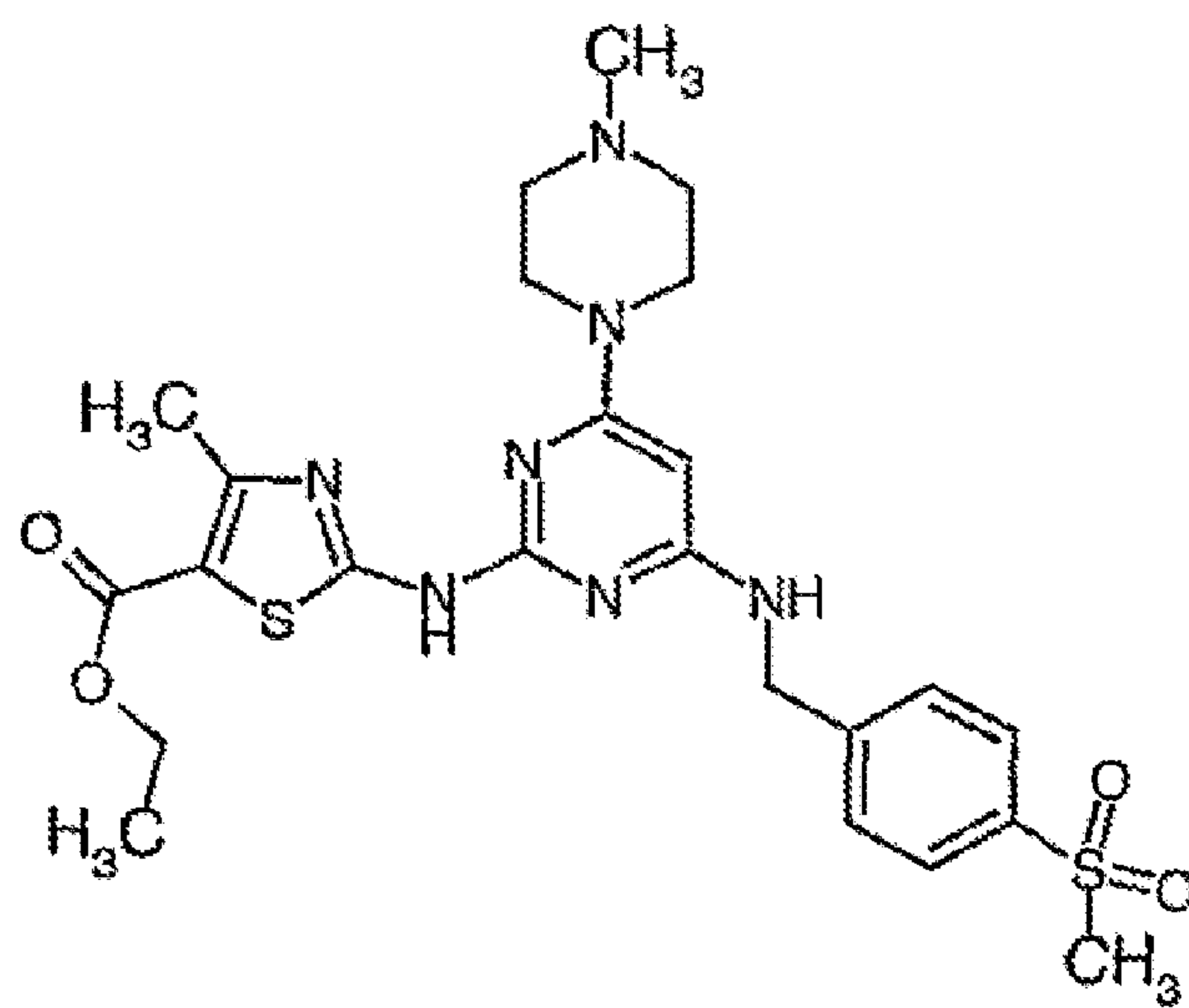
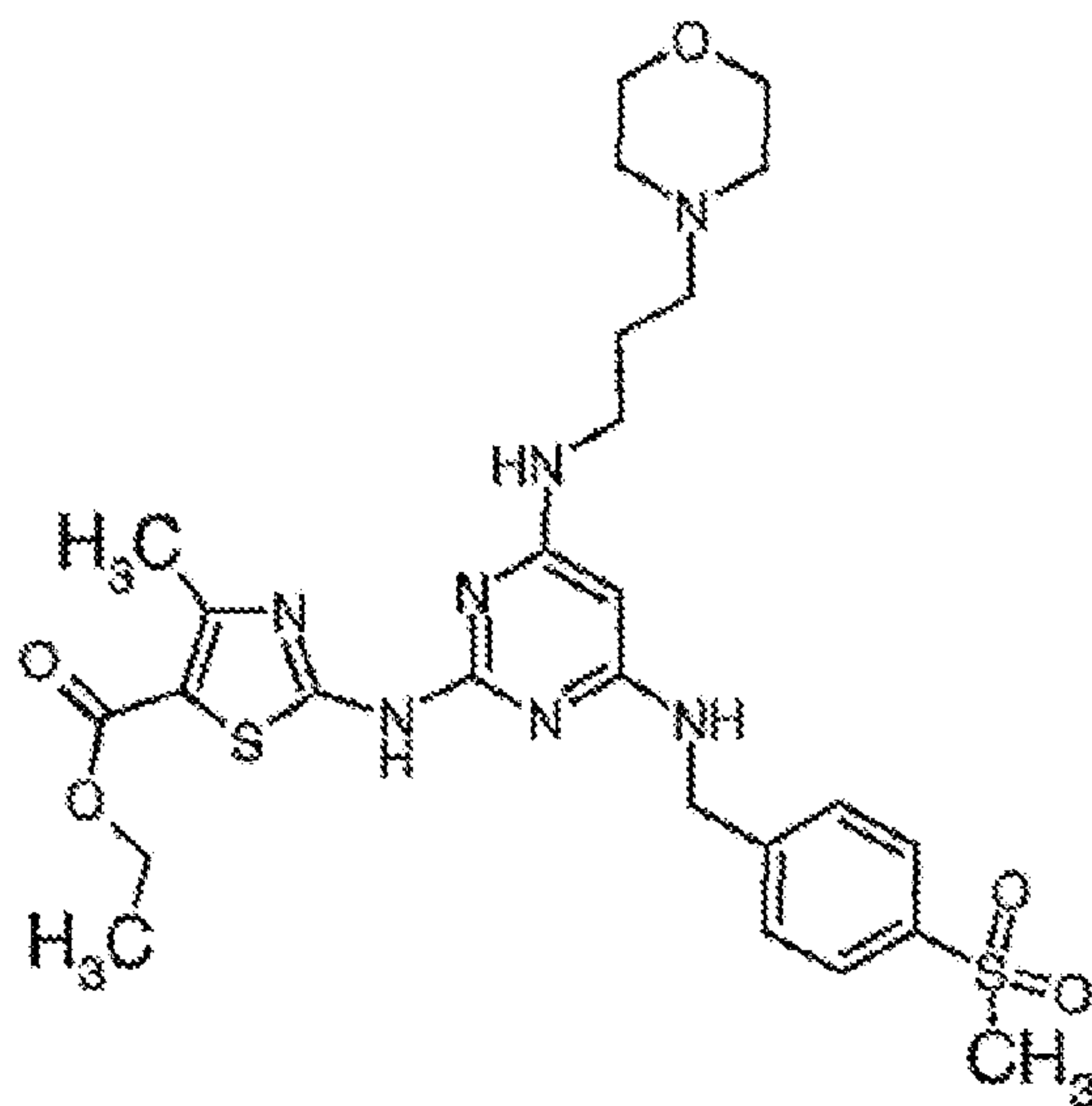
Ethoxycarbonylpiperidine-1-carbamoyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-
 pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[4-[4-(3-
 Hydroxymethyl-piperidine-1-carbonyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-
 2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; 2-[4-[4-(N-2-Hydroxyethyl-
 5 N-ethylcarbamoyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-
 methyl-5-thiazolecarboxylic acid ethyl ester; 2-[4-[4-(Thiomorpholine-1-carbonyl)-
 phenyl]-6-(4-hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-5-
 thiazolecarboxylic acid ethyl ester; 2-[4-[4-(Morpholine-1-carbonyl)-phenyl]-6-(4-
 hydroxy-piperidin-1-yl)-pyrimidin-2-ylamino]-4-methyl-5-thiazolccarboxylic acid ethyl
 10 ester; and 2-[4-[4-(4-Chloro-phenylcarbamoyl)-phenyl]-6-(4-hydroxy-piperidin-1-yl)-
 pyrimidin-2-ylamino]-4-methyl-5-thiazolecarboxylic acid ethyl ester; or a stereoisomer, a
 pharmaceutically acceptable salt, or a hydrate thereof.

In another related embodiment, PDE7 inhibitors useful in the methods of the
 present invention include the following compounds:

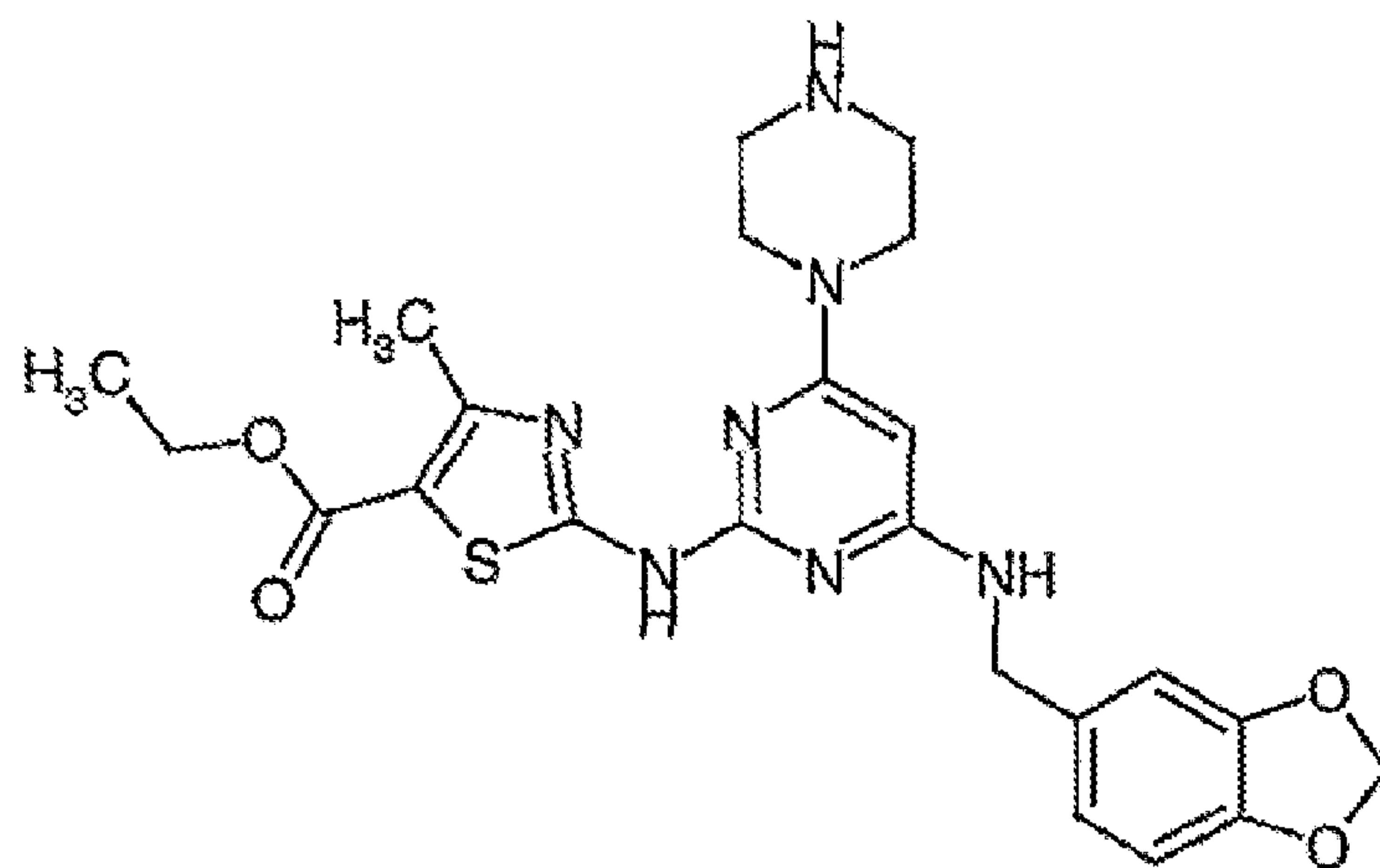
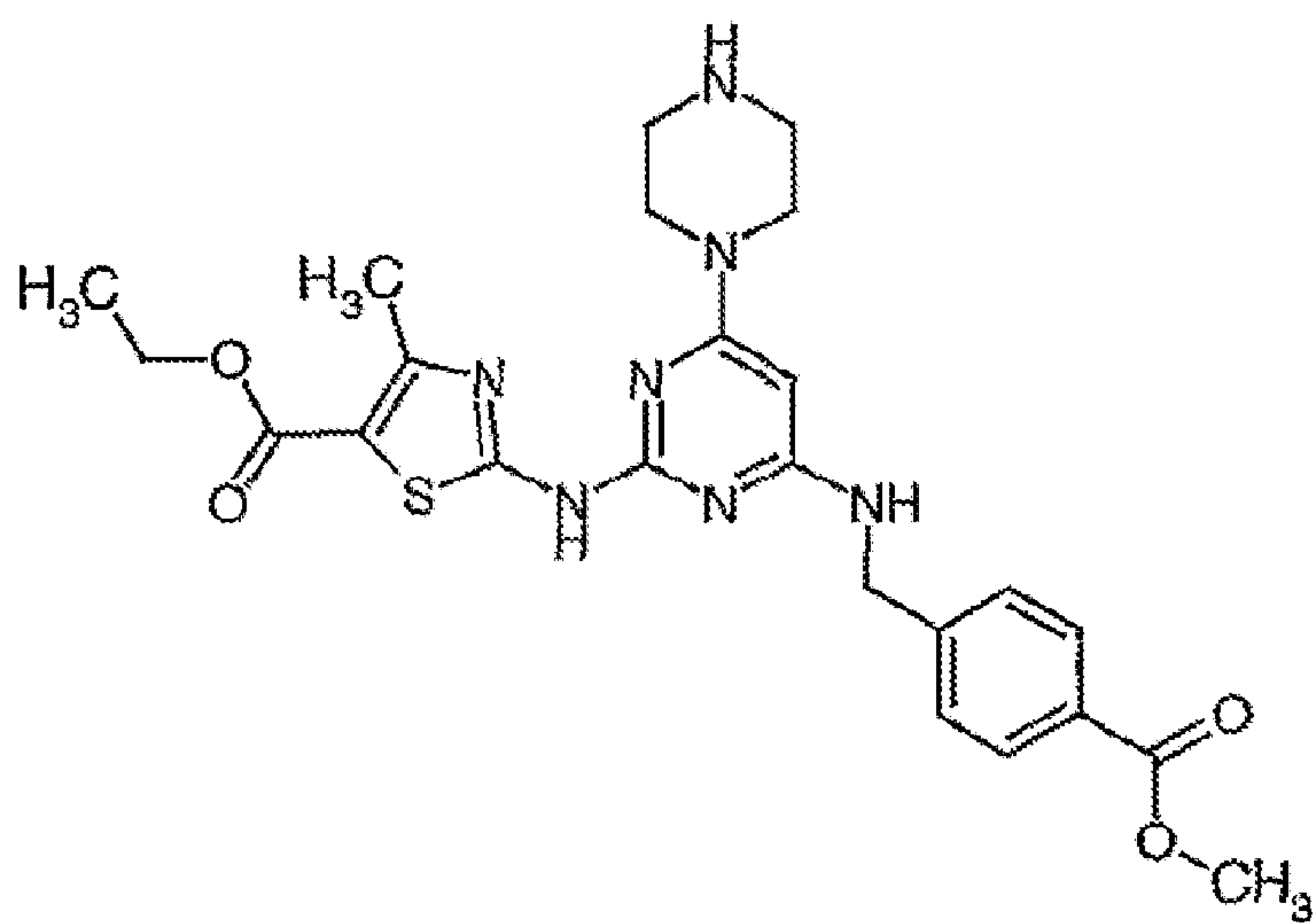
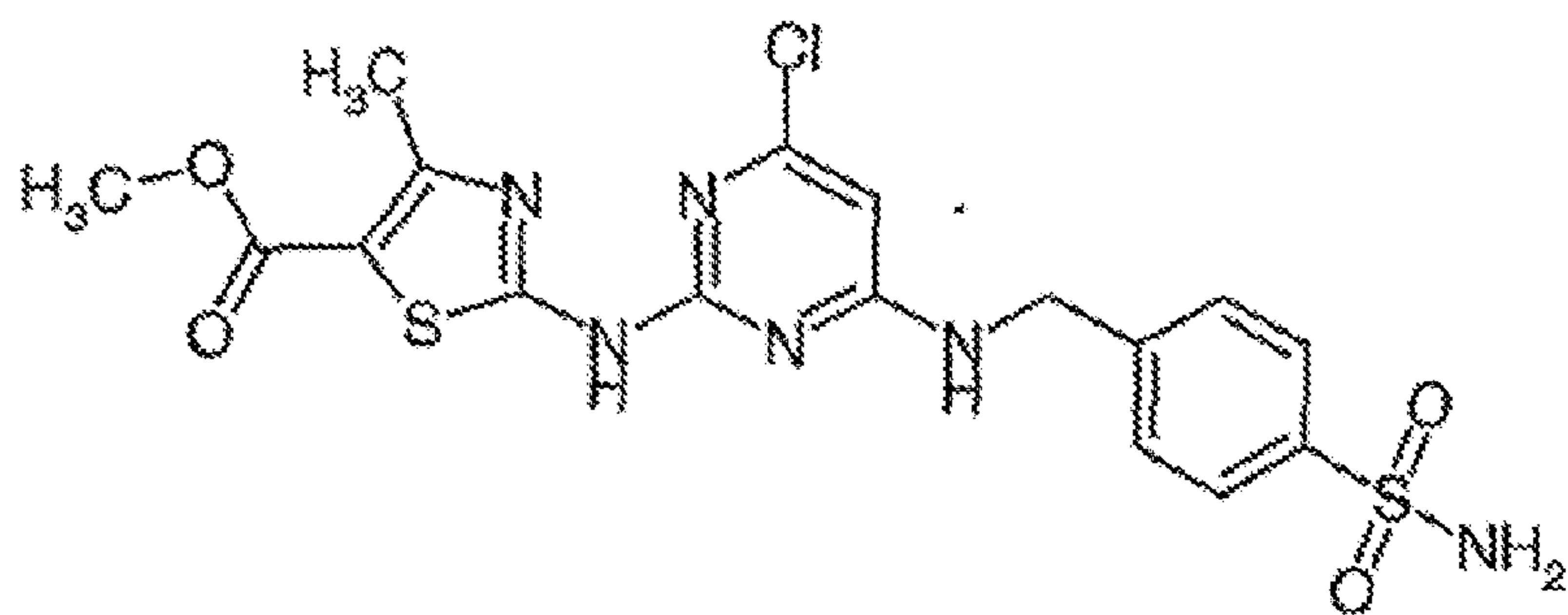


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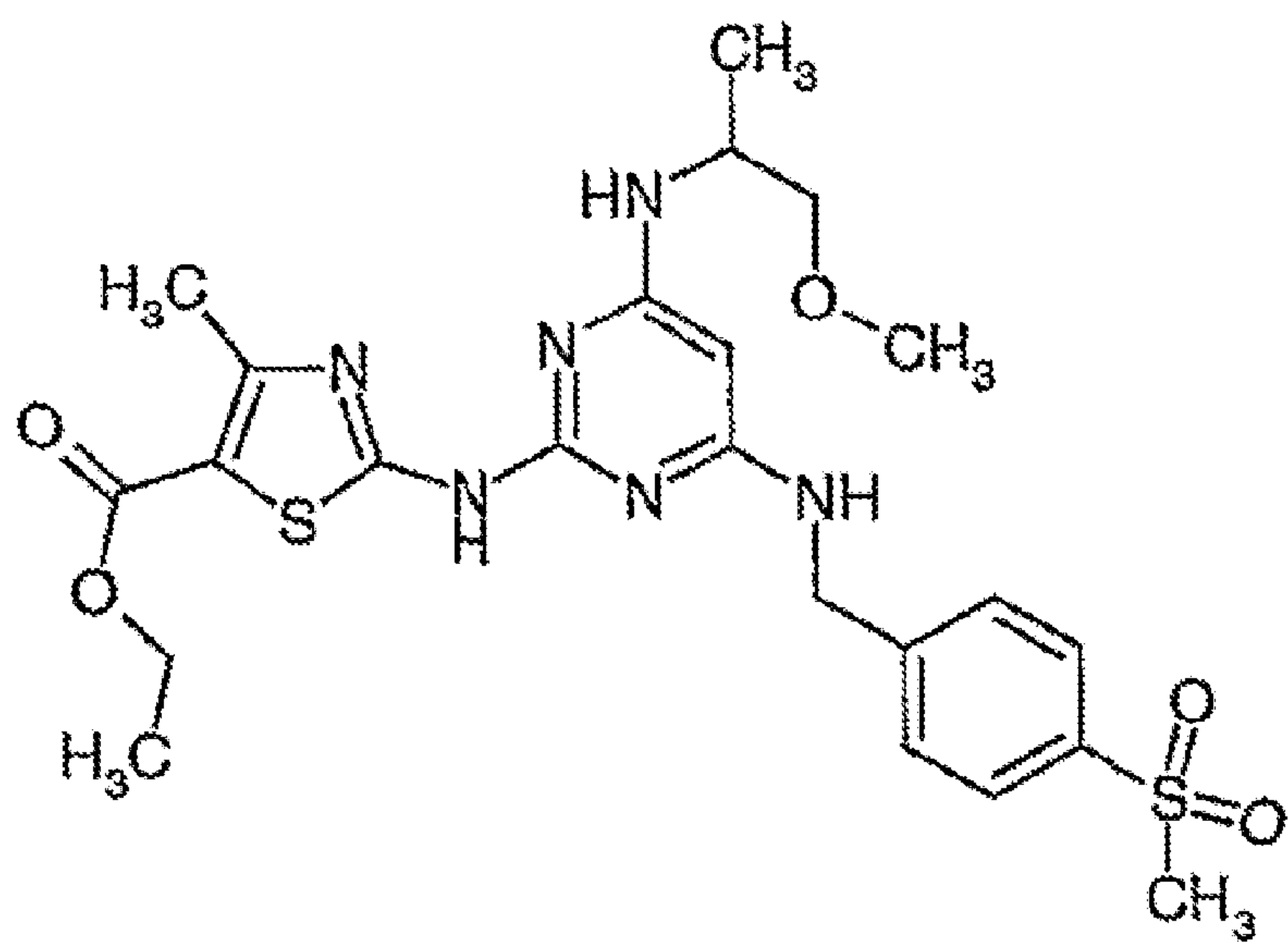
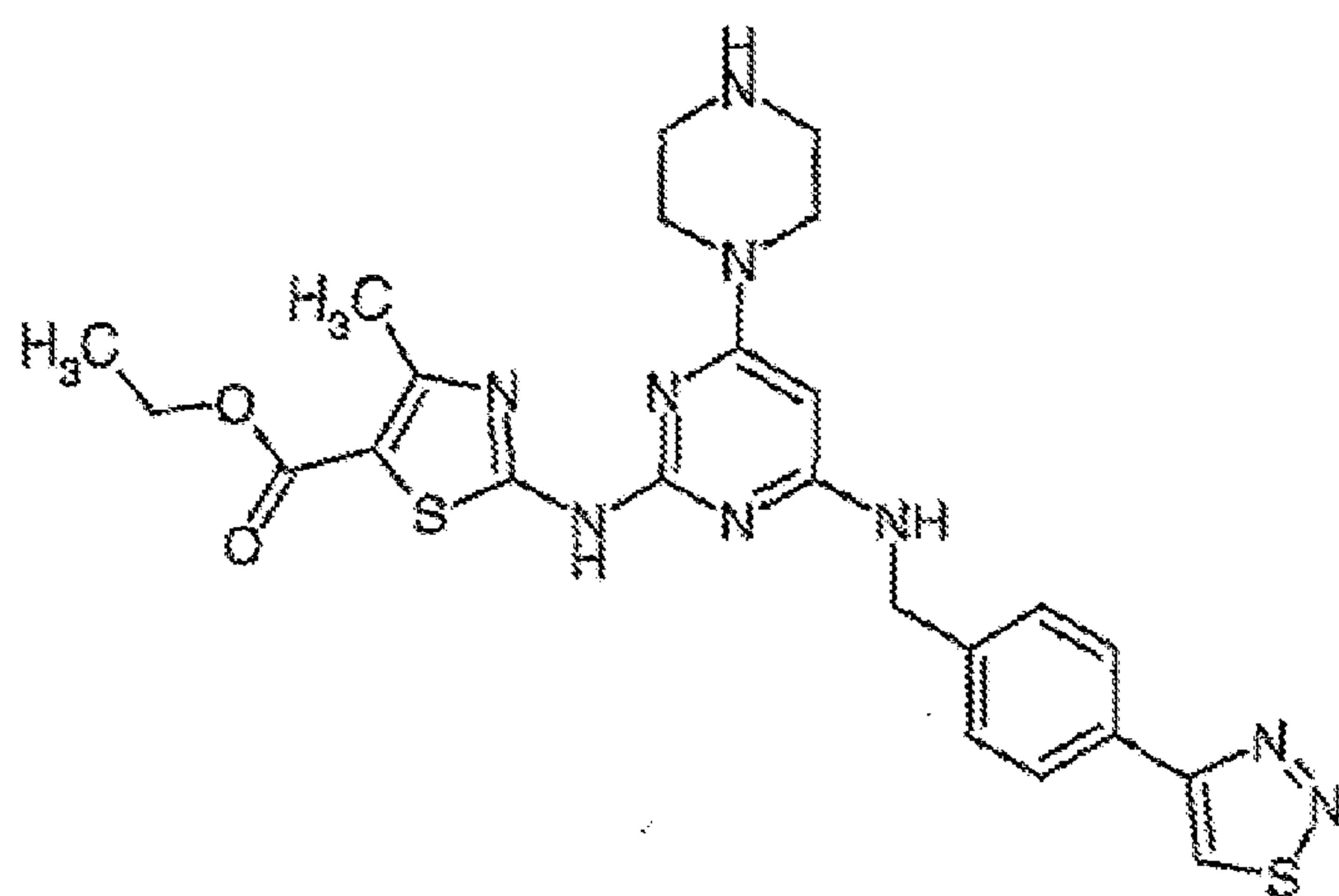
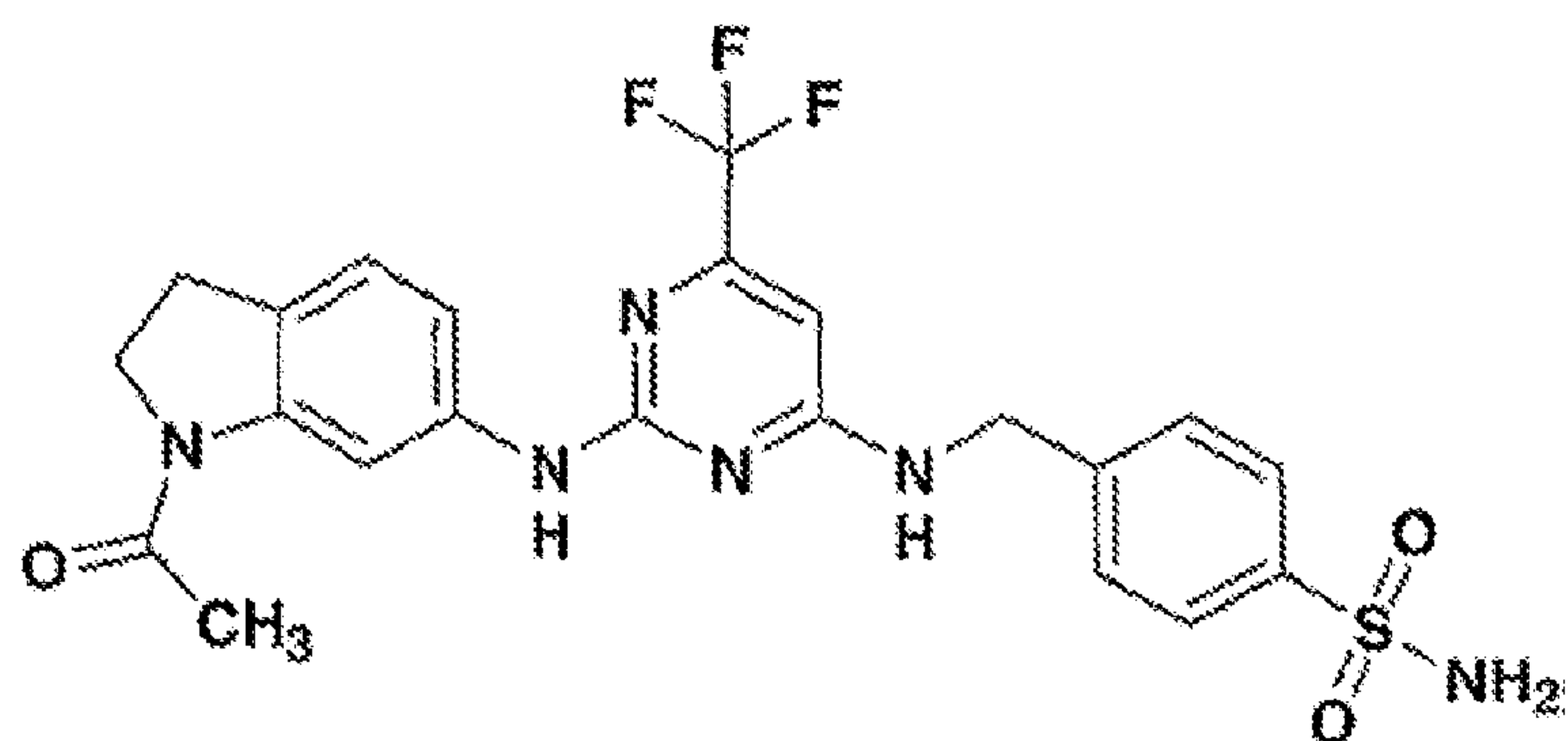
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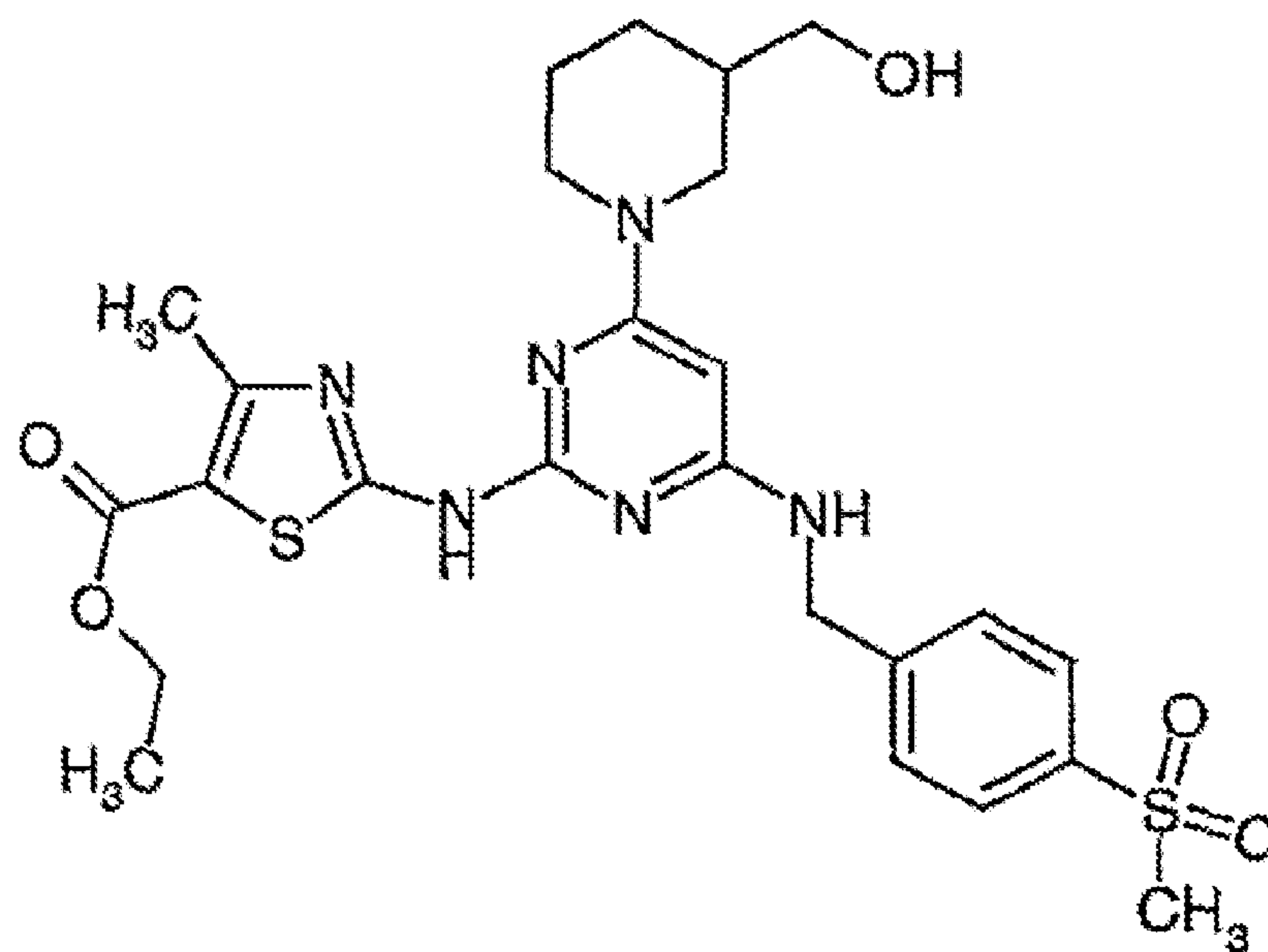
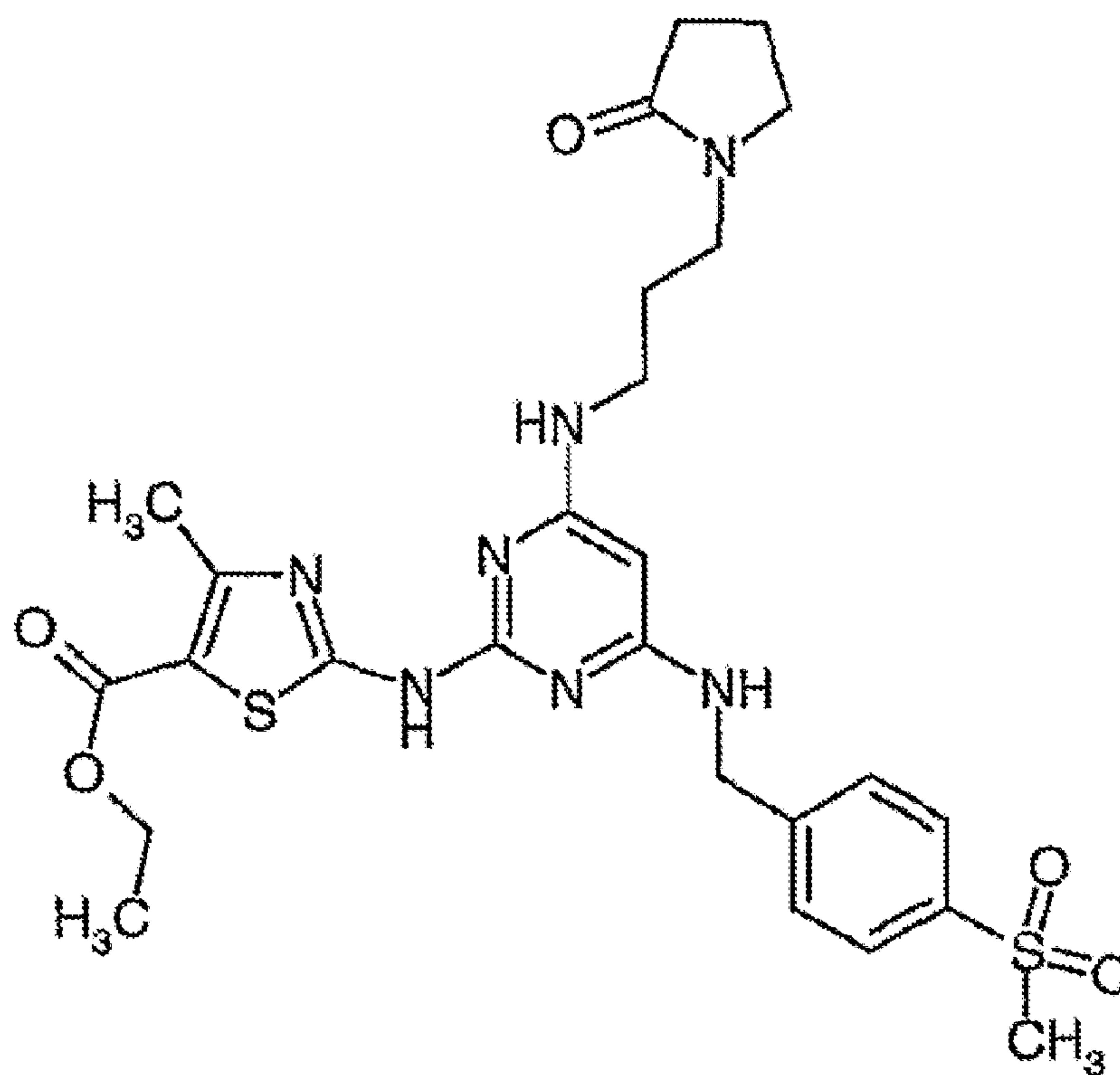
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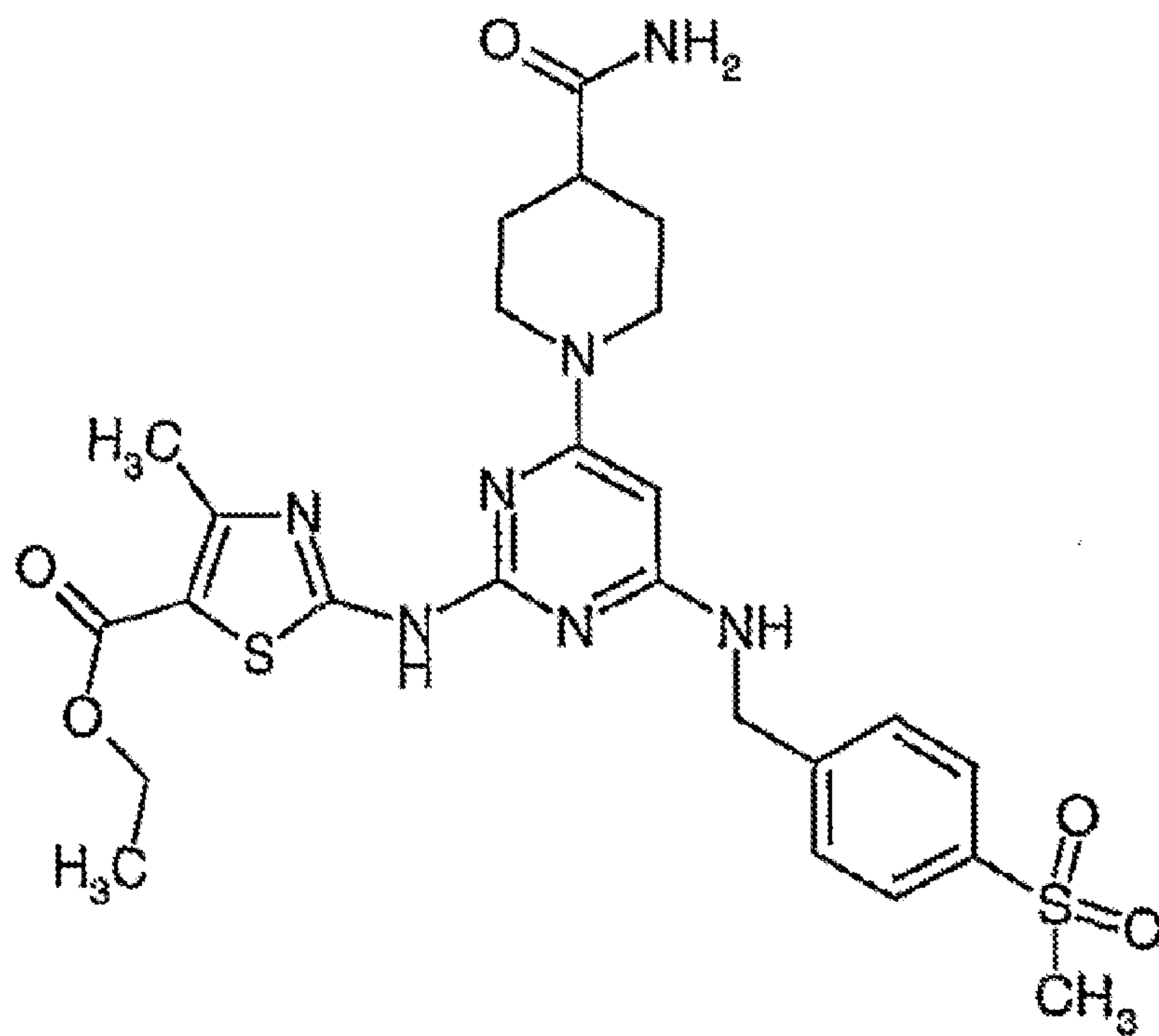
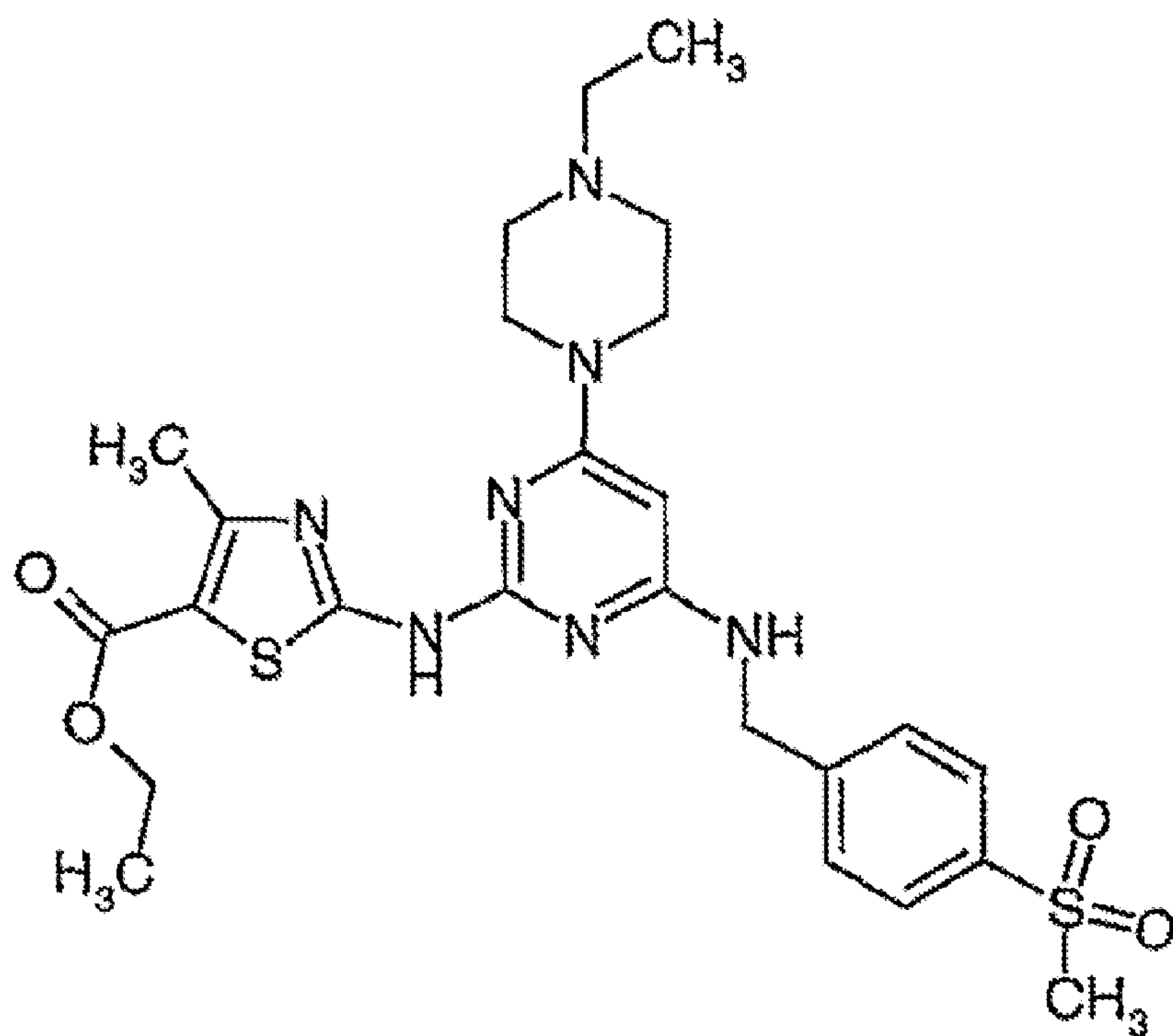
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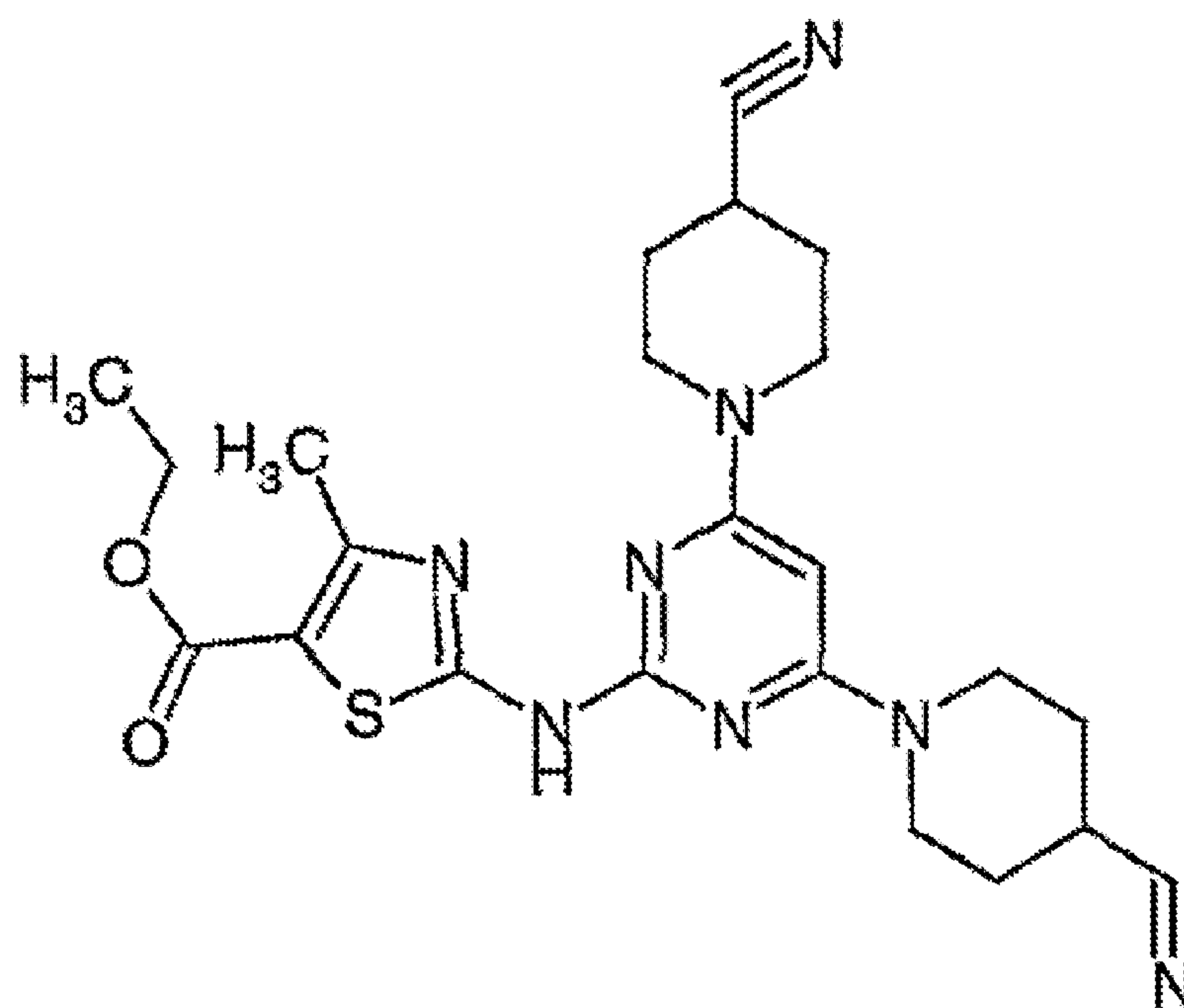
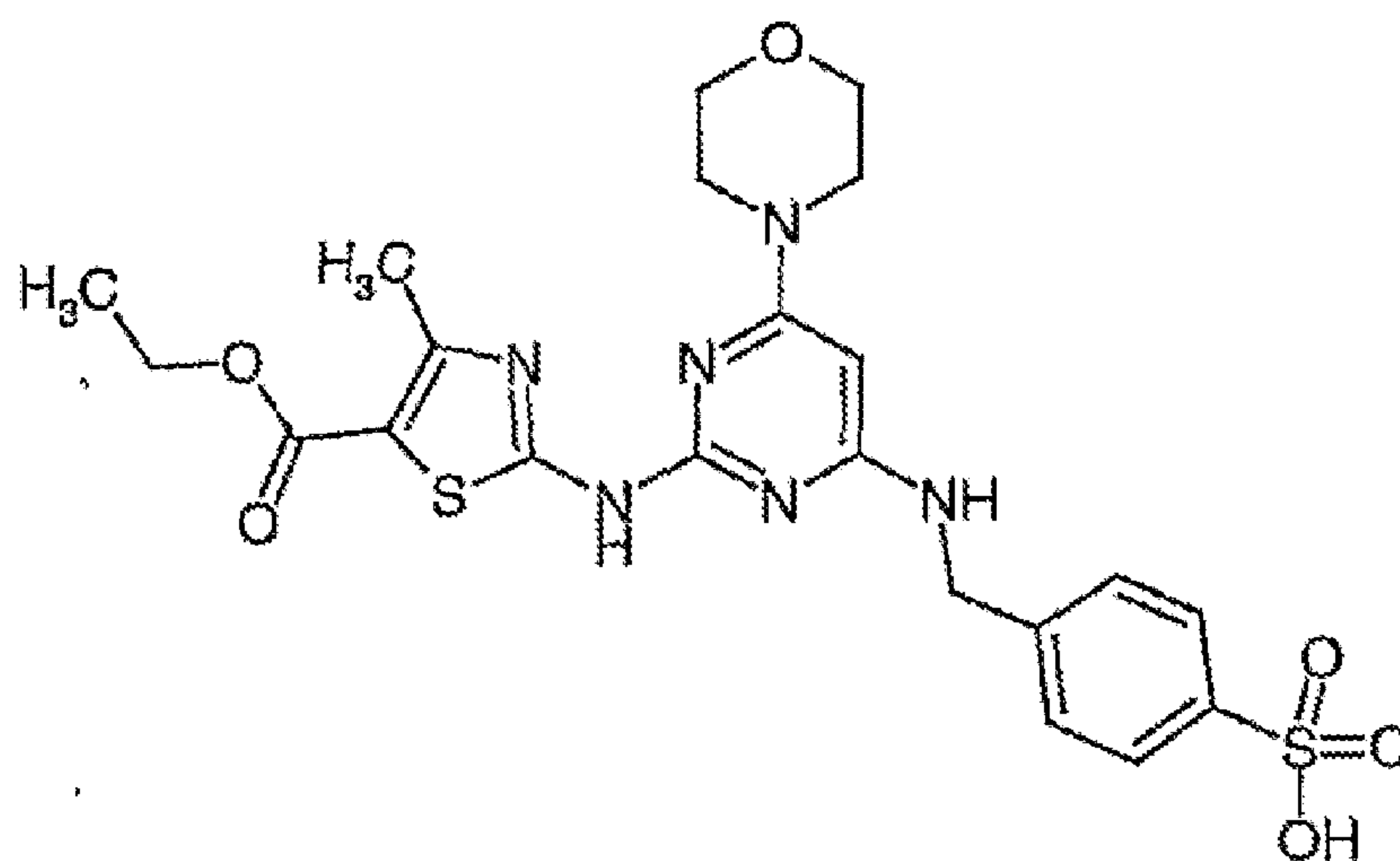
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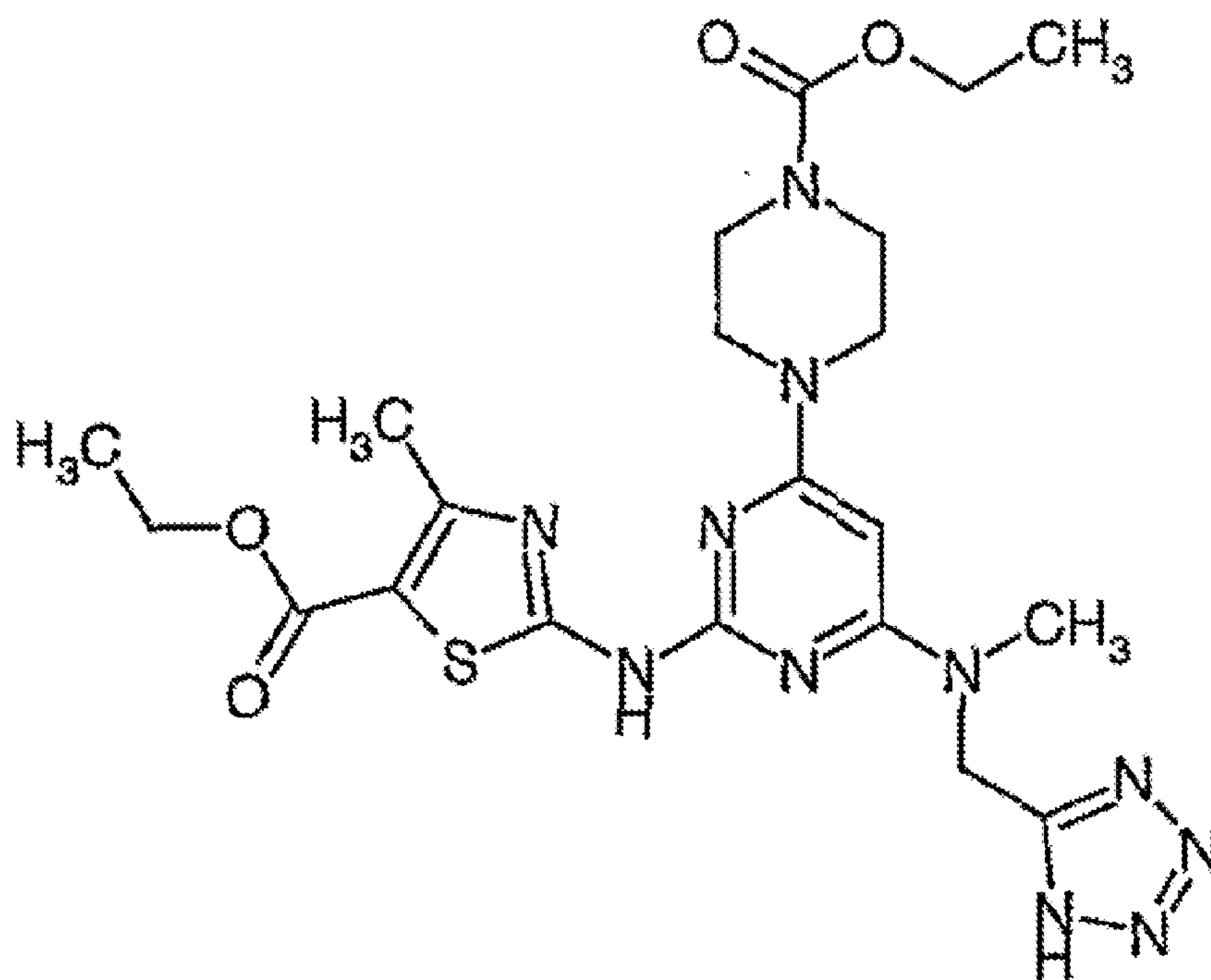
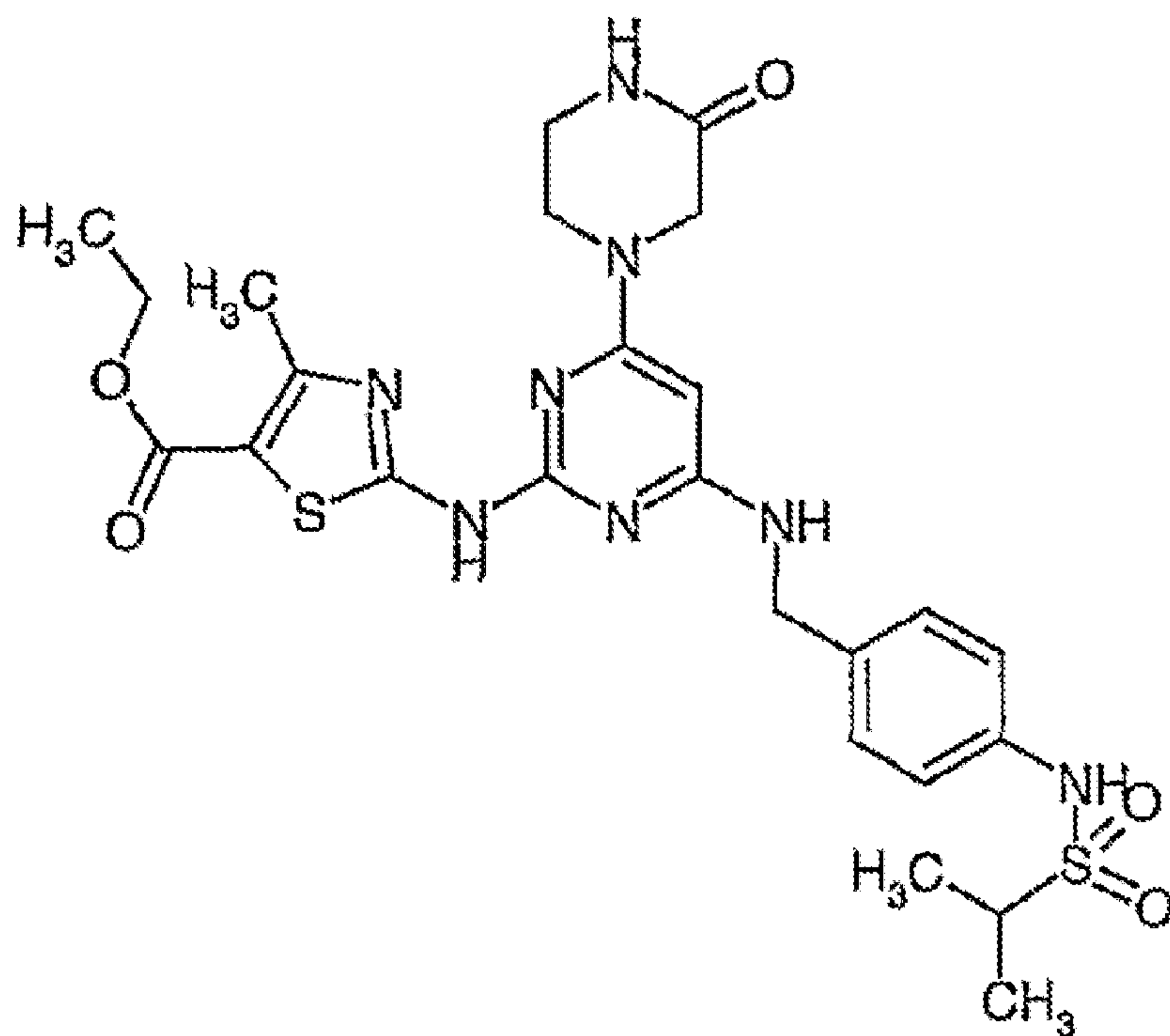
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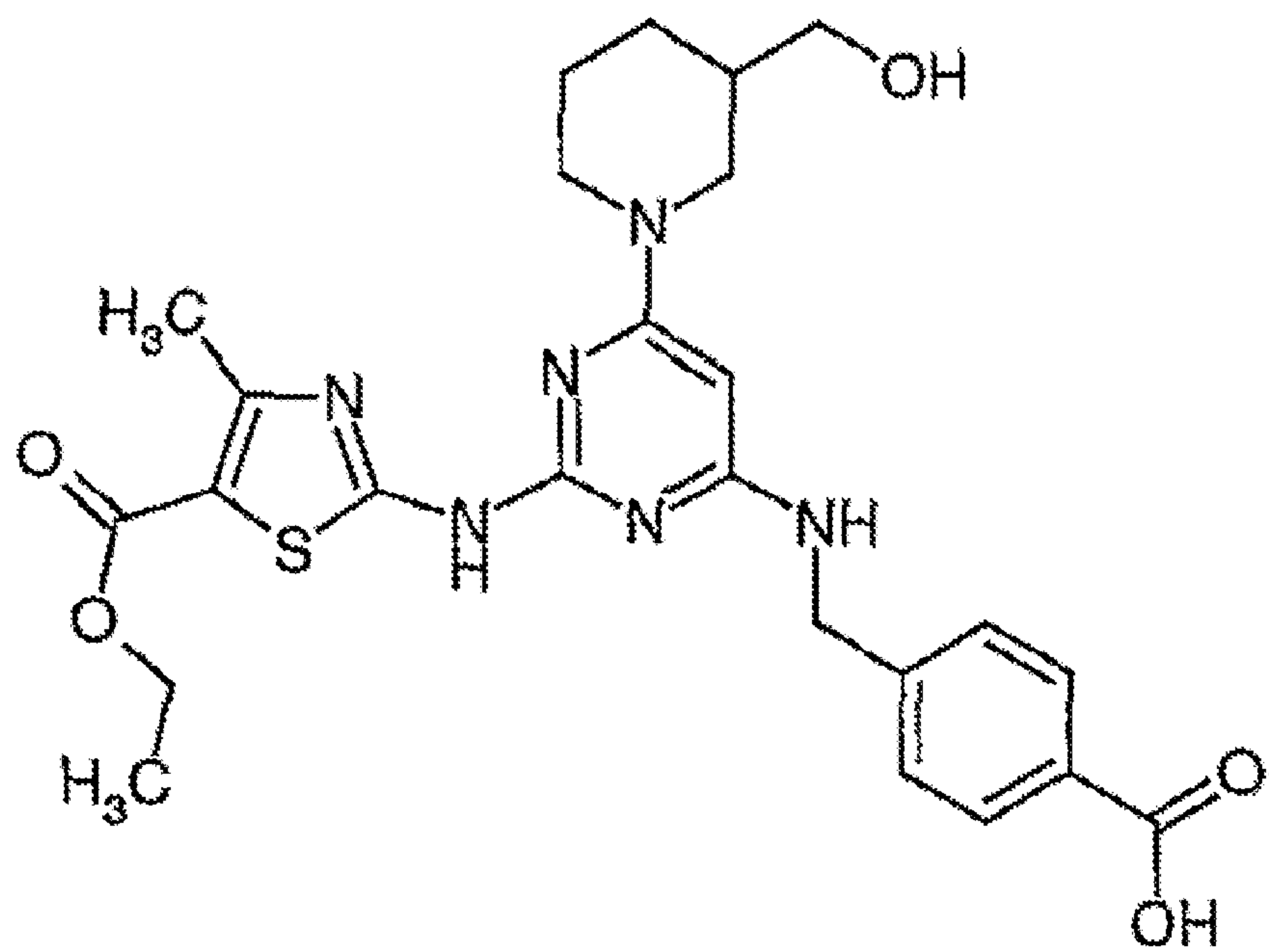
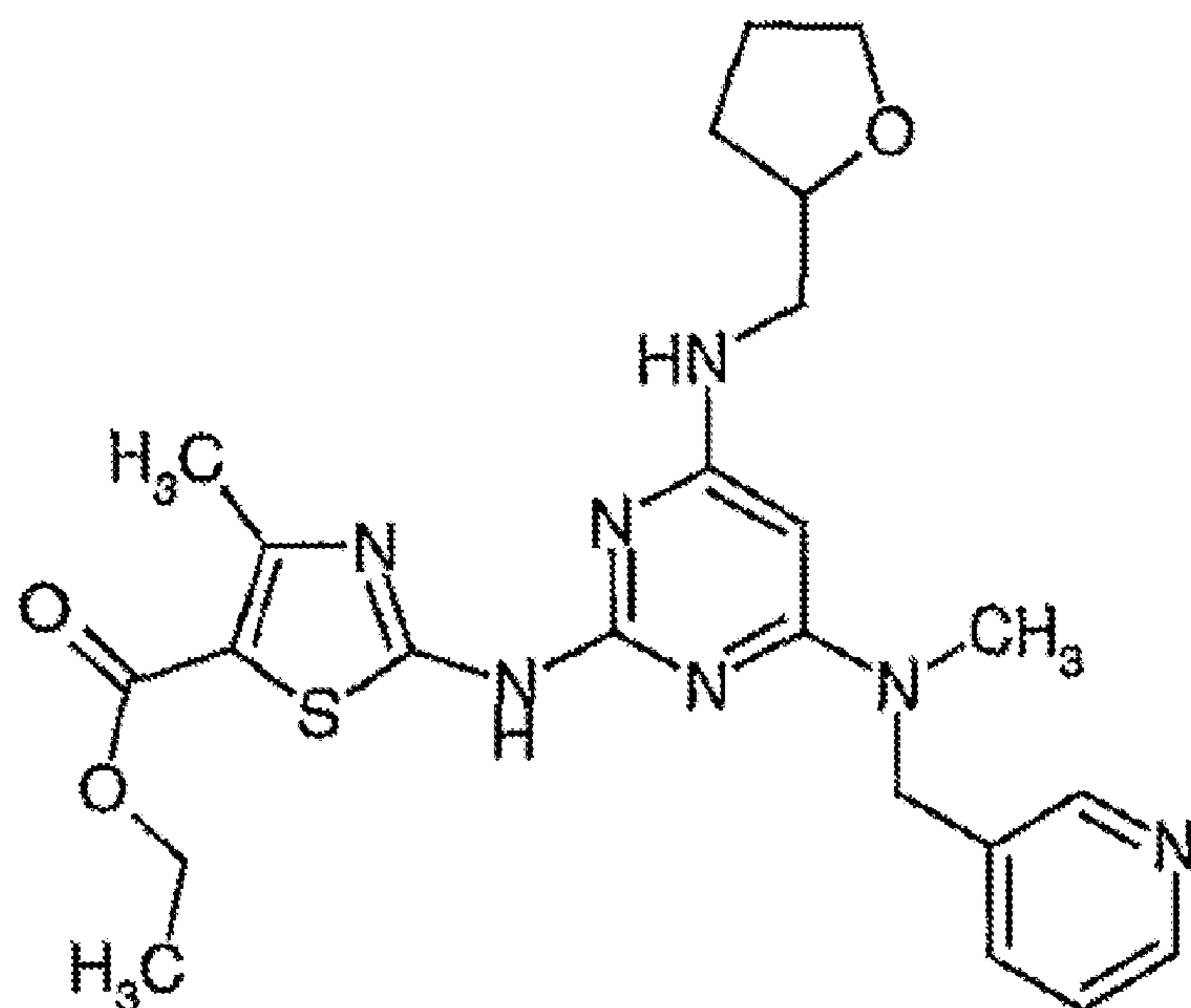
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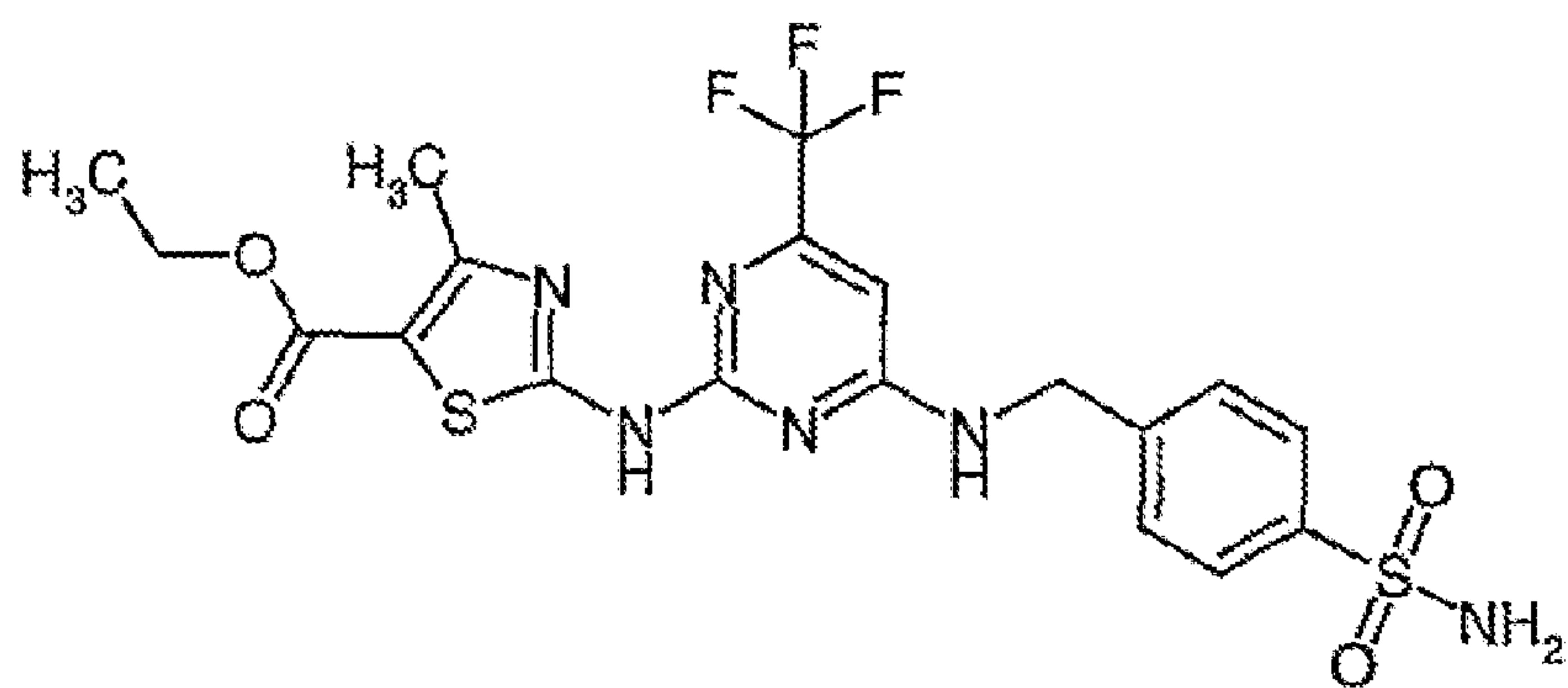
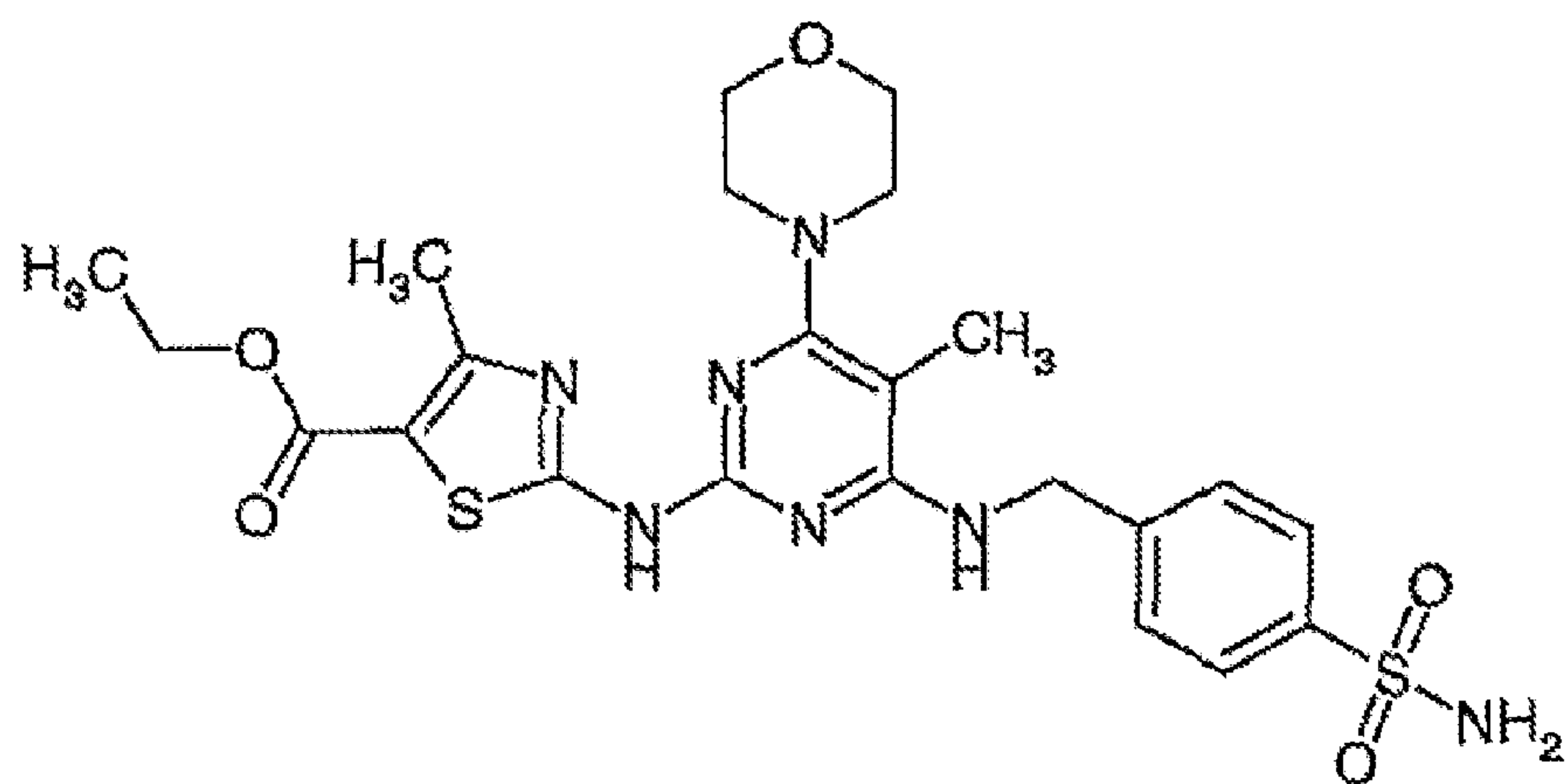
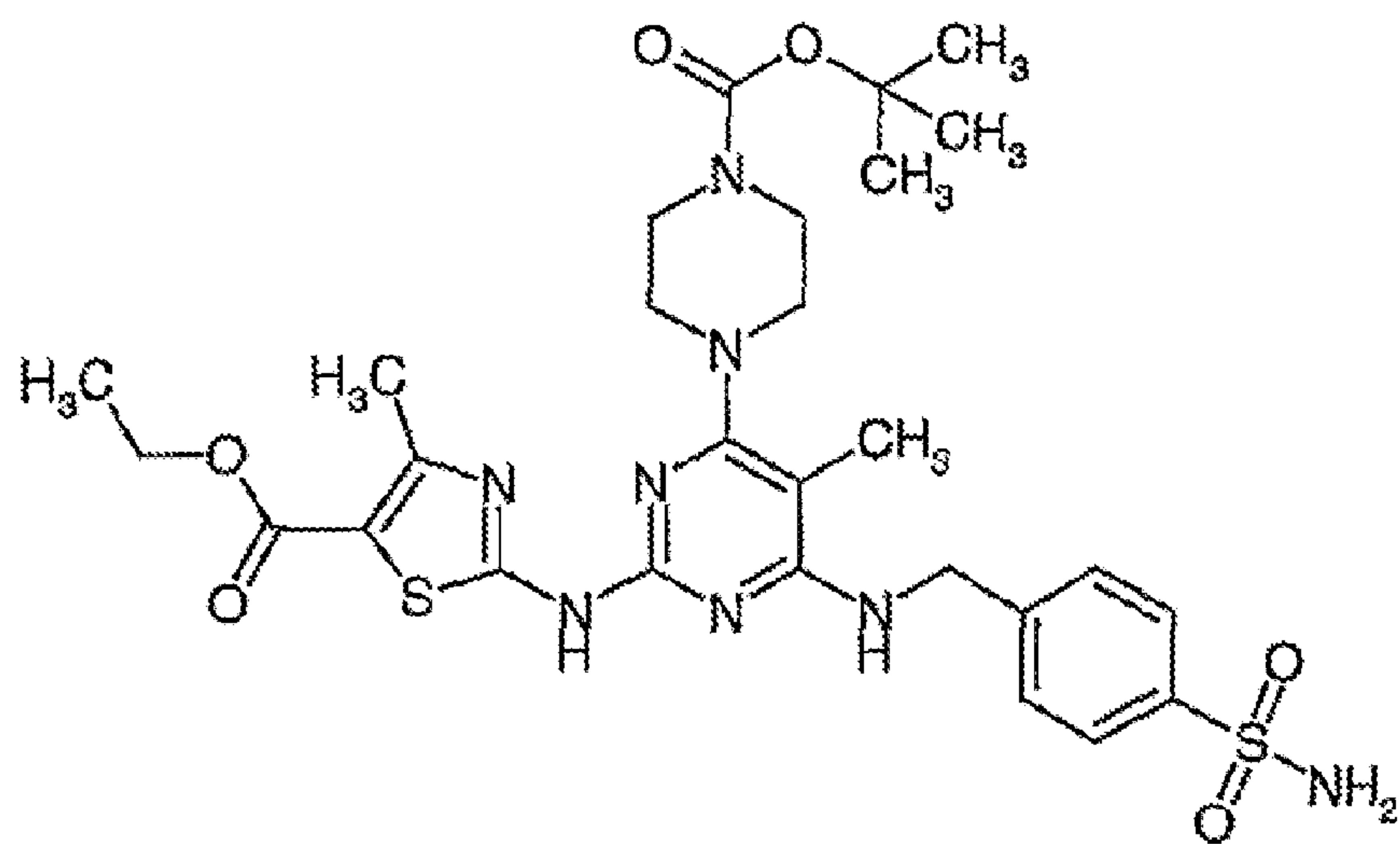
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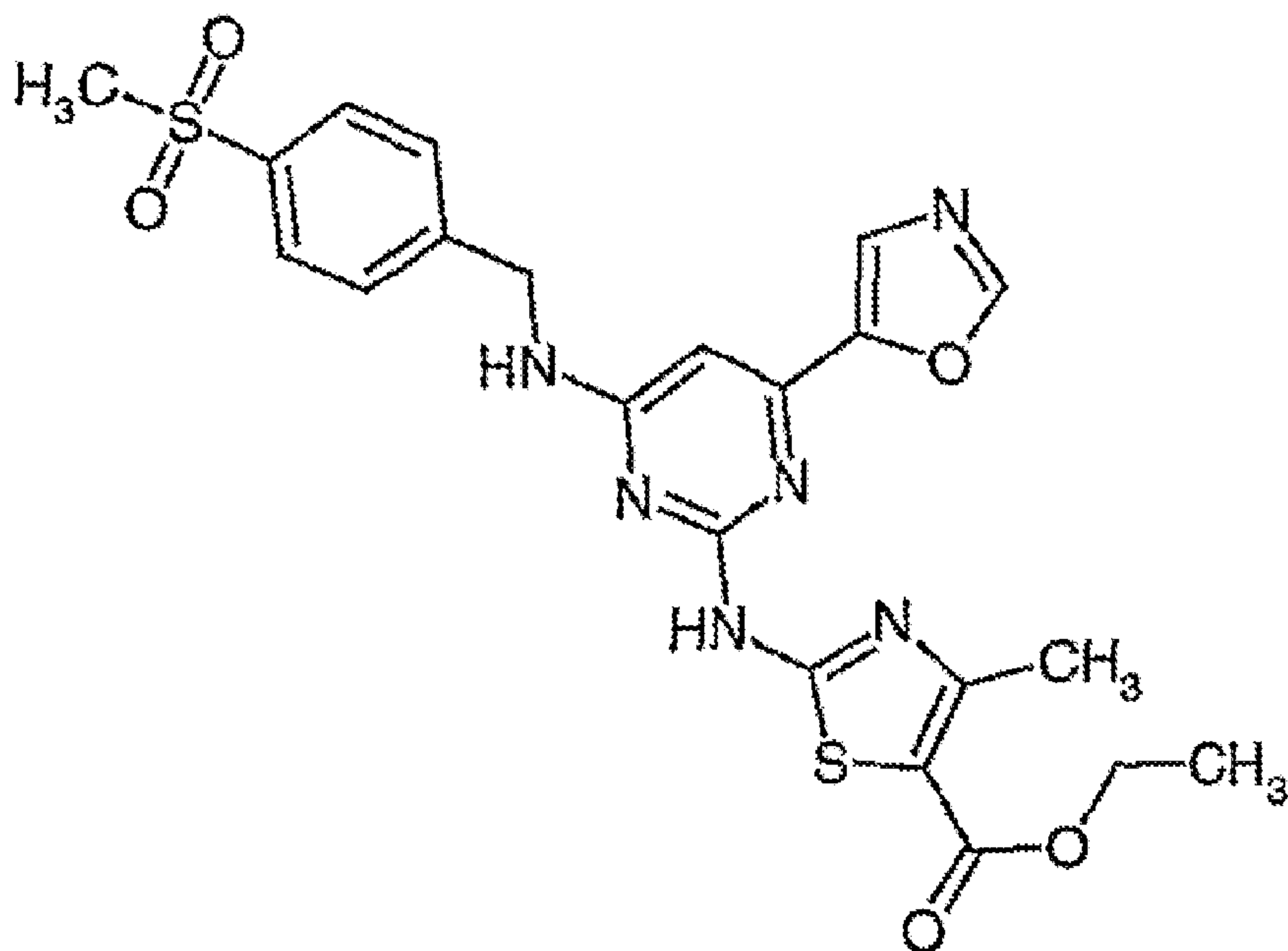
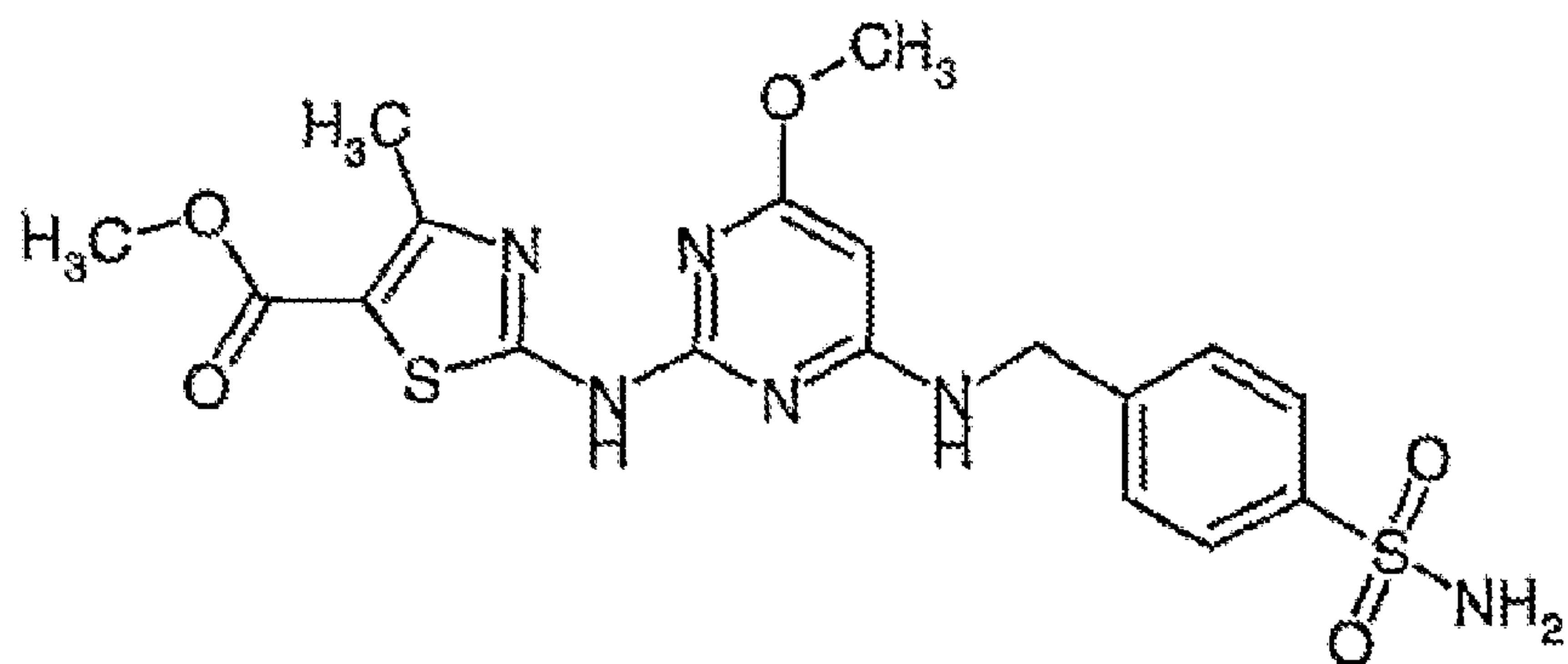
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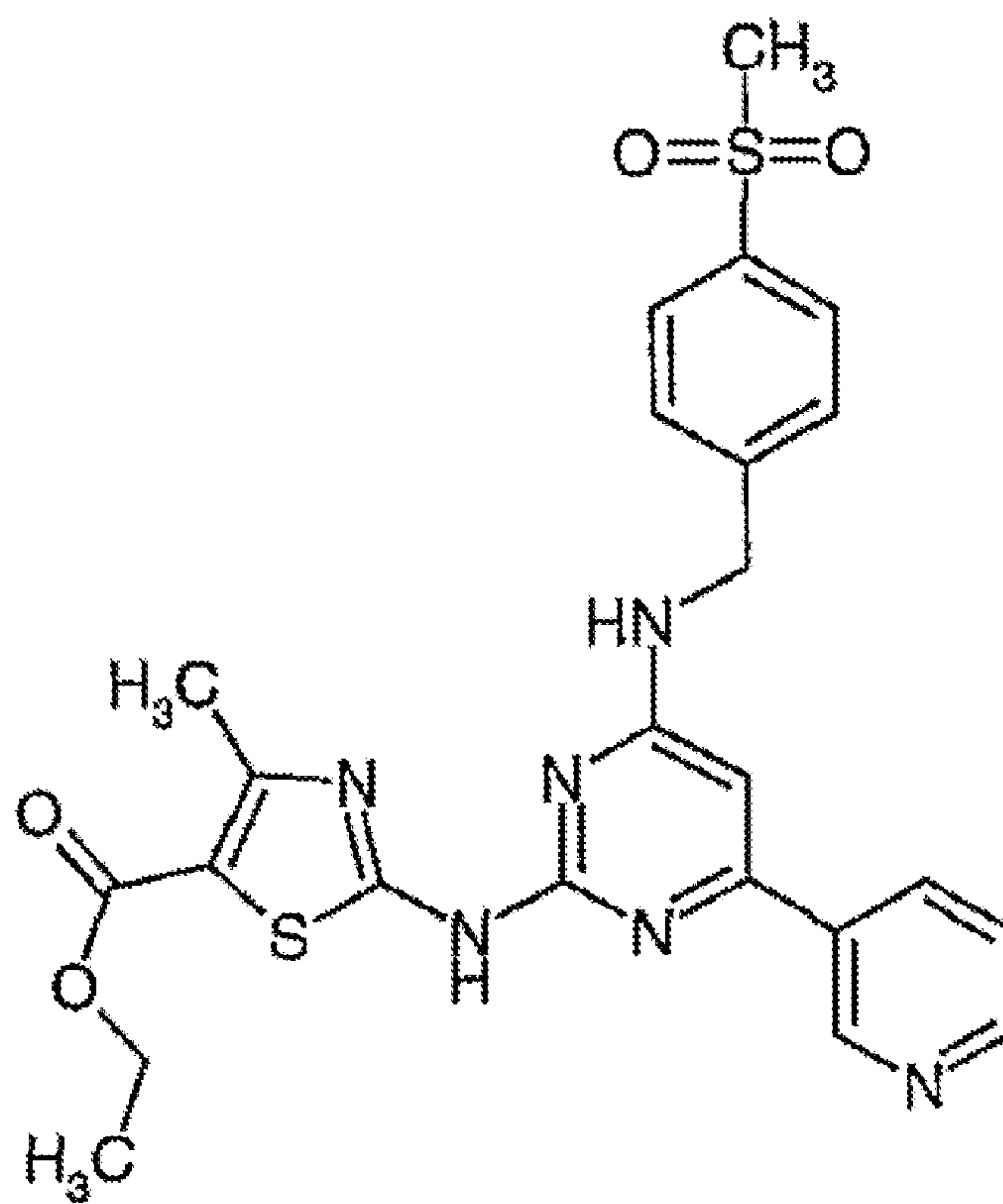
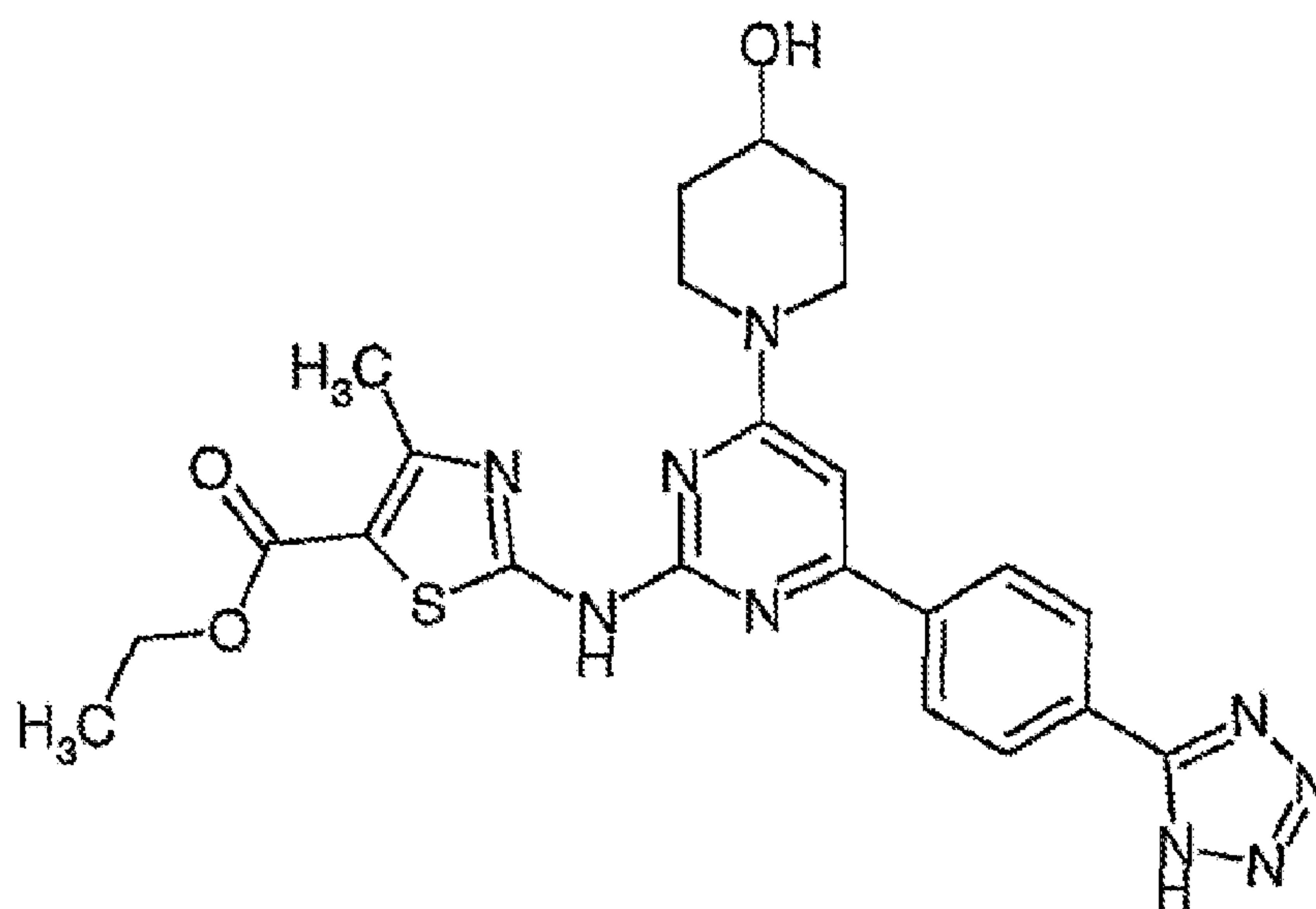
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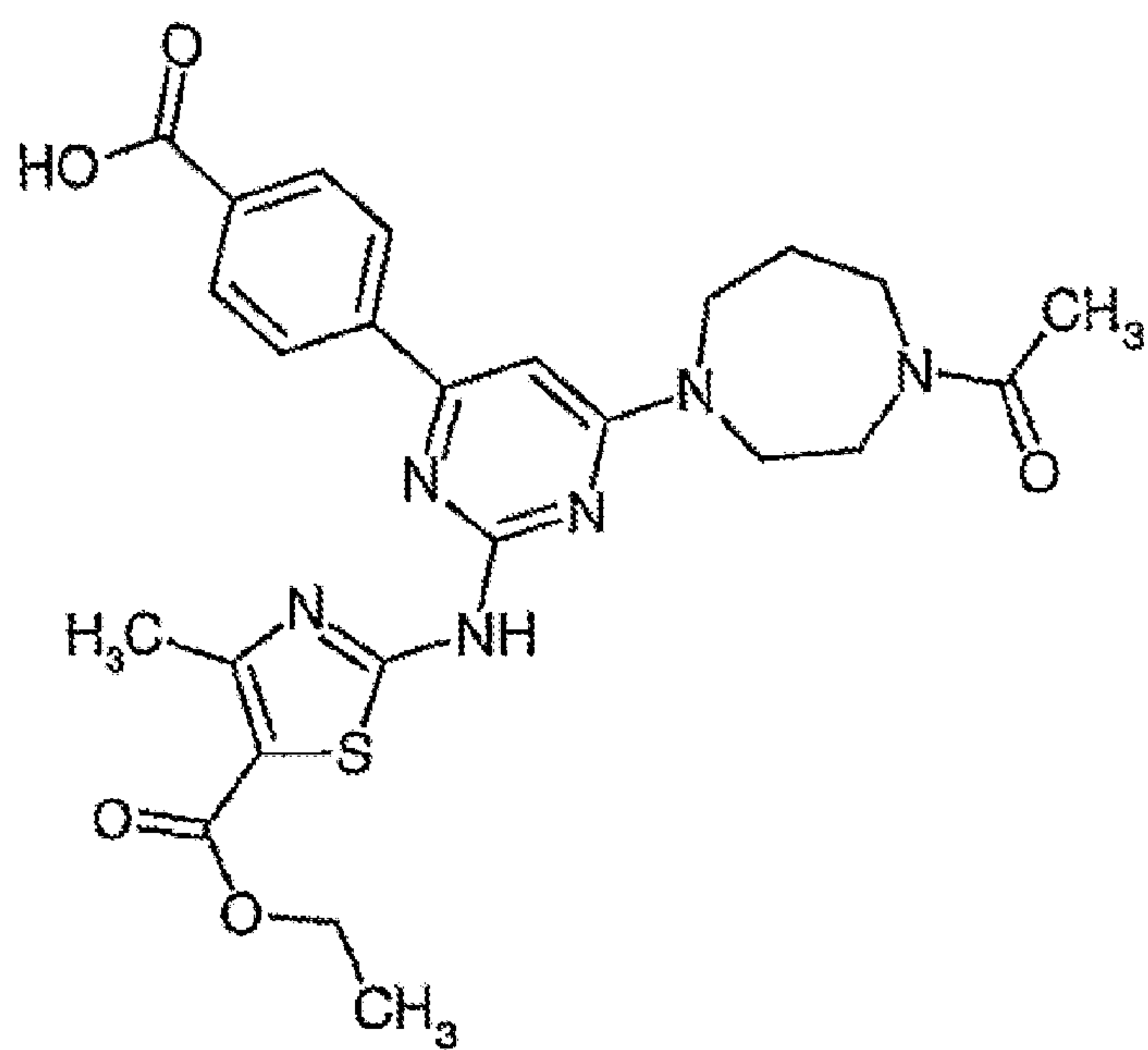
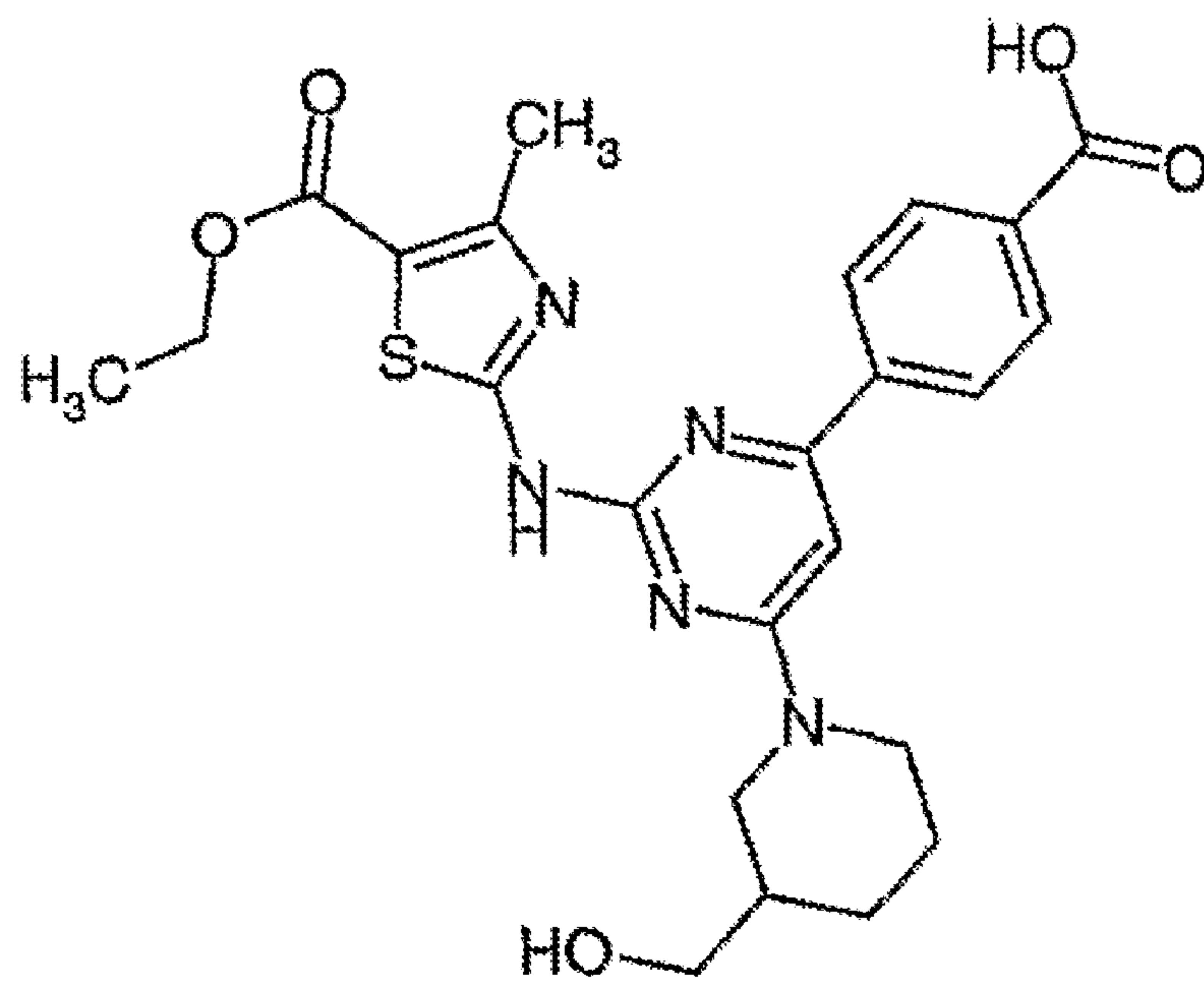
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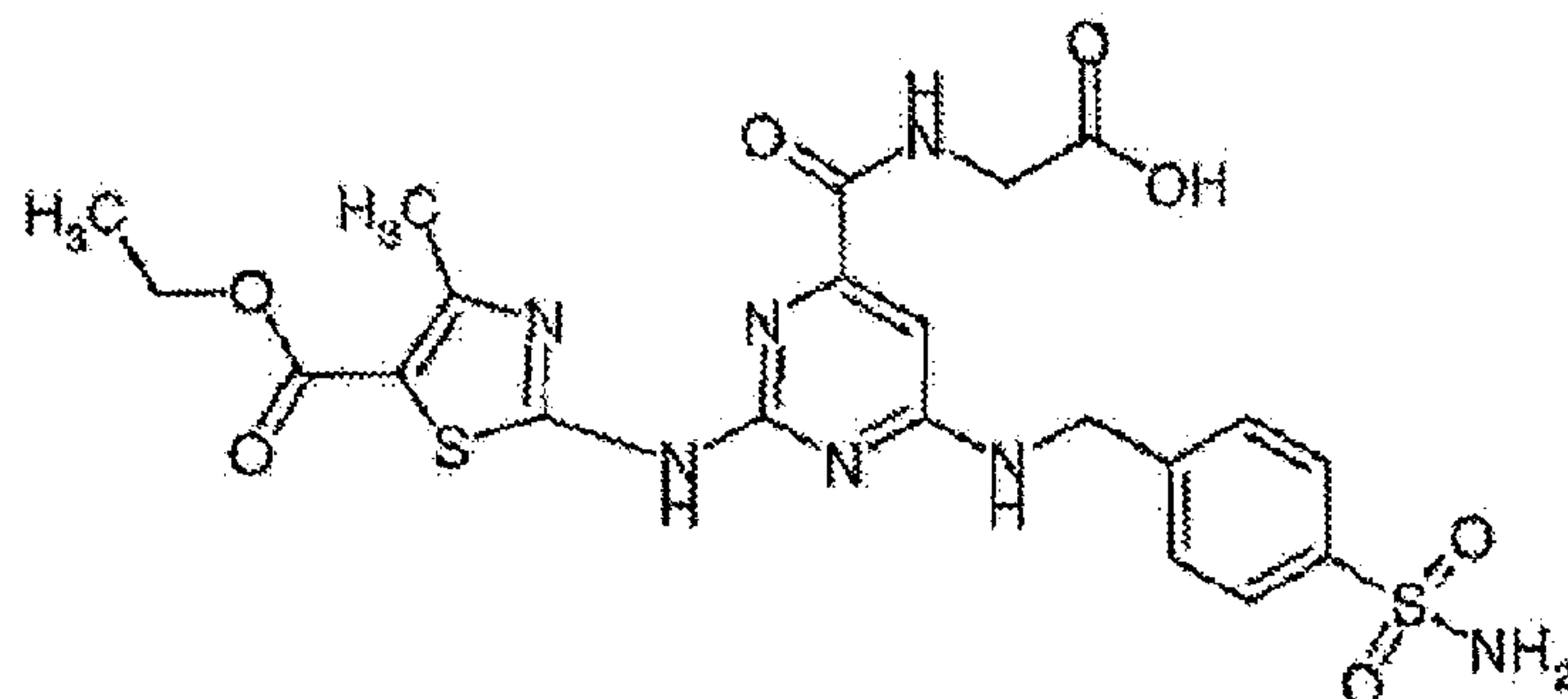


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and

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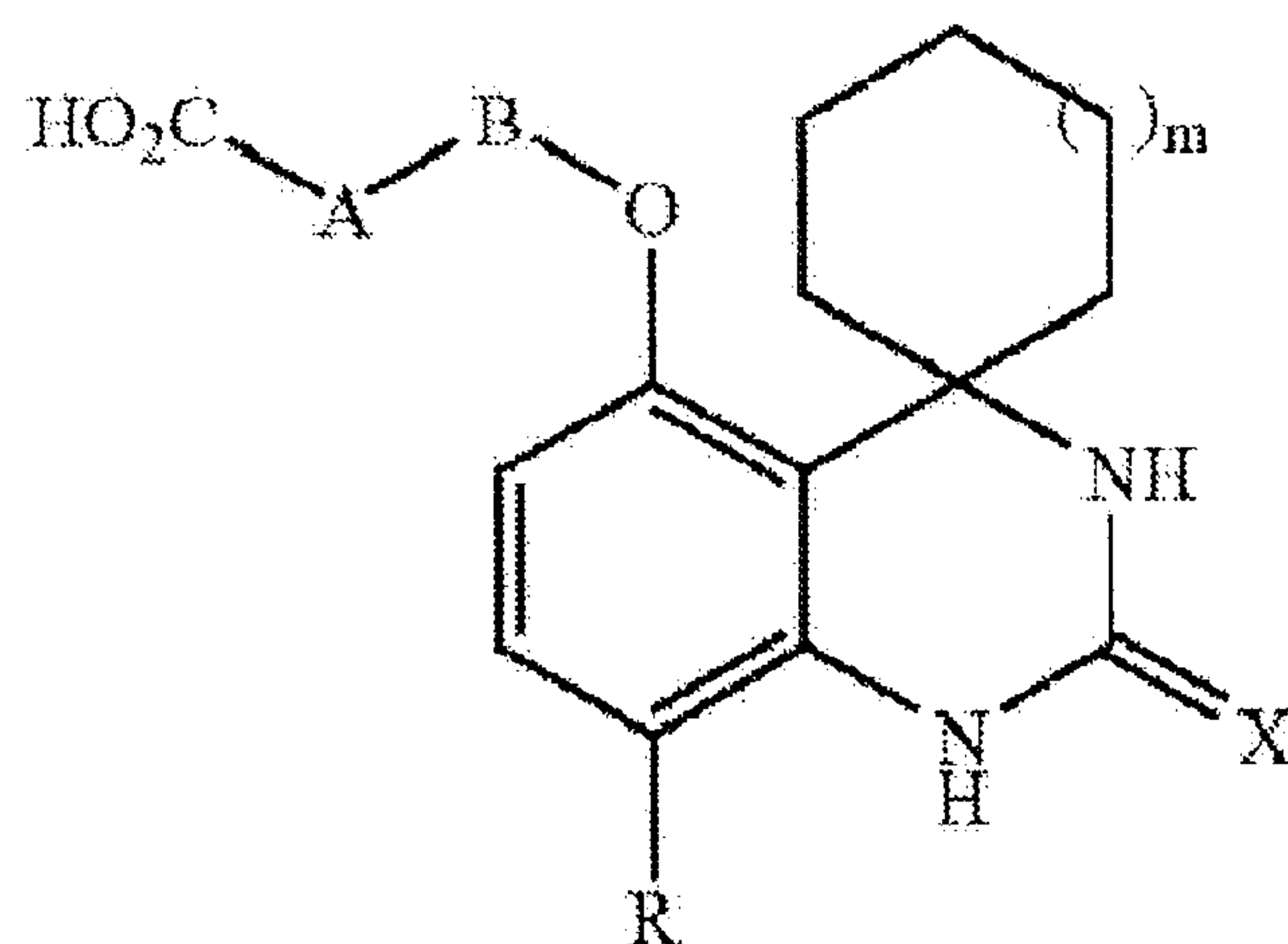
or a stereoisomer, a pharmaceutically acceptable salt, or a hydrate thereof.

The preparation of these compounds is described in U.S. Pat. No. 7,087,614, U.S. 20030162802, and WO 2002/102313.

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In another embodiment, PDE7 inhibitors useful in the methods of the invention are selected from those compounds generally or specifically disclosed in US 2007/0129388 and WO 2007/063391.

In one embodiment, PDE7 inhibitors useful in the methods of the
10 invention have the formula:



(44)

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

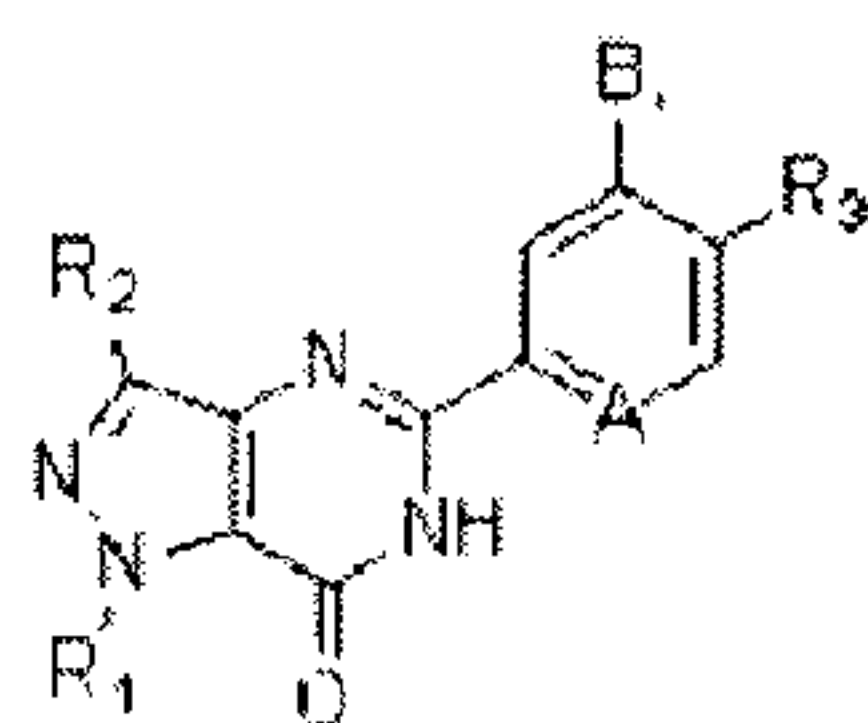
NOTE: For additional volumes please contact the Canadian Patent Office.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. Use of a phosphodiesterase 7 (PDE7) inhibitor that is selective for PDE7 relative to any other PDE enzyme from the PDE1-6 and PDE8-11 enzyme families and a dopamine receptor agonist for treating an addiction that is an addiction to an addictive substance or that is the practice of a compulsive behavior associated with a primary impulse-control disorder or an obsessive- compulsive disorder in a subject determined to have or to be at risk of developing an addiction, wherein each of the PDE7 inhibitor and the dopamine receptor agonist contribute to the effective treatment or reduction of use of the addictive agent or practice of the compulsive behavior.
2. The use of Claim 1, wherein the subject is addicted to an addictive agent selected from the group consisting of: alcohol, nicotine, marijuana, a marijuana derivative, an opioid agonist, a benzodiazepine, a barbiturate, and a psychostimulant.
3. The use of Claim 1, wherein the addiction is a compulsive behavior associated with a primary impulse-control disorder or an obsessive- compulsive disorder selected from the group consisting of: binge eating, food addiction, pathological gambling, pathological use of electronic devices, pathological use of electronic video games, pathological use of electronic communication devices, pathological use of cellular telephones, addiction to pornography, sex addiction, compulsive spending, anorexia, bulimia, intermittent explosive disorder, kleptomania, pyromania, trichotillomania, compulsive over- exercising, and compulsive overworking.
4. The use of Claim 1, wherein the dopamine receptor agonist is selected from bromocriptine, pergolide, pramipexole, ropinirole, cabergoline, apomorphine, lisuride, rotigotine, quinagolide and fenoldopam.
5. The use of Claim 1, wherein the selective PDE7 inhibitor has an IC_{50} for inhibiting PDE7A, PDE7B, or PDE7A and PDE7B for which the lesser of the IC_{50} for inhibiting PDE7A

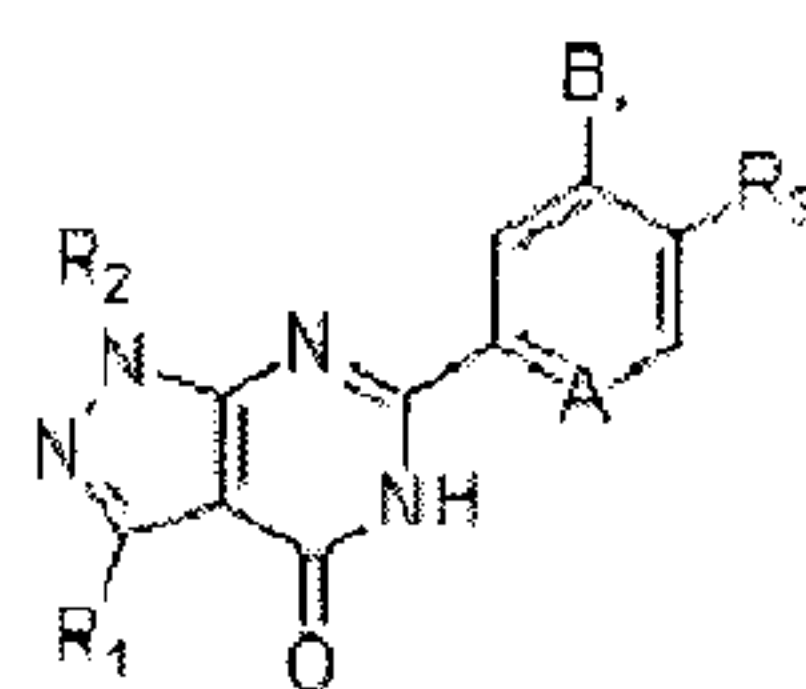
activity and the IC₅₀ for inhibiting PDE7B activity is less than one-tenth the IC₅₀ that the agent has for inhibiting the activity of any other PDE enzyme from the PDE1-6 and PDE8-11 enzyme families.

6. The use of Claim 1, wherein the PDE7 inhibitor is:



(1A)

or



(1B)

wherein:

A is N or CR₄;

B is a hydrogen or a halogen atom;

R₁ is optionally substituted C₃₋₇ cycloalkyl or tert-butyl;

R₂ is hydrogen, methyl, or ethyl;

R₃ is hydrogen, nitro, cyano or halogen, NR₅R₆, C(=X)R₇, SO₂NR₅R₆, OR₈, NR₈CONR₅R₆, NR₈SO₂R₉, NR₈CO₂R₉, a heteroaryl group, optionally substituted C₁₋₃ alkyl, optionally substituted C₁₋₆ alkenyl, or optionally substituted saturated or unsaturated heterocycloalkyl;

R₄ is hydrogen, or C₁₋₃ alkoxy substituted by one or more fluorine atoms;

R₅ and R₆ are the same or different, and are a hydrogen atom, optionally substituted C₁₋₆ alkyl, optionally substituted heterocycloalkyl, or optionally substituted acyl or, together with the nitrogen atom which they are bound to, form azetidiny, pyrrolidinyl, piperidinyl, morpholino, thiomorpholino, piperazinyl, or homopiperazinyl, each of these groups being optionally

substituted by optionally substituted C₁₋₄ alkyl, OH, C₁₋₃ alkoxy, CO₂H, NR₅R₆, an oxo group, NR₉COR₇, or C(=O)R₇;

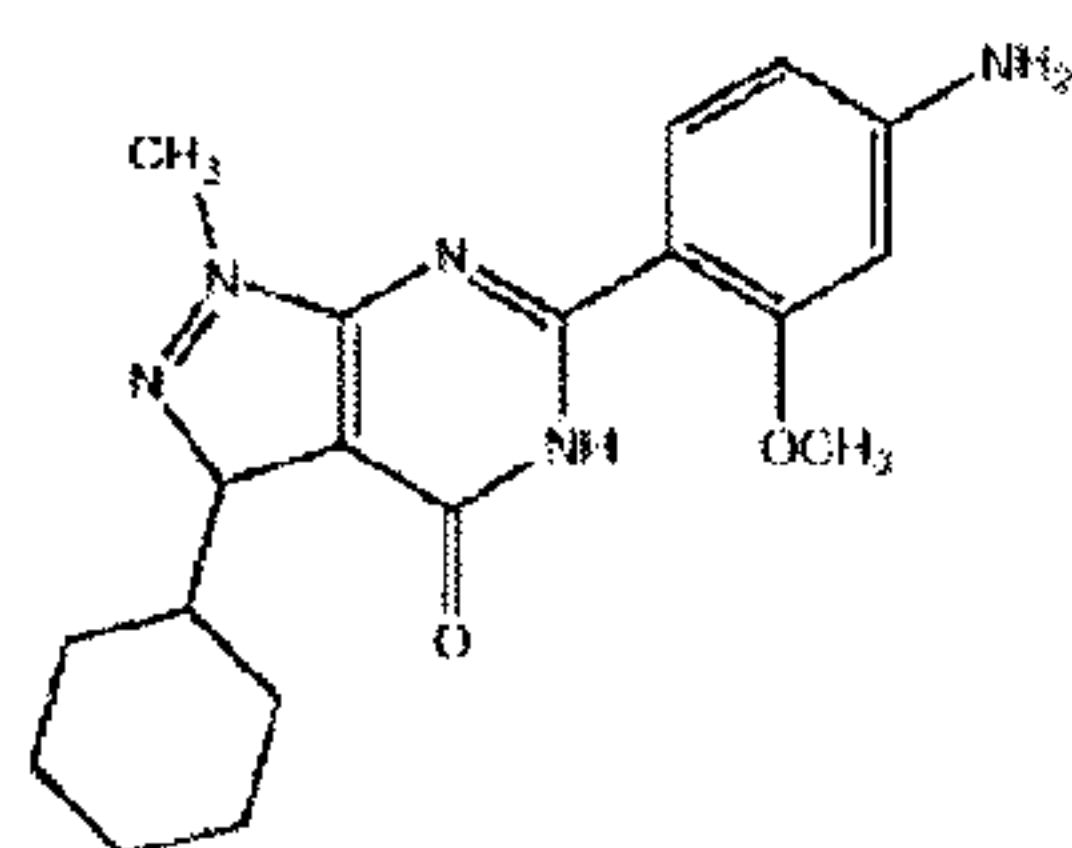
R₇ is optionally substituted C₁₋₆ alkyl, OH, OR₈, or NR₅R₆;

R₈ is hydrogen, an optionally substituted C₁₋₆ alkyl group, or optionally substituted heterocycloalkyl;

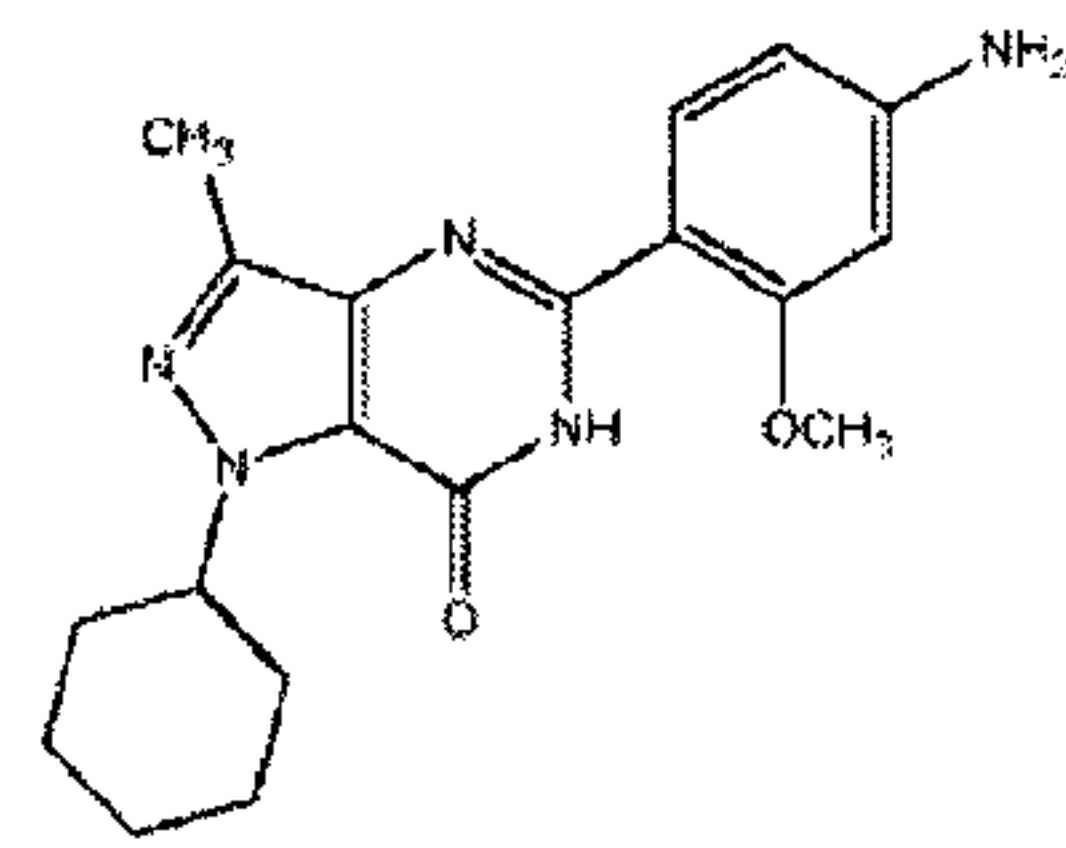
R₉ is an optionally substituted C₁₋₆ alkyl group; and

X represents O, S, or NH.

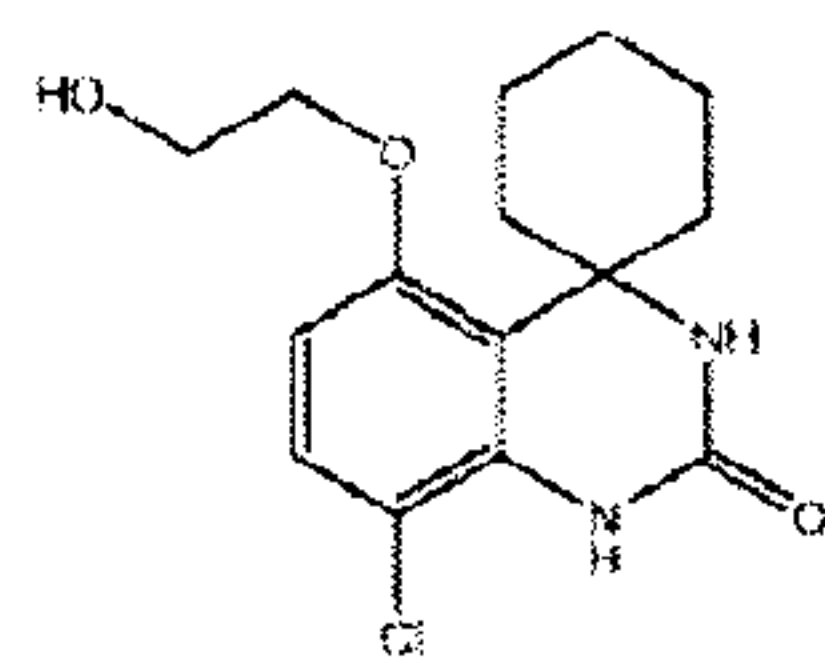
7. The use of Claim 1, wherein the PDE7 inhibitor is selected from the following compounds:



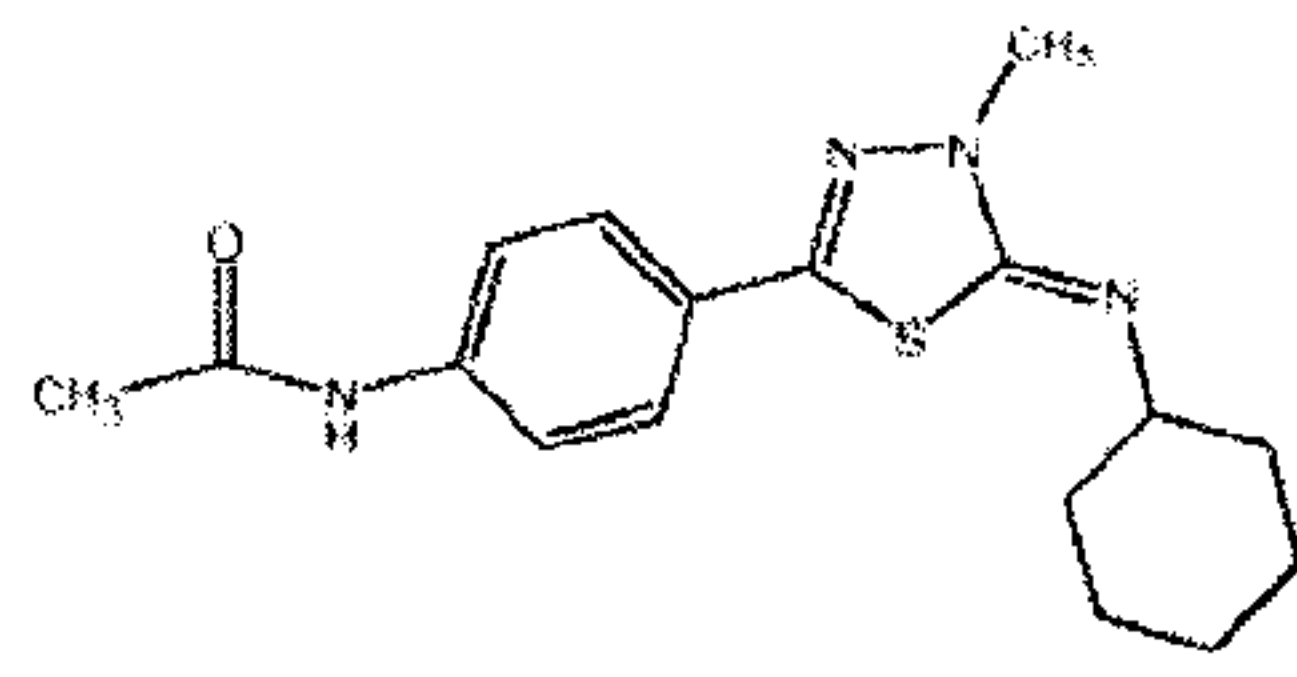
(1);



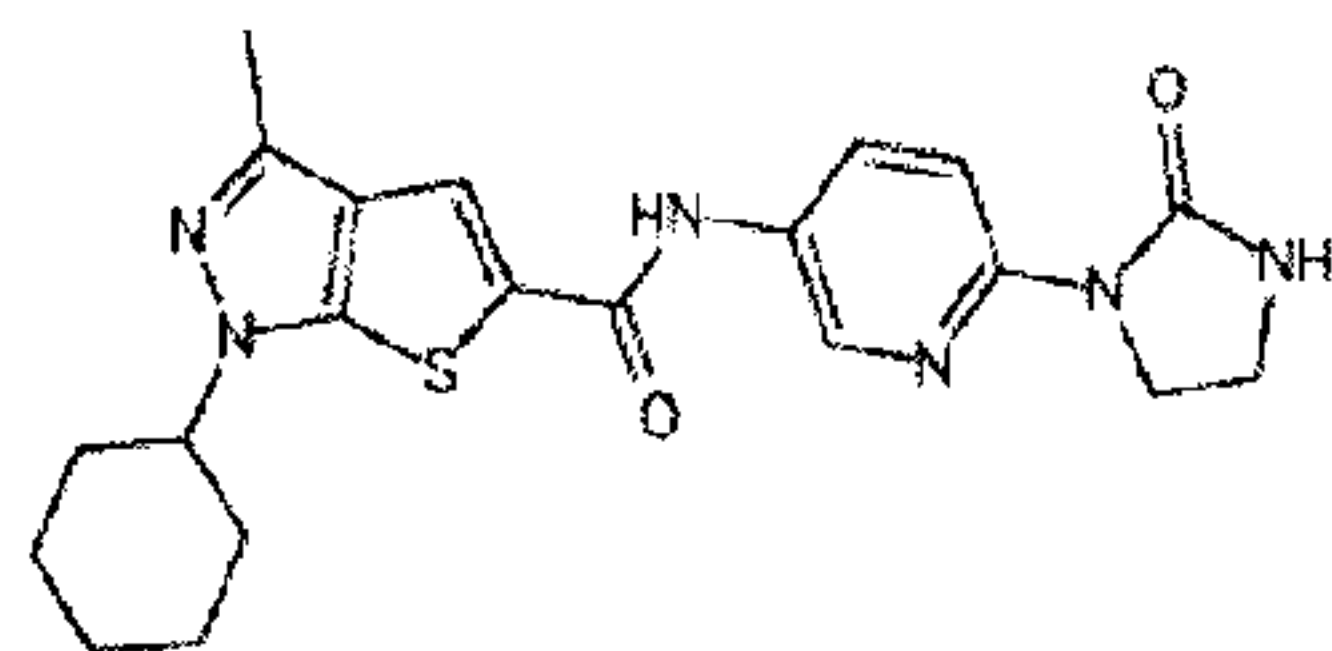
(2);



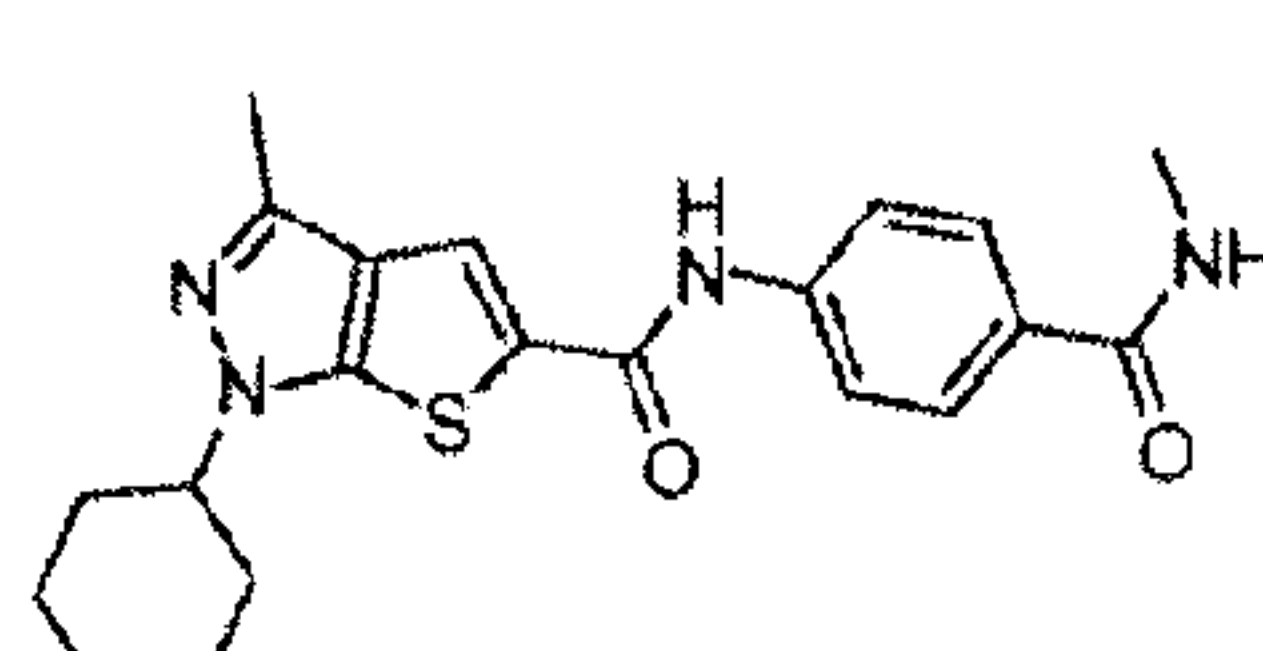
(3);



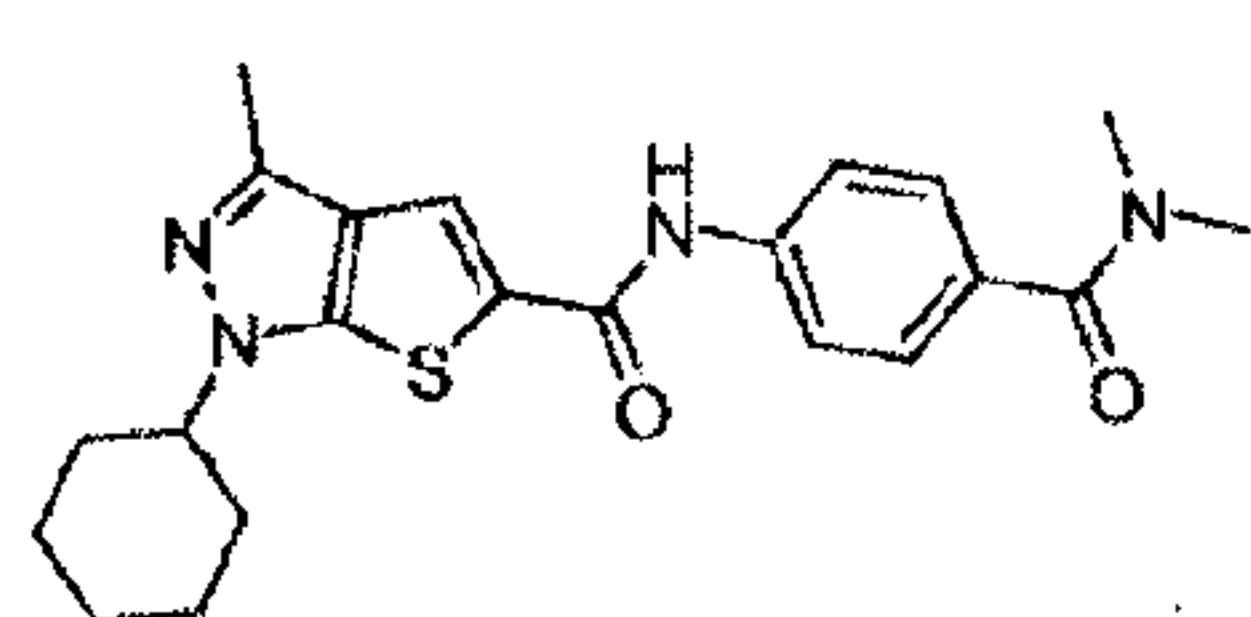
(4);



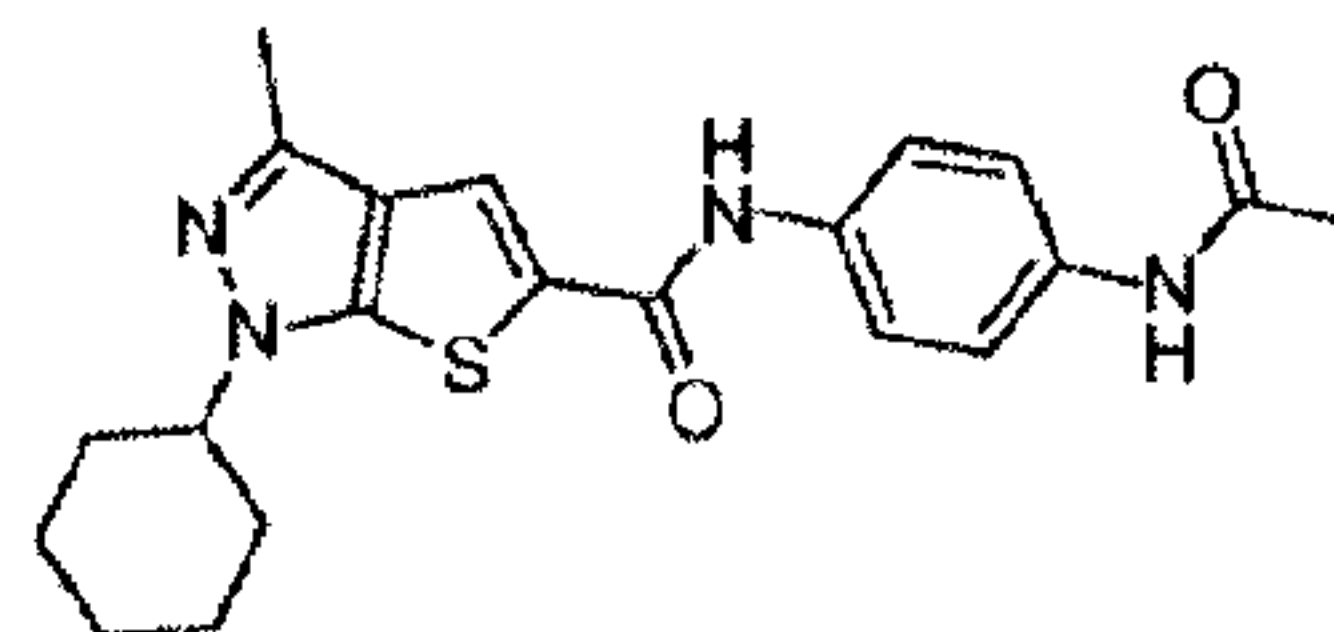
(6A);



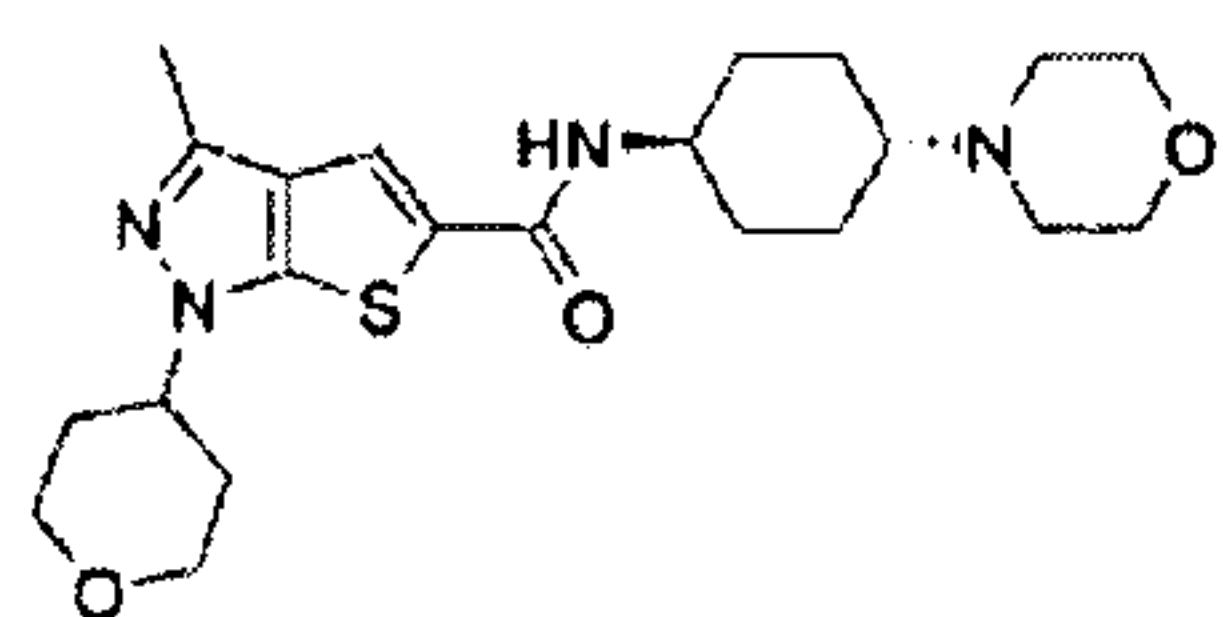
(6B);



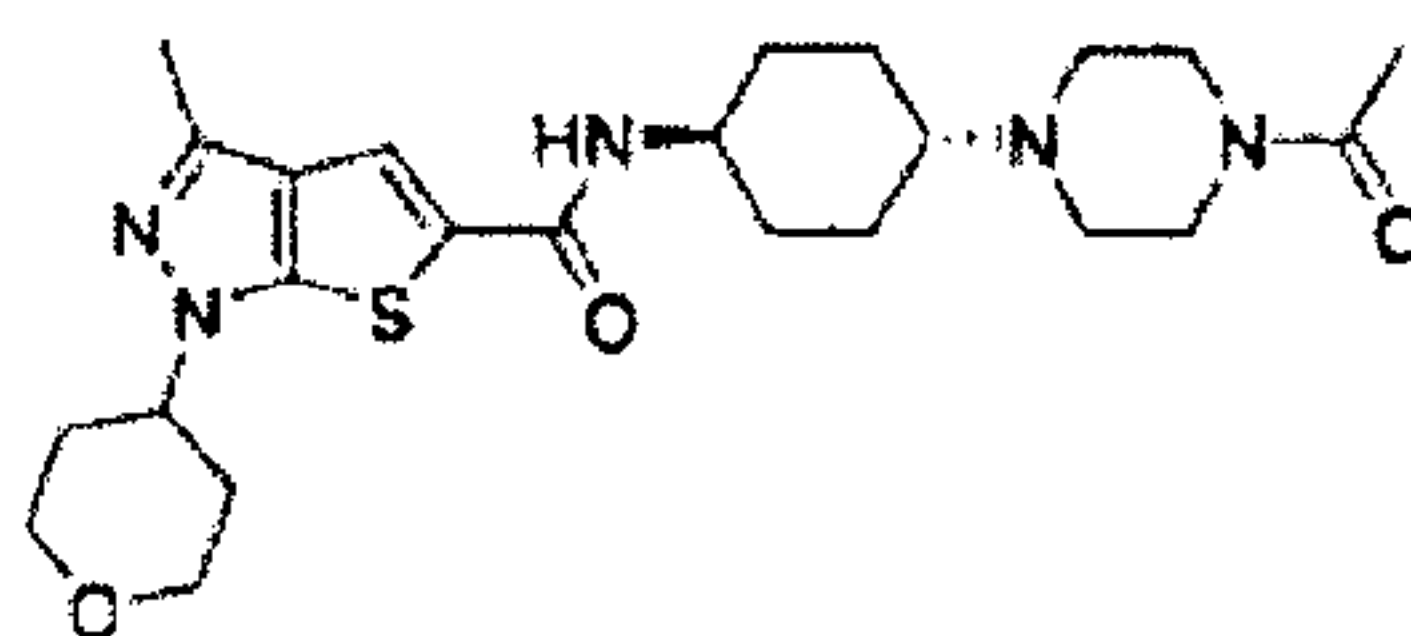
(6C);



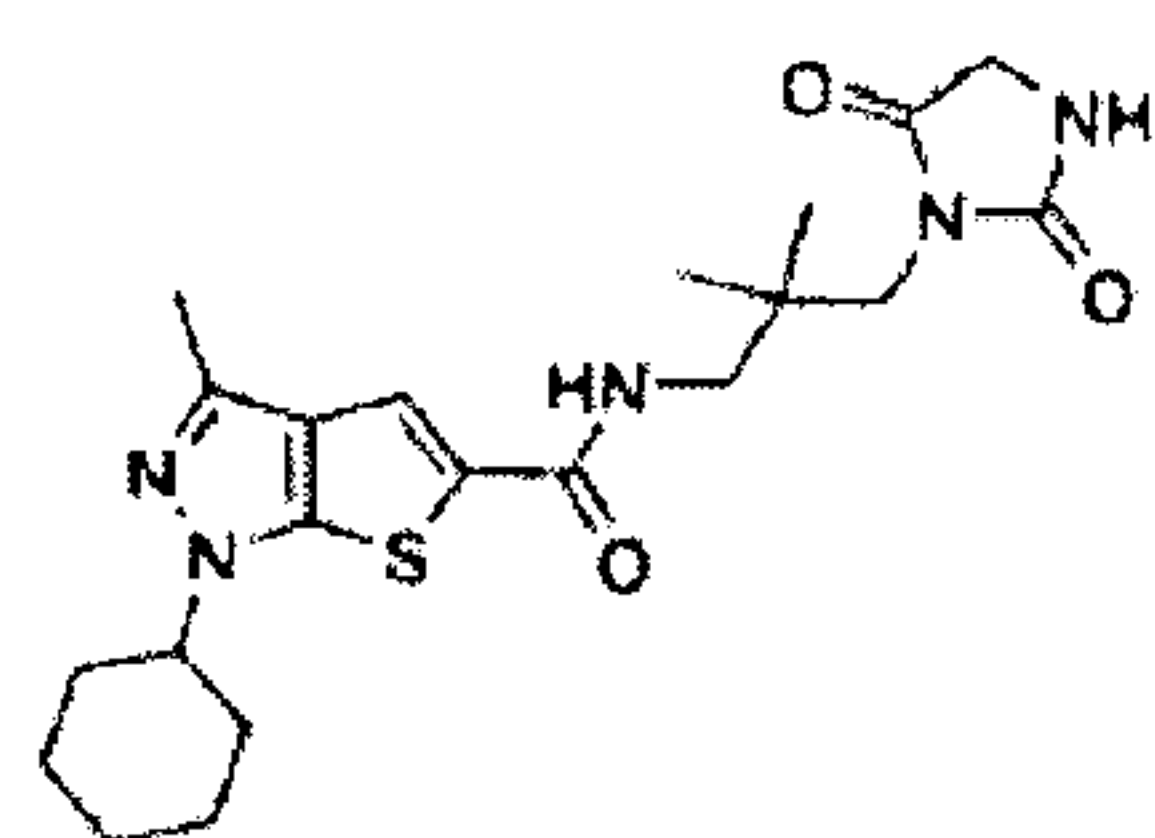
(6D);



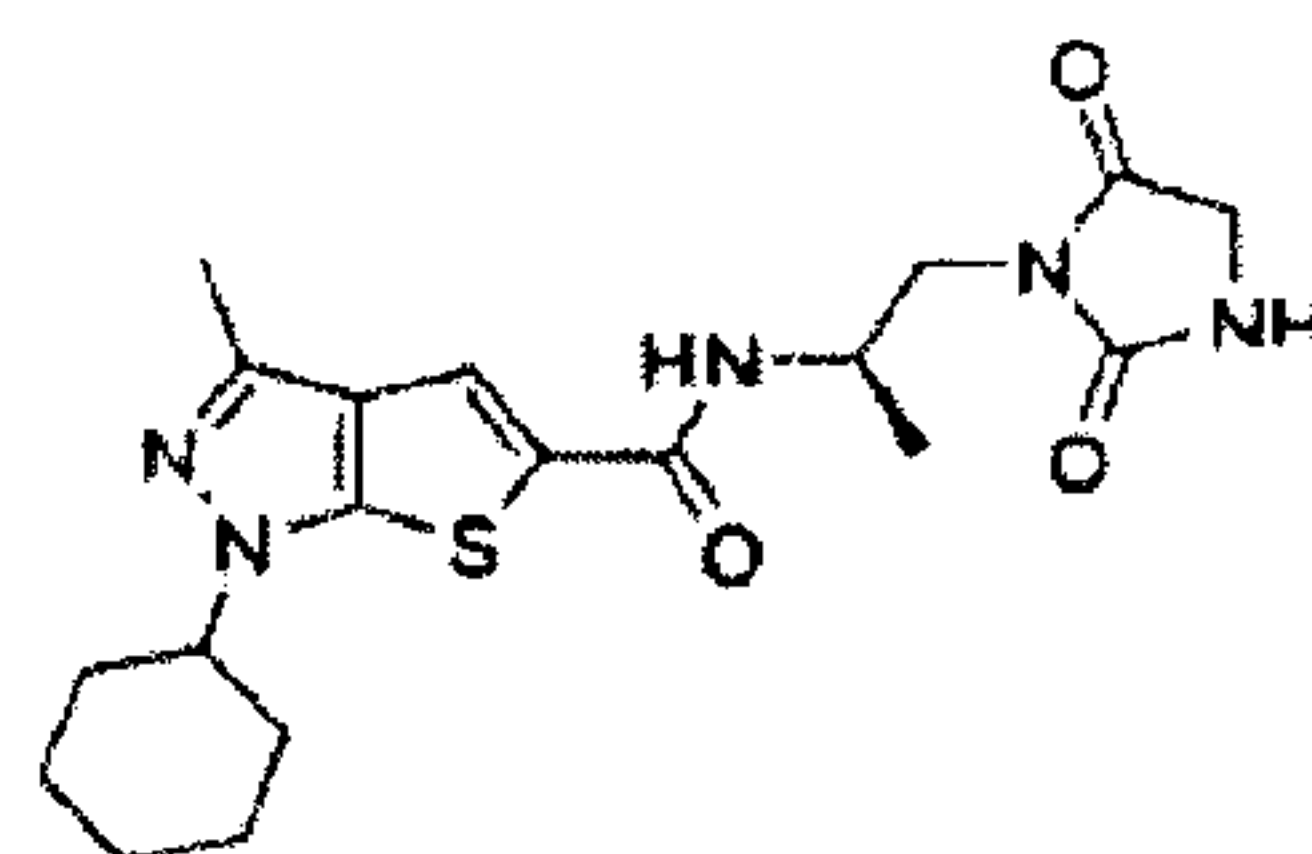
(6E);



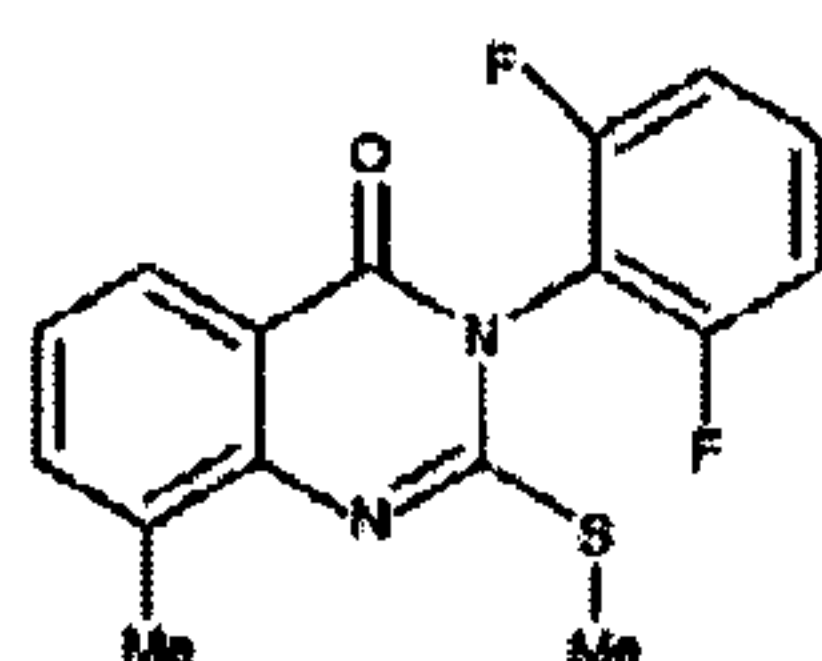
(6F);



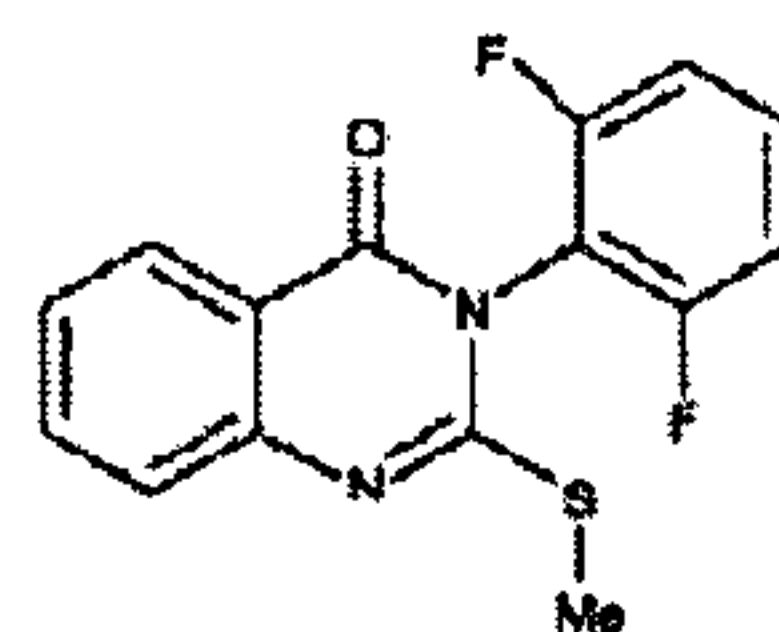
(6G);



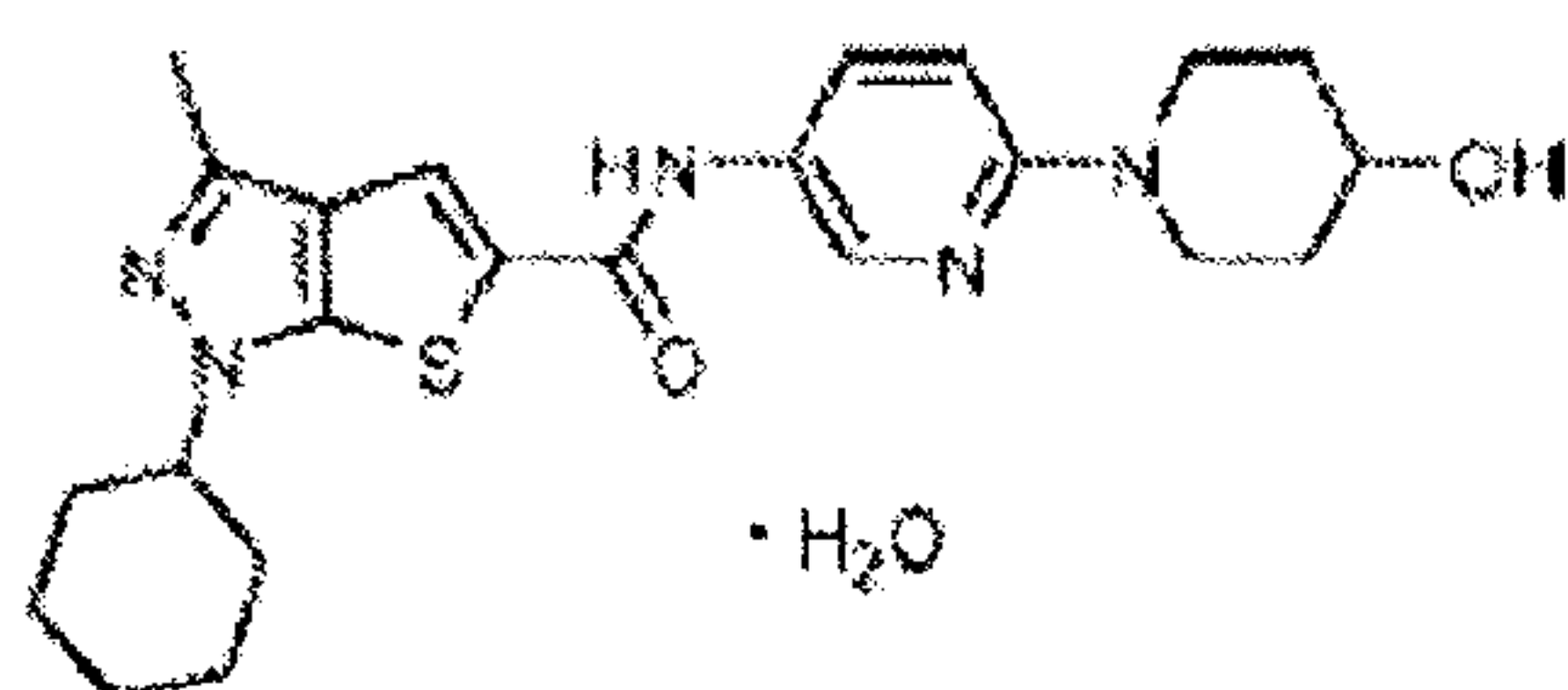
(6H);



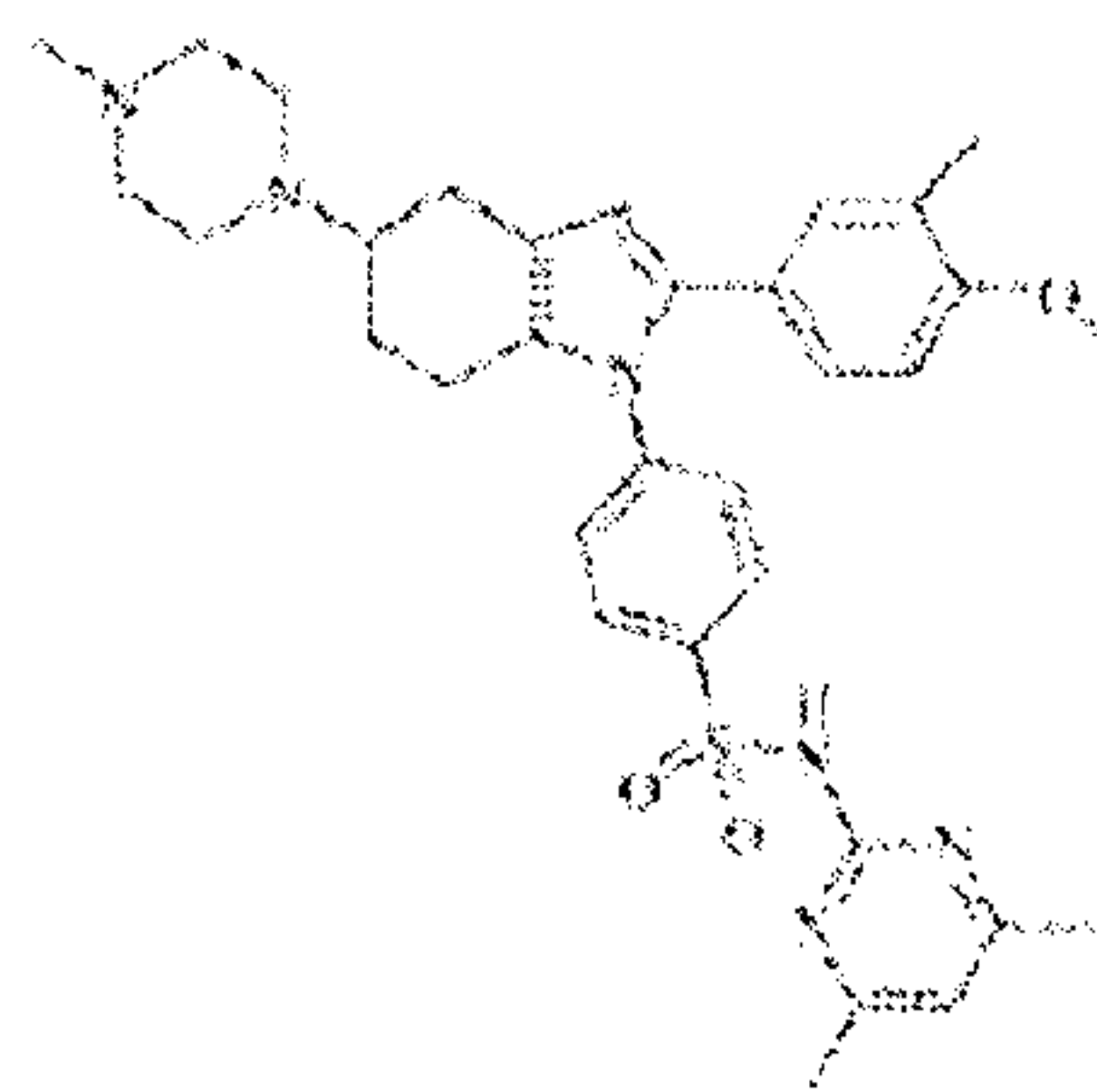
(43A);



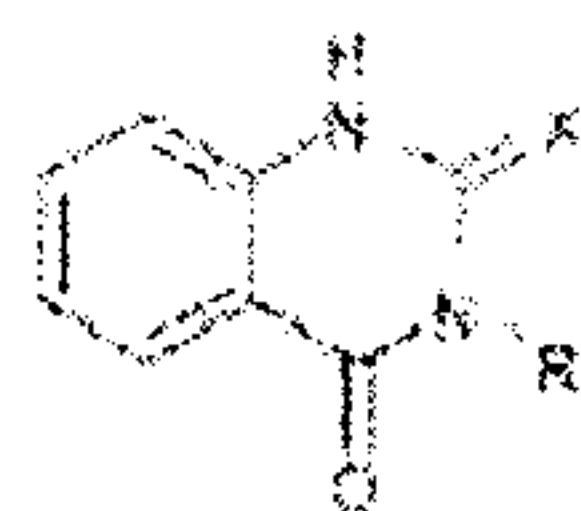
(43B);



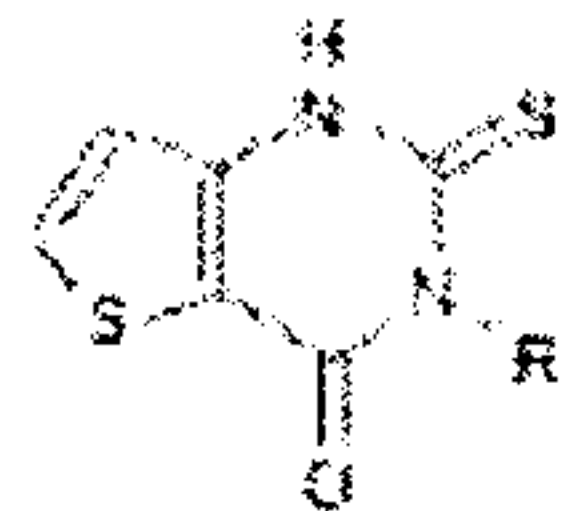
(45);



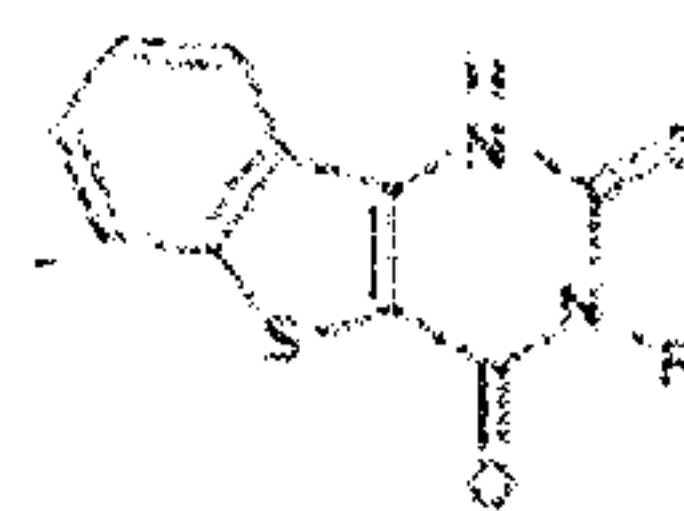
(46);



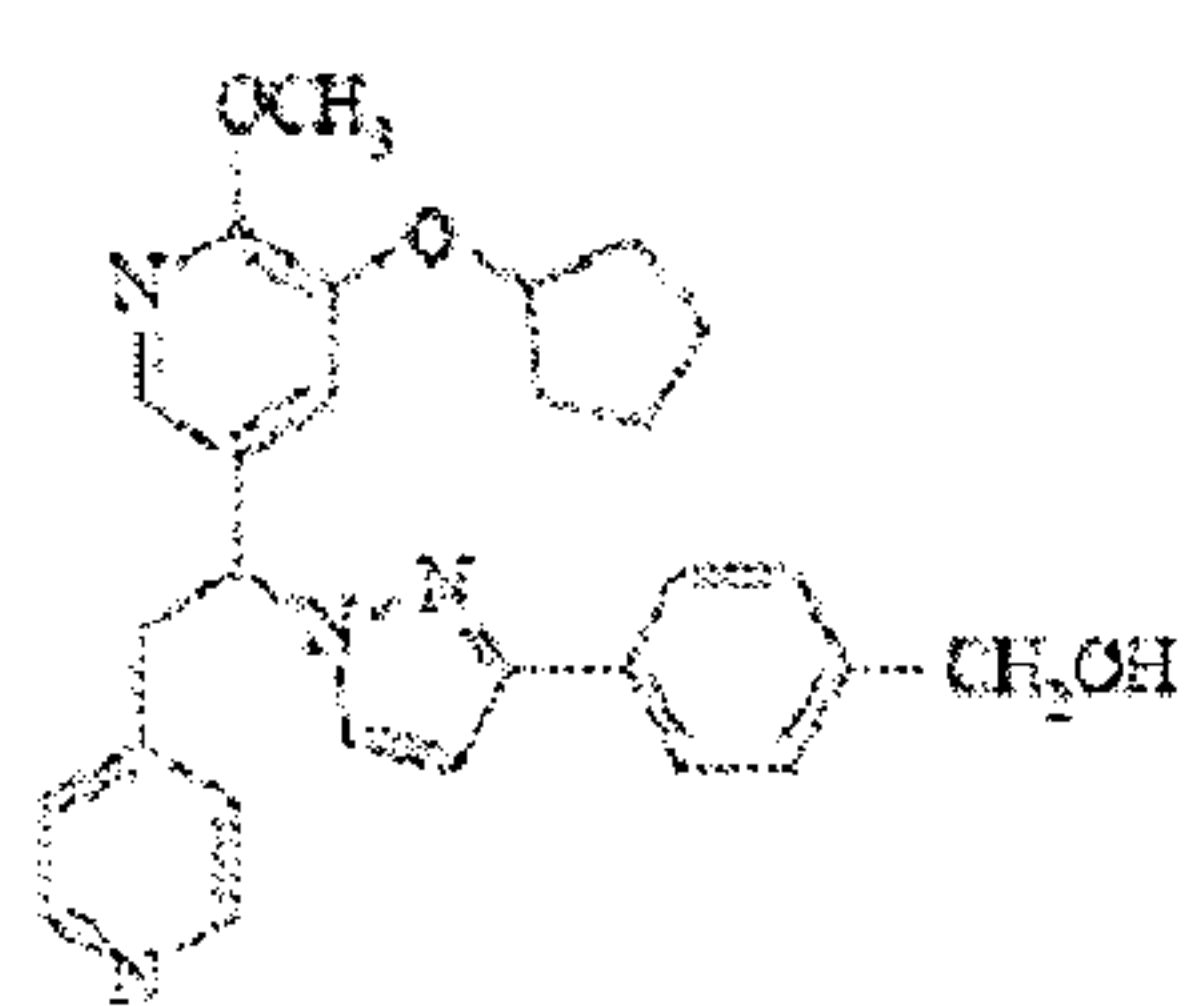
(47);



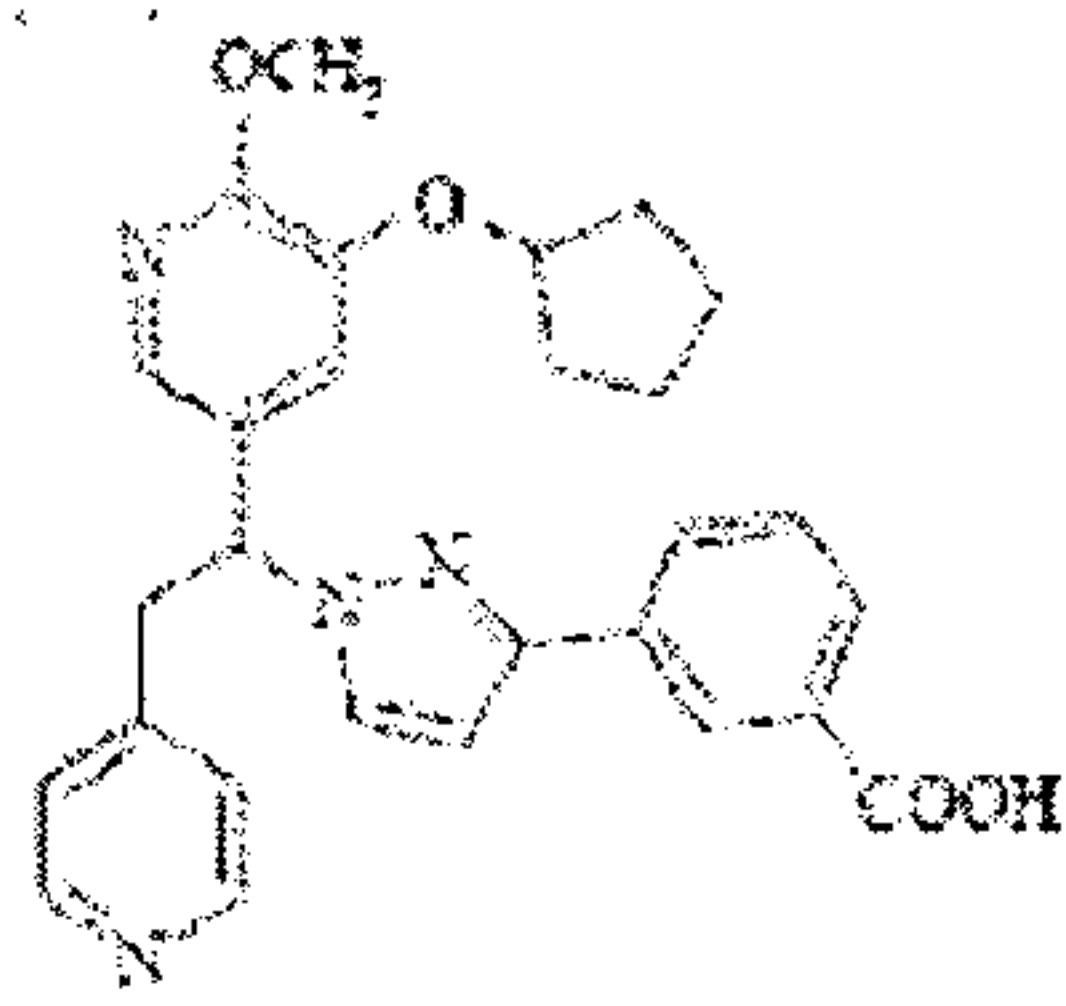
(48);



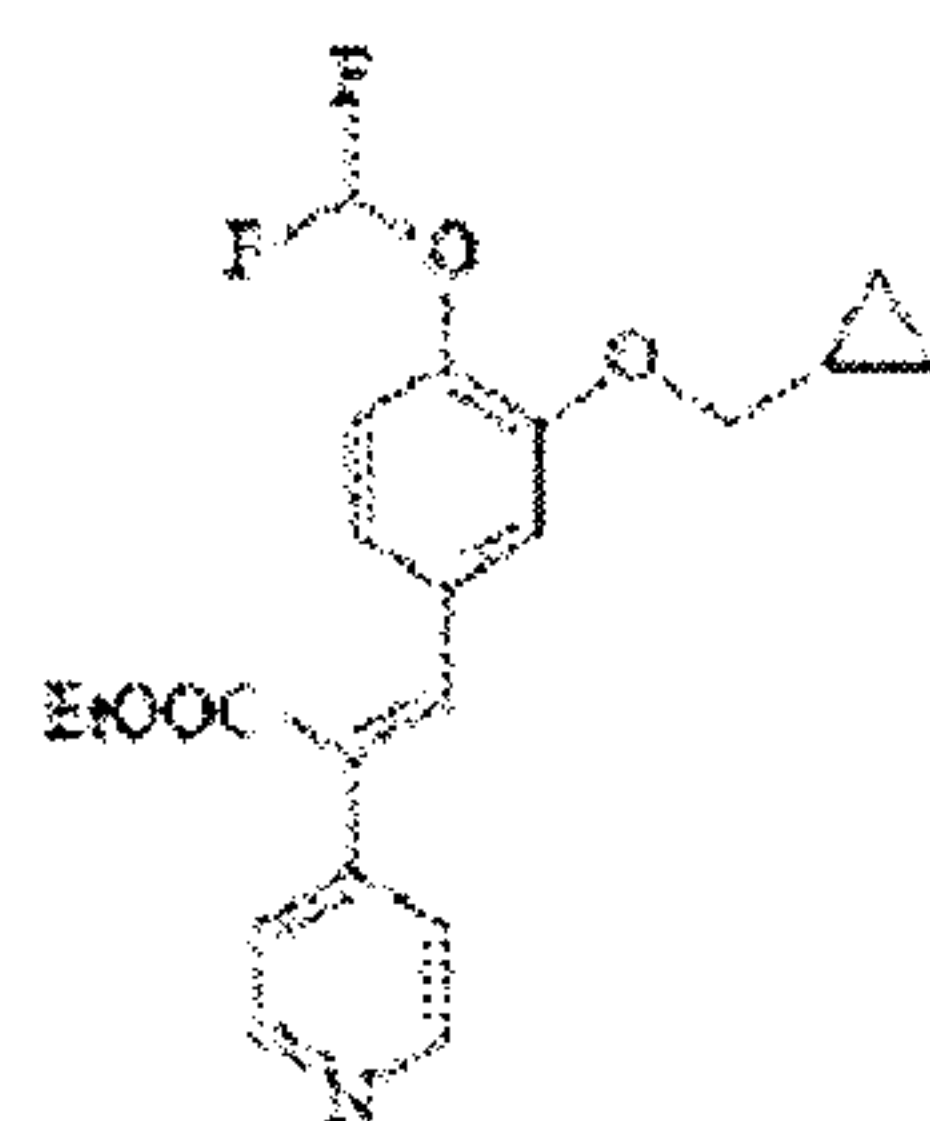
(49);



(51);

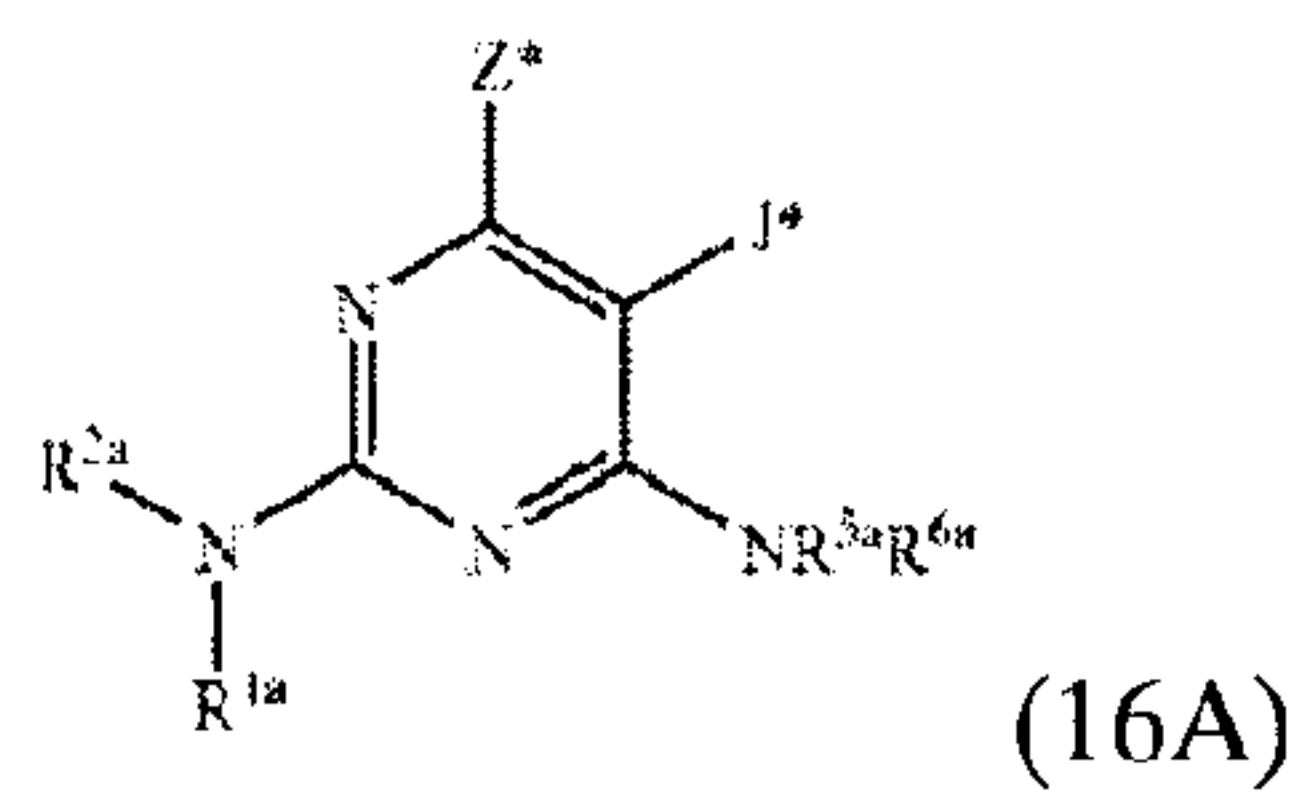


(52); and



(53).

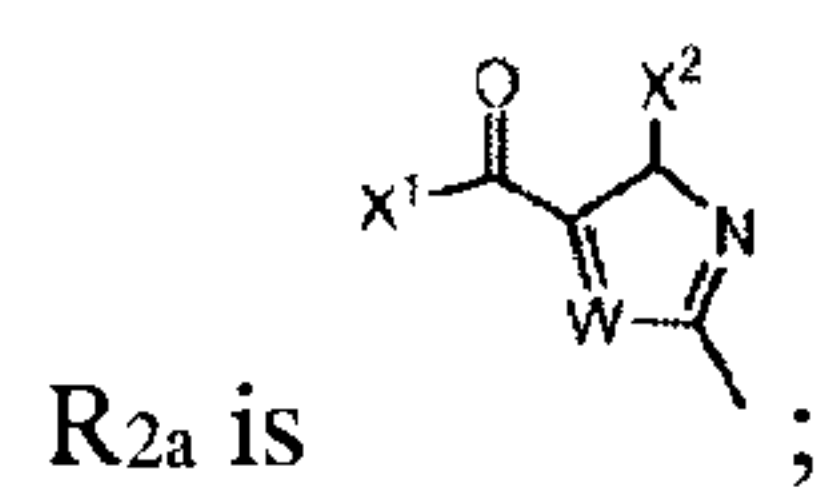
8. The use of Claim 1, wherein the PDE7 inhibitor is:



(16A)

wherein:

R_{1a} is hydrogen or alkyl;



W is S;

X₁ is alkoxy;

X₂ is alkyl;

Z* is halogen, haloalkyl, oxazolyl, NR_{3a}R_{4a}, C(O)-N(H)-alkylene-COOH, or phenyl which is unsubstituted or substituted with heteroaryl, CO_tH, or CO_tT₆;

R_{3a} is hydrogen or alkyl;

R_{4a} is alkyl, alkoxy, unsubstituted or substituted (heteroaryl) alkyl, unsubstituted or substituted heterocyclo, unsubstituted or substituted (heterocyclo) alkyl, or (aryl) alkyl wherein the aryl group is substituted with one or two groups T₁ and/or T₂ and/or further substituted with a group T₃; or

R_{3a} and R_{4a} together with the nitrogen atom to which they are attached combine to form an unsubstituted or substituted heterocyclo ring;

R_{5a} is an unsubstituted or substituted (heteroaryl) alkyl, or (aryl) alkyl wherein the aryl group is substituted with one or two groups T₁ and/or T₂ and/or further substituted with a group T₃; or

R_{5a} and R_{6a} together with the nitrogen atom to which they are attached combine to form an unsubstituted or substituted heterocyclo ring;

R_{6a} is hydrogen or alkyl;

J* is hydrogen or alkyl;

T₁ and T₂ are independently alkoxy, alkoxycarbonyl, heteroaryl, SO₃H, or SO₂R_{8a} where R_{8a} is alkyl, amino, alkylamino or dialkylamino; or

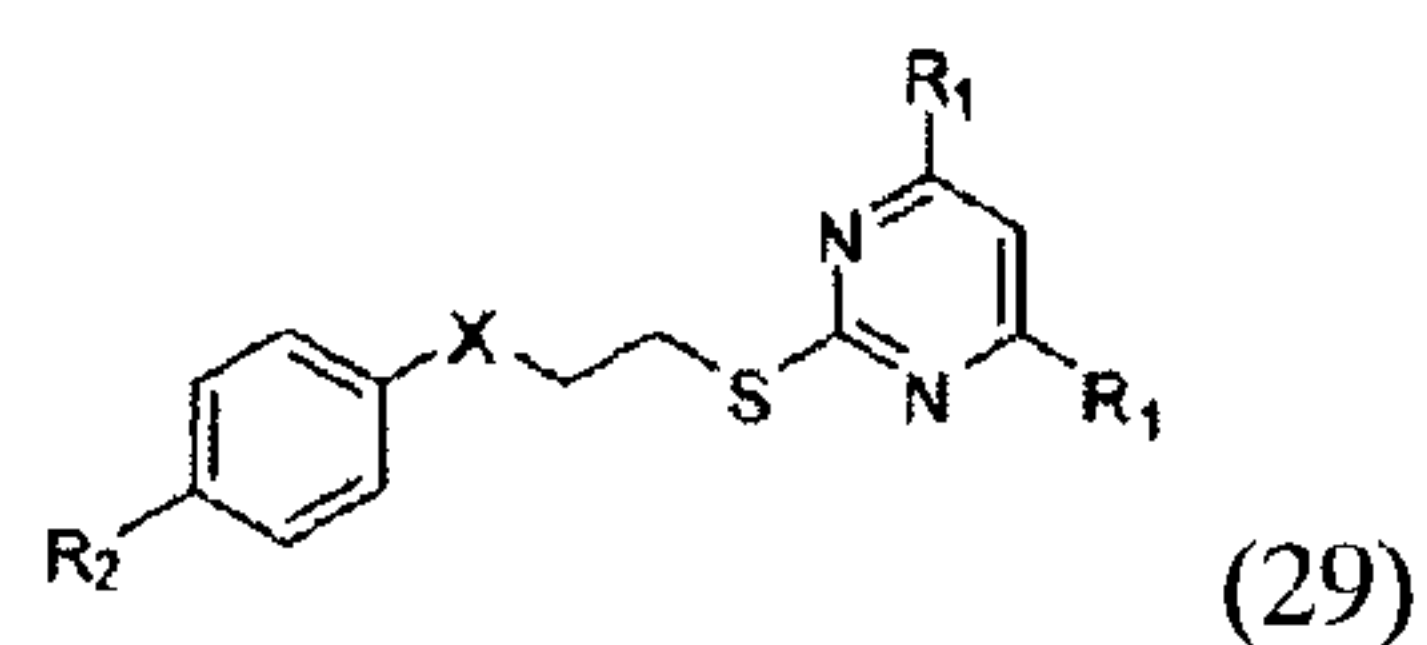
T₁ and T₂ together with the aryl ring to which they are attached combine to form a bicyclic ring;

T₃ is H, alkyl, halo, halo alkyl, or cyano;

t is 1 or 2; and

T6 is alkyl, halo alkyl, cycloalkyl, alkoxy, or heteroaryl.

9. The use of Claim 1, wherein the PDE7 inhibitor is selected from the following compounds:

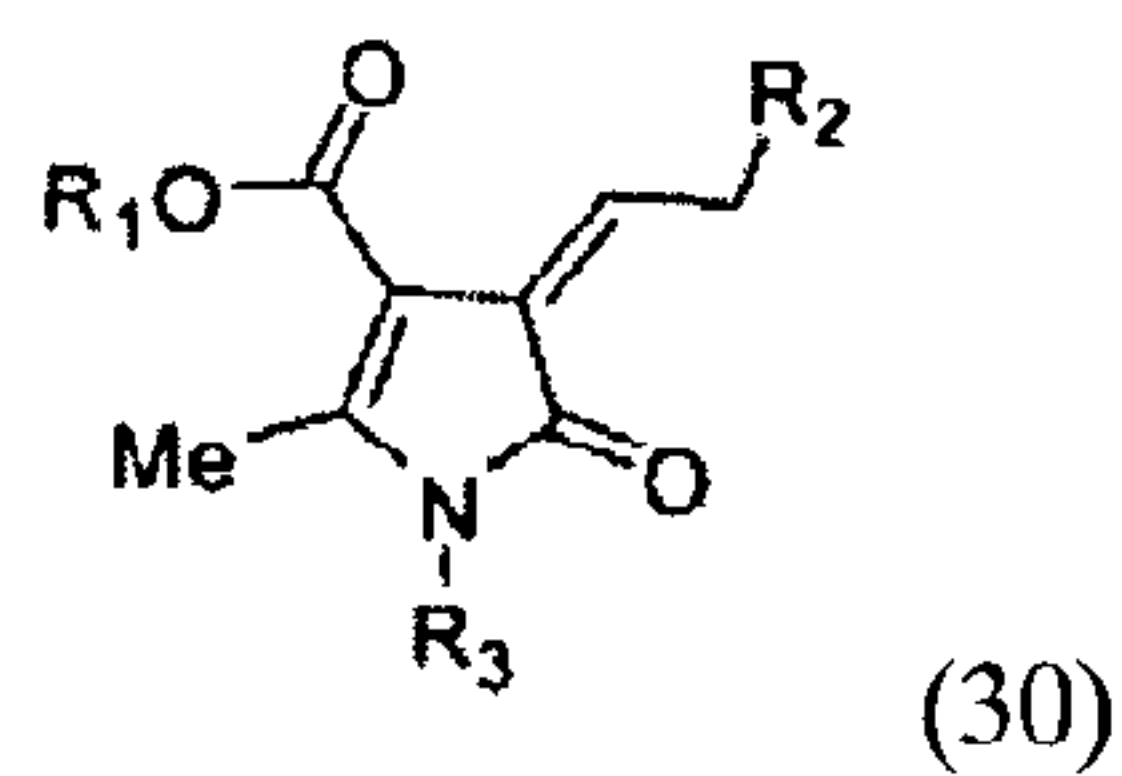


wherein:

X is SO, or SO₂,

R1 is H, or alkyl,

R2 is alkyl, or halogen;

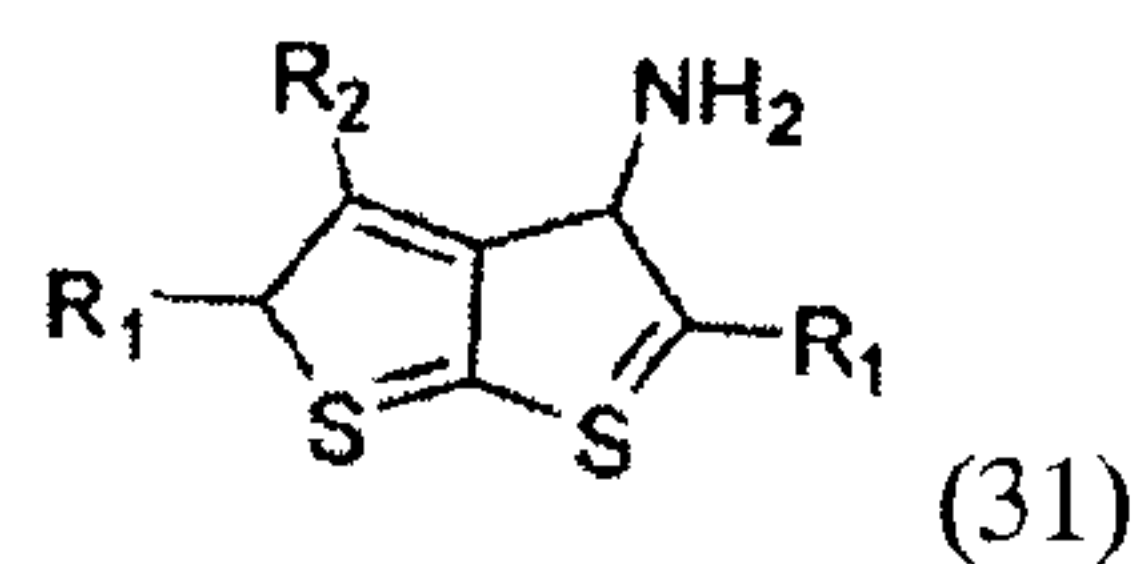


wherein:

R1 is alkyl,

R2 is aryl or heteroaryl,

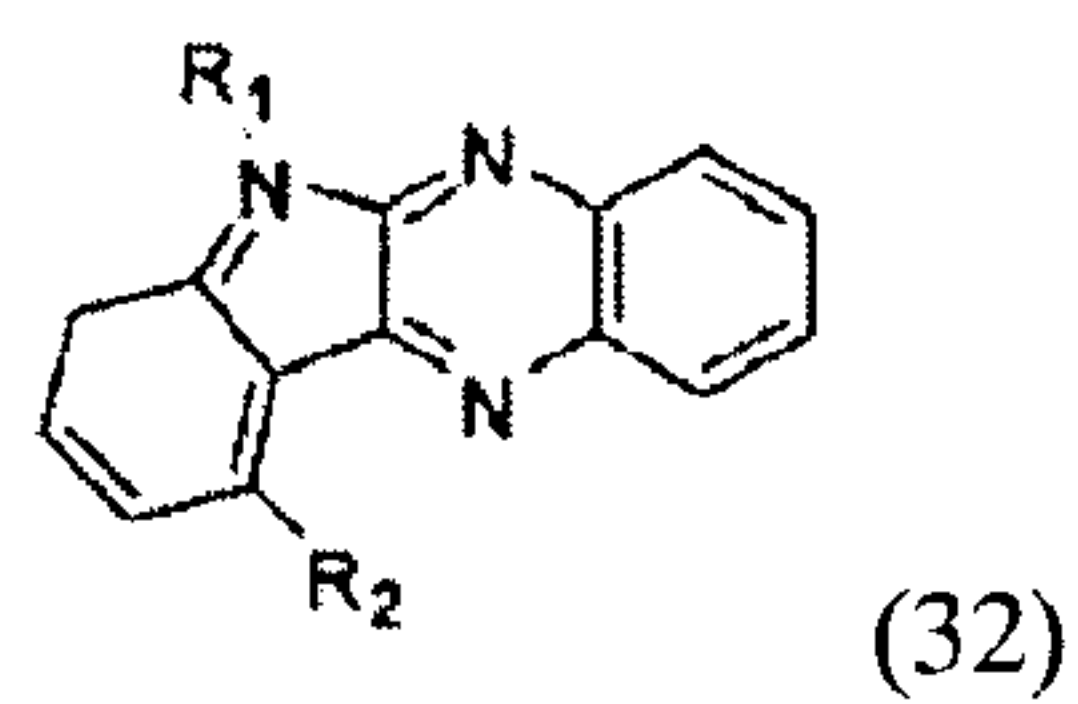
R3 is alkyl, aryl, cycloalkyl, or alkyl aryl;



wherein:

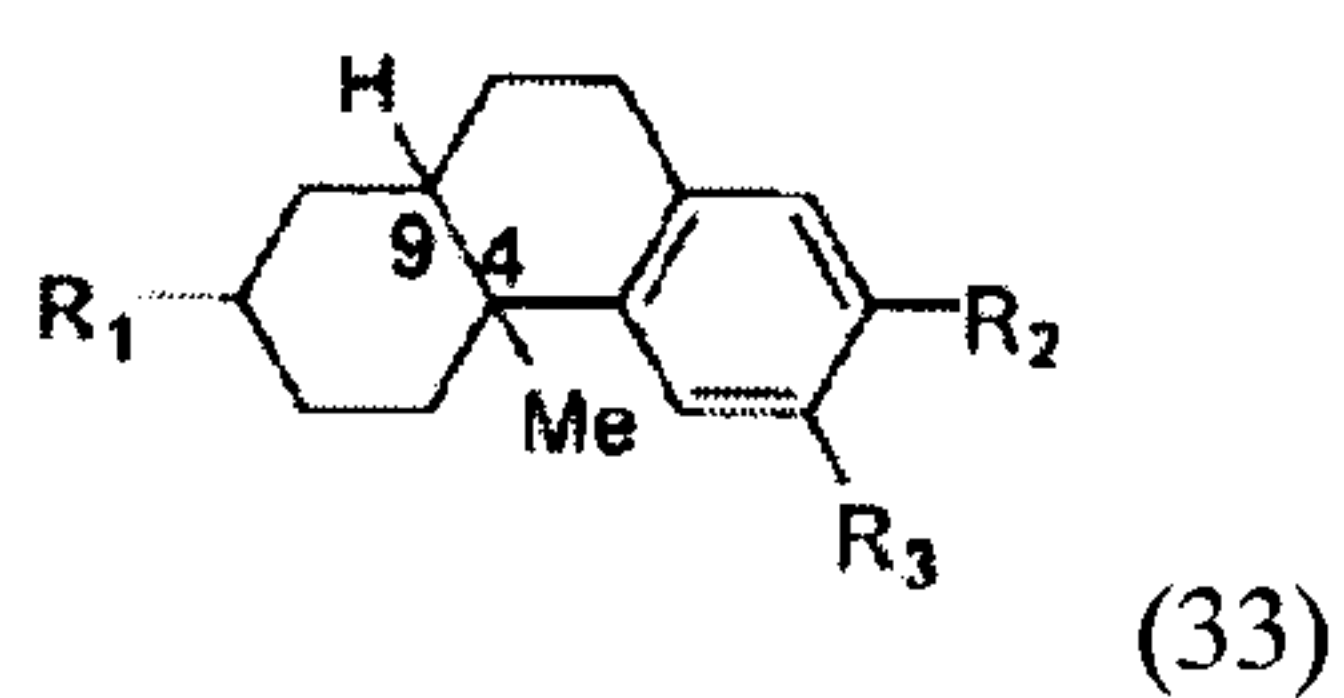
R1 is nitrile, or alkylcarboxylate,

R2 is alkyl, aryl, or heteroaryl;



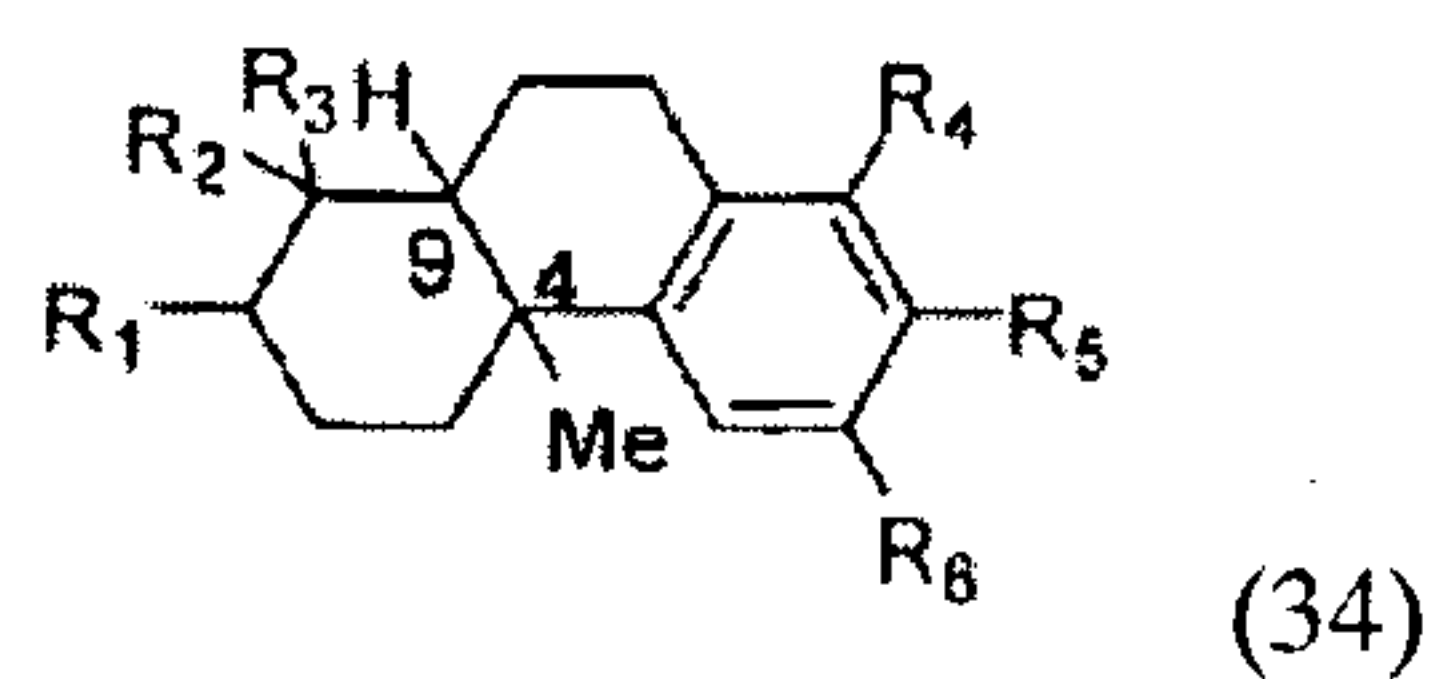
wherein:

R1 is alkyl, alkenyl, or alkylcarboxylic acid,
R2 is halogen;



wherein:

R1 is CO, or alkylalcohol,
R2 is alkyl,
R3 is alkoxy, and
the C4 and C9 stereocenters are independently (R) or (S);



wherein:

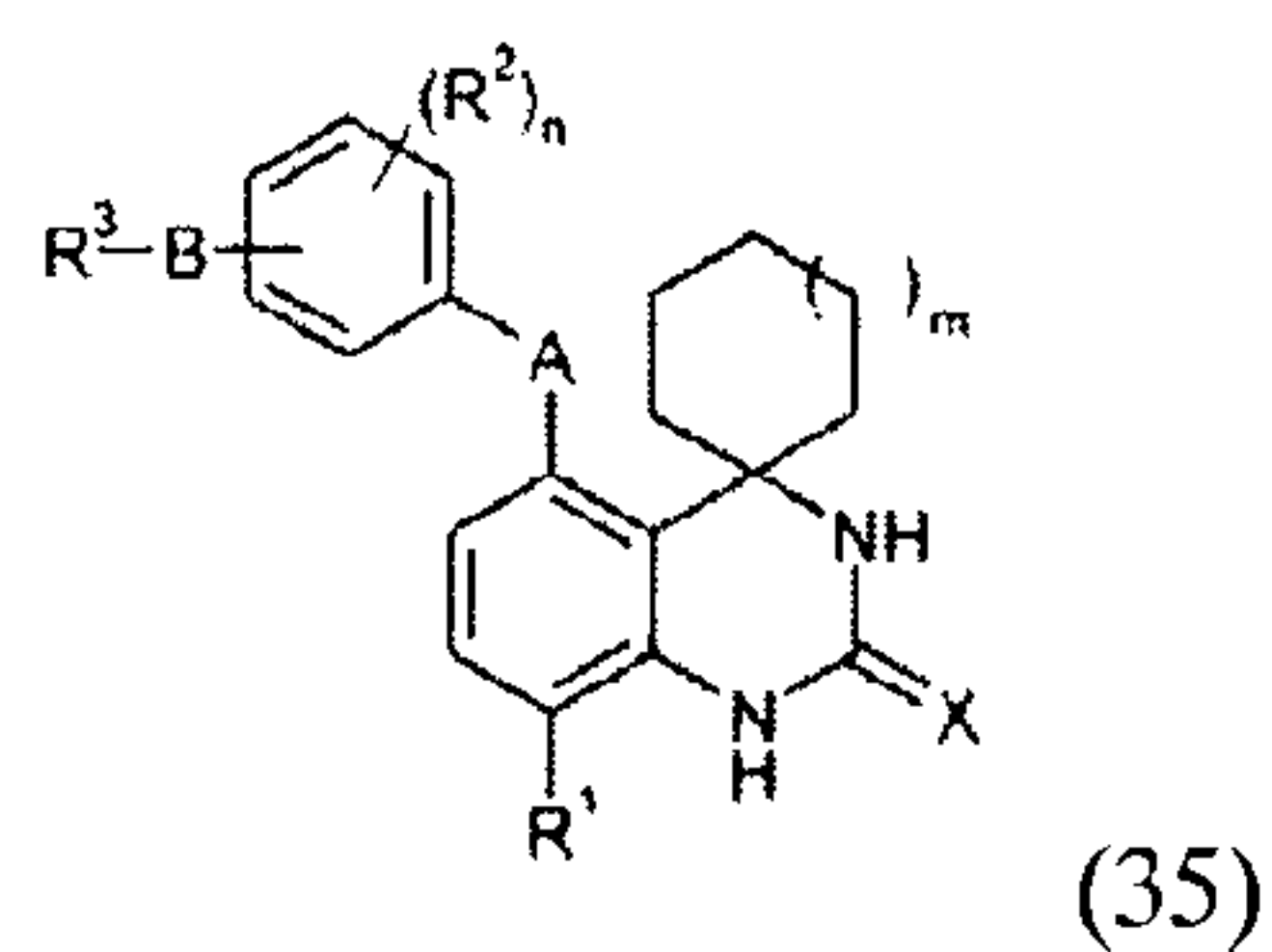
R1 is hydrogen, hydroxyl, carbonyl, or alkylalcohol,

R2 and R3 are independently selected from hydrogen, alkyl, alkylcarboxylate,
and carboxylic acid,

R4 is hydrogen, or alkyl,

R5 is hydrogen, alkyl, hydroxyl, or acetate,

R6 is hydrogen, or alkoxy, and the C4 and C9 stereocenters are independently (R) or (S);



wherein:

m is 0, 1 or 2,

n is 0, 1, 2 or 3,

X is O, S or N-CN,

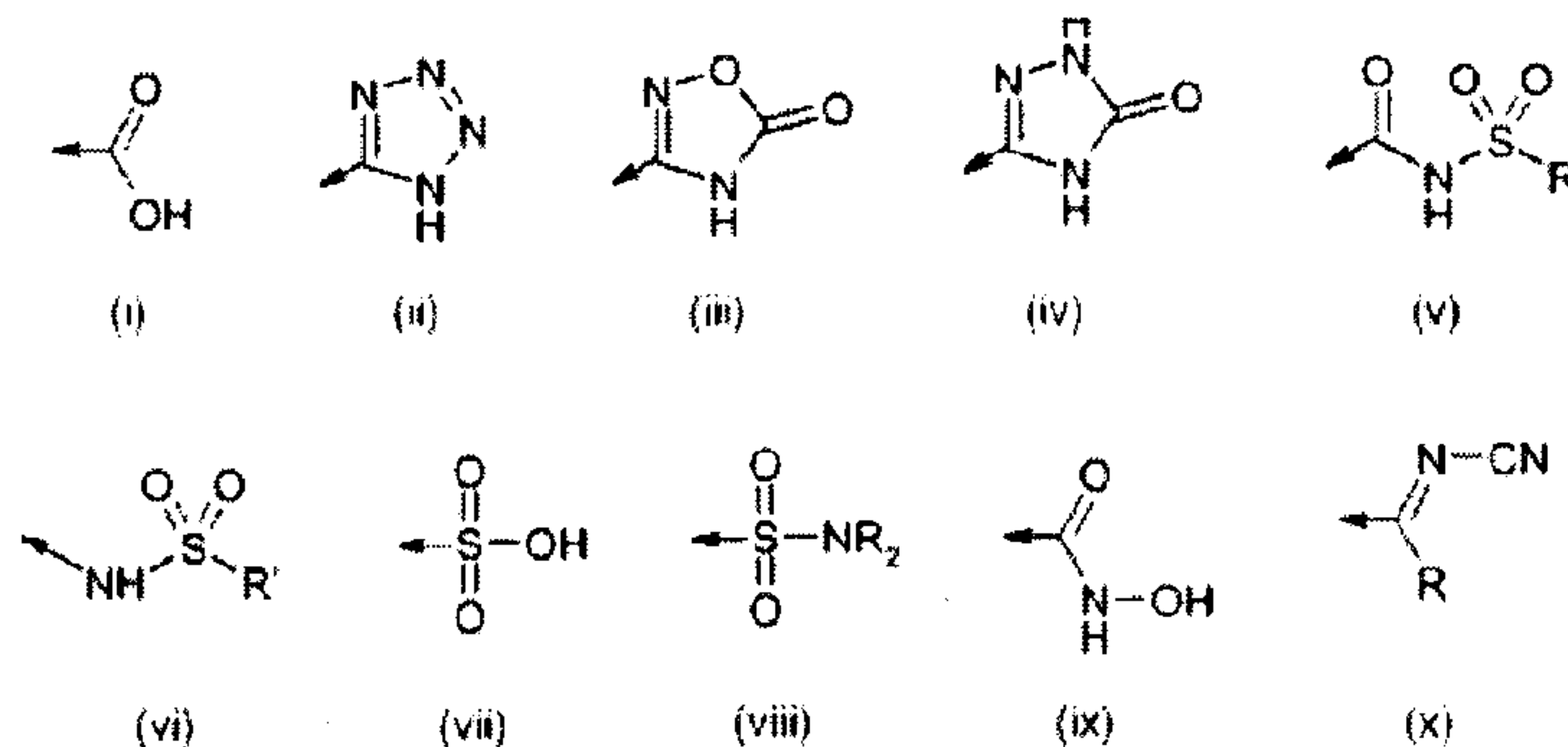
R¹ is halogen or CN,

A is a single bond, CH₂, O or S,

B is a single bond, CH₂ or OCH₂,

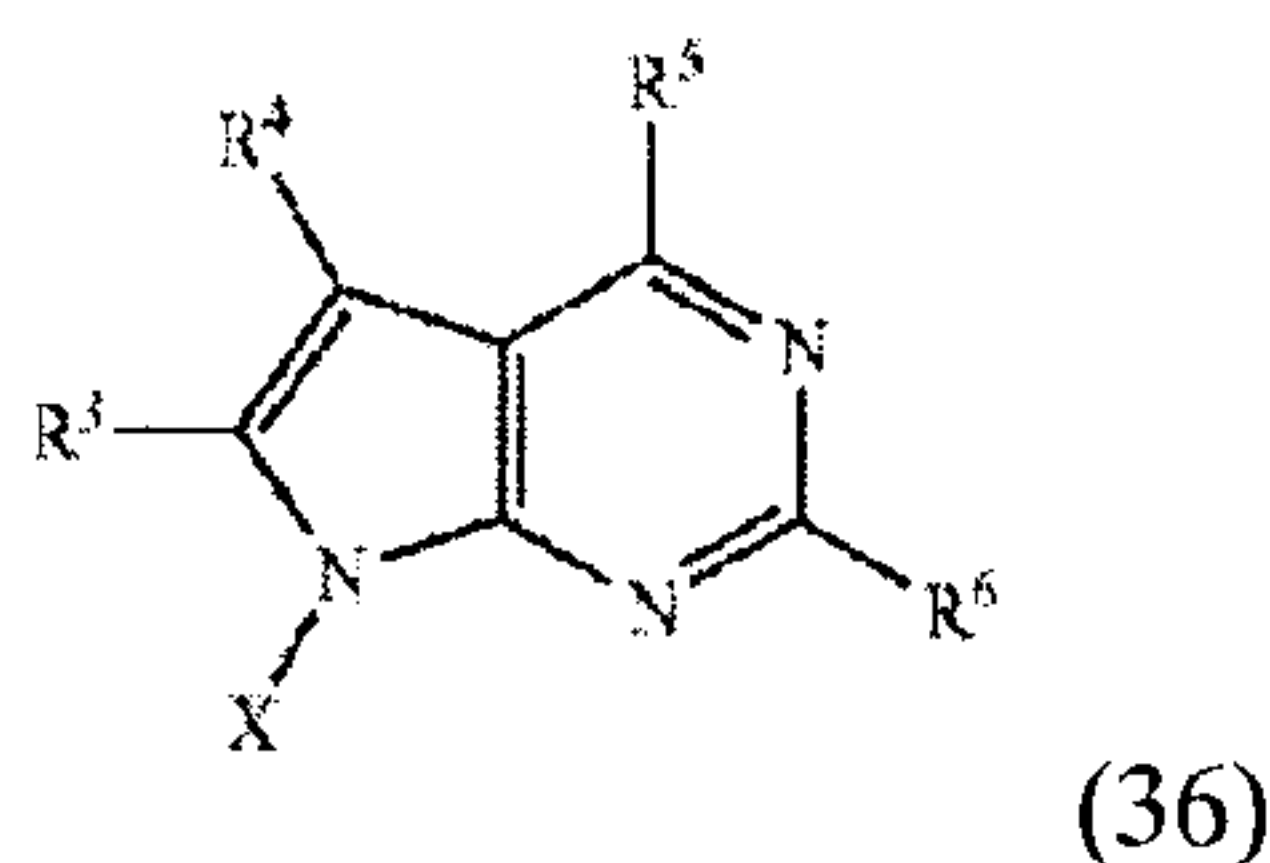
each R² is independently halogen, (C₁₋₆)alkyl optionally substituted by 1 to 3 fluorine atoms, OH, (C₁₋₆)alkylthio or CN,

R³ is selected from the following groups (i) to (x):



R is H or (C₁₋₆)alkyl optionally substituted by 1 to 3 fluorine atoms, R' is (C₁₋₆)alkyl optionally substituted by 1 to 3 fluorine atoms, or

a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof; and



wherein:

X is phenyl or Het, each of which is unsubstituted or monosubstituted or polysubstituted by R1 and/or R2,

R1 and R2 are each, independently of one another, A, OH, OA, SA, SOA, SO₂A, SO₂NH₂, SO₂NHA, SO₂AA', CN, NO₂, NH₂, NHA, NAA', NHCOA, NHCOOA, COOH, COOA, CONH₂, CONHA, CONAA' or Hal,

R1 and R2 together are alternatively -OCH₂O- or -OCH₂CH₂O-,

R3 is A, OH, OA, SA, SOA, SO₂A, SO₂NH₂, SO₂NHA, SO₂AA', CN, NO₂, NH₂, NHA, NHB, NAA', NHCOA, NHCOOA, NHCOB, NHCOOB, COOH, COOA, COOB, CONH₂, CONHA, CONHB, CONAA' or Hal,

R4 is branched or unbranched alkyl or alkenyl having up to 10 carbon atoms, which may be substituted by from 1 to 5 F and/or Cl atoms and/or in which one or more CH₂ groups may be replaced by O, S, SO, SO₂, NH, NA, NHCO, NACO, NHCOO or NACOO, or cycloalkyl or cycloalkenyl having from 3 to 7 carbon atoms, in which one or two CH₂ groups may be replaced by O, S, SO, SO₂, SO₂NH, SO₂NA, NH, NHA, NHCONH, NACONH, NACONA, NHCO, NACO, NHCOO or NACOO,

R5 is OH, OA, SA, SOA, SO₂A, SO₂NH₂, SO₂NHA, SO₂AA', CN, NO₂, NH₂, NHA, NAA', NHCOA, NHCOOA, COOH, COOA, CONH₂, CONHA, CONAA' or Hal,

R6 is H, OH, OA, SA, SOA, SO₂A, SO₂NH₂, SO₂NHA, SO₂AA', CN, NO₂, NH₂, NHA, NAA', NHCOA, NHCOOA, COOH, COOA, CONH₂, CONHA, CONAA' or Hal, A and A' are each, independently of one another, branched or unbranched alkyl or alkenyl having up to 10 carbon atoms, which may be substituted by from 1 to 5 F and/or Cl atoms and/or in which one or more CH₂ groups may be replaced by O, S, SO, SO₂, NH, NR₇, NHCO, NR₇CO, NHCOO or NR₇COO,

A and A' together are alternatively alkylene having from 3 to 7 carbon atoms, in which one or two CH₂ groups may be replaced by CHR₇, CHR₇R₈, O, S, SO, SO₂, NH, NR₇, NHCO, NR₇CO, NHCOO or NR₇COO,

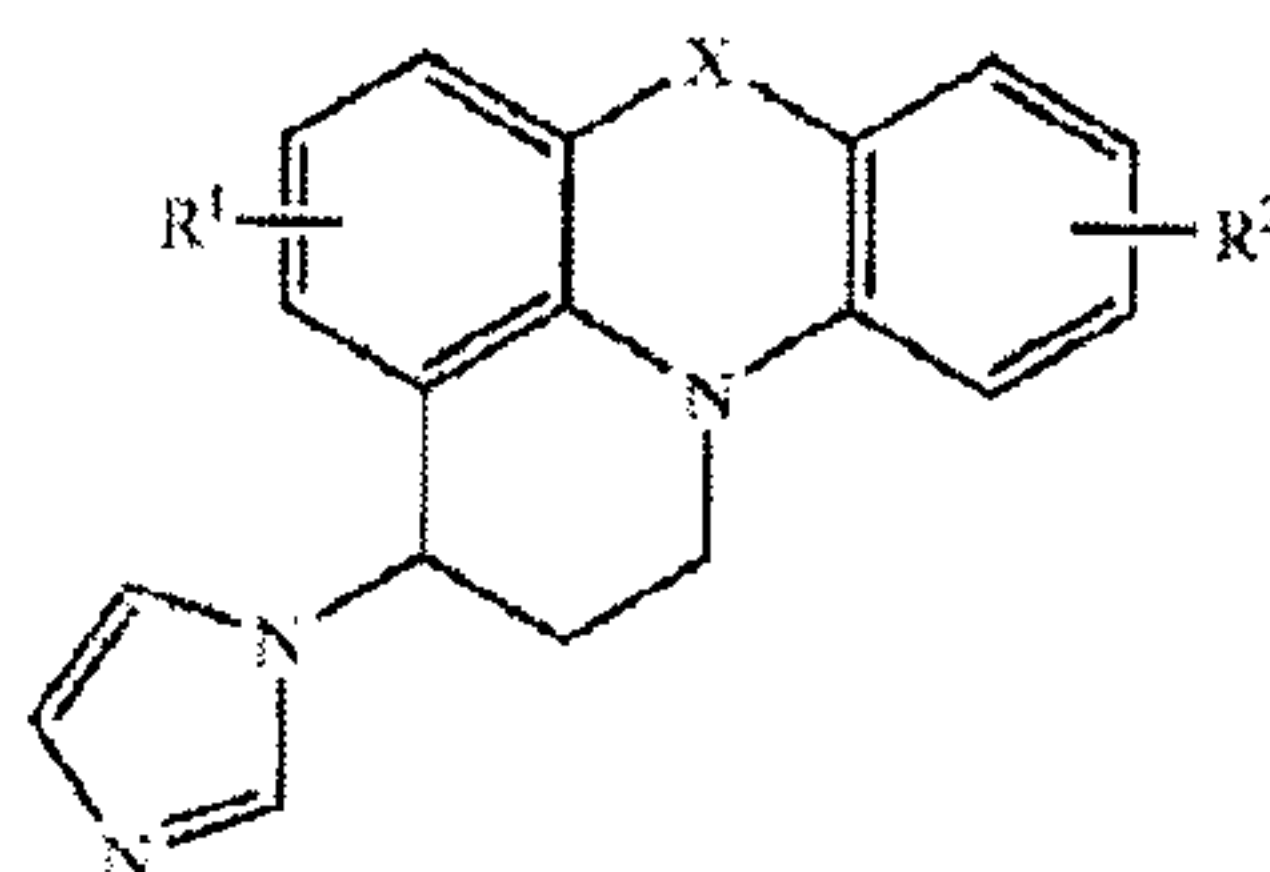
B is phenyl or Het, each of which is unsubstituted or monosubstituted or polysubstituted by R₁ and/or R₂, Het is an aromatic 5- or 6-membered heterocyclic ring having 1-3 N, O and/or S atoms which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A", Hal or CF₃,

R7 and R8 are each, independently of one another, branched or unbranched alkyl or alkenyl having up to 5 carbon atoms, which may be substituted by from 1 to 5 F and/or Cl atoms and/or in which one or more CH₂ groups may be replaced by O, S, SO, SO₂ or NH,

A" is alkyl having from 1 to 6 carbon atoms, and

Hal is F, Cl, Br or I, and pharmaceutically acceptable salts, prodrugs, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

10. The use of Claim 1, wherein the PDE7 inhibitor is selected from the following compounds:



(37)

wherein:

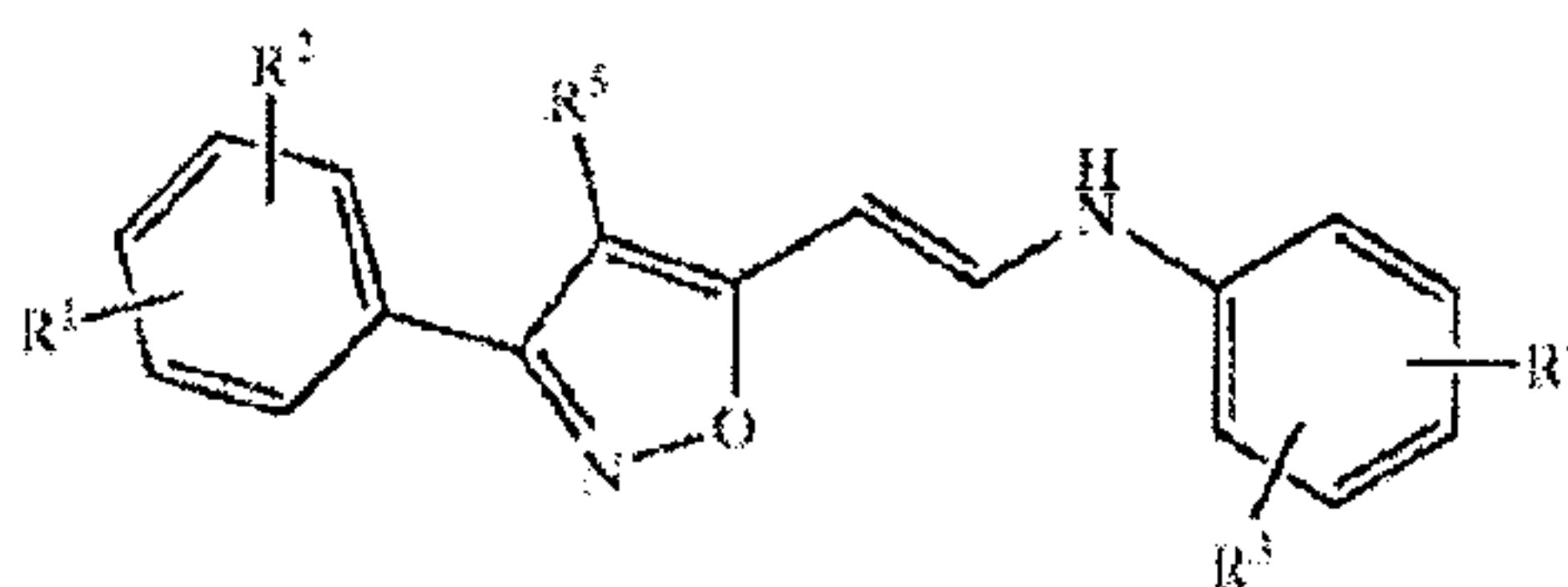
R1 and R2 are each, independently of one another, A1, OA1, SA1 or Hal,

A1 is H, A, alkenyl, cycloalkyl or alkylencycloalkyl,

A is alkyl having 1-10 carbon atoms,

Hal is F, Cl, Br or I, and

x is O, S, SO or SO₂;



(38)

wherein:

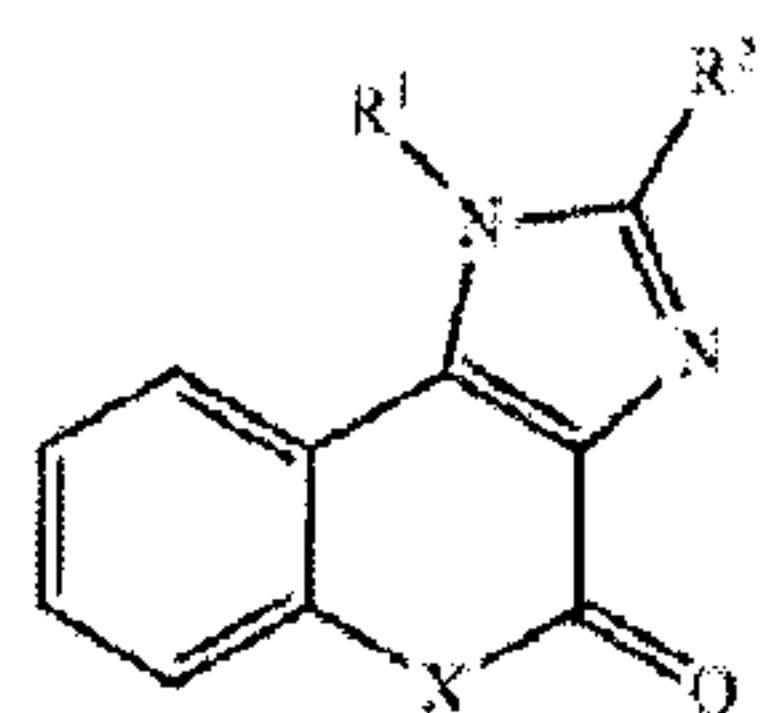
R1, R2, R3, R4 are each, independently of one another, Hal, OA1, SA1, A, H, COOA1, CN or CONA1A2,

R5 is COOA1, CN or CONA1A2,

A1, A2 are each, independently of one another, H, A, alkenyl, cycloalkyl or alkylencycloalkyl,

A is alkyl having 1 to 10 C atoms,

Hal is F, Cl, Br or I;



(39)

wherein:

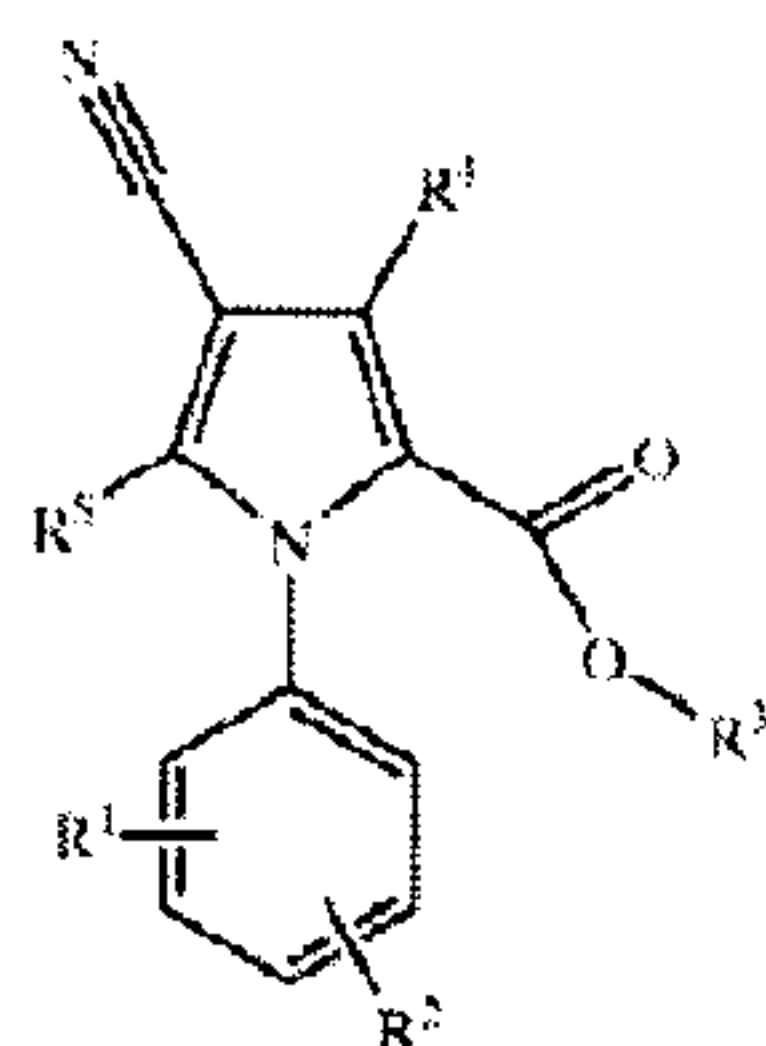
R1 is H, A, benzyl, indan-5-yl, 1,2,3,4-tetrahydronaphthalen-5-yl, dibenzothien-2-yl, or phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal, A, A- CONH, benzyloxy, alkoxy, COOH or COOA,

R2 is H or A,

X is O or S,

Hal is F, Cl, Br or I,

A is alkyl with 1 to 6 C atoms;



(40)

wherein:

R1 and R2 are each, independently of one another H, A, OA, SA or Hal,

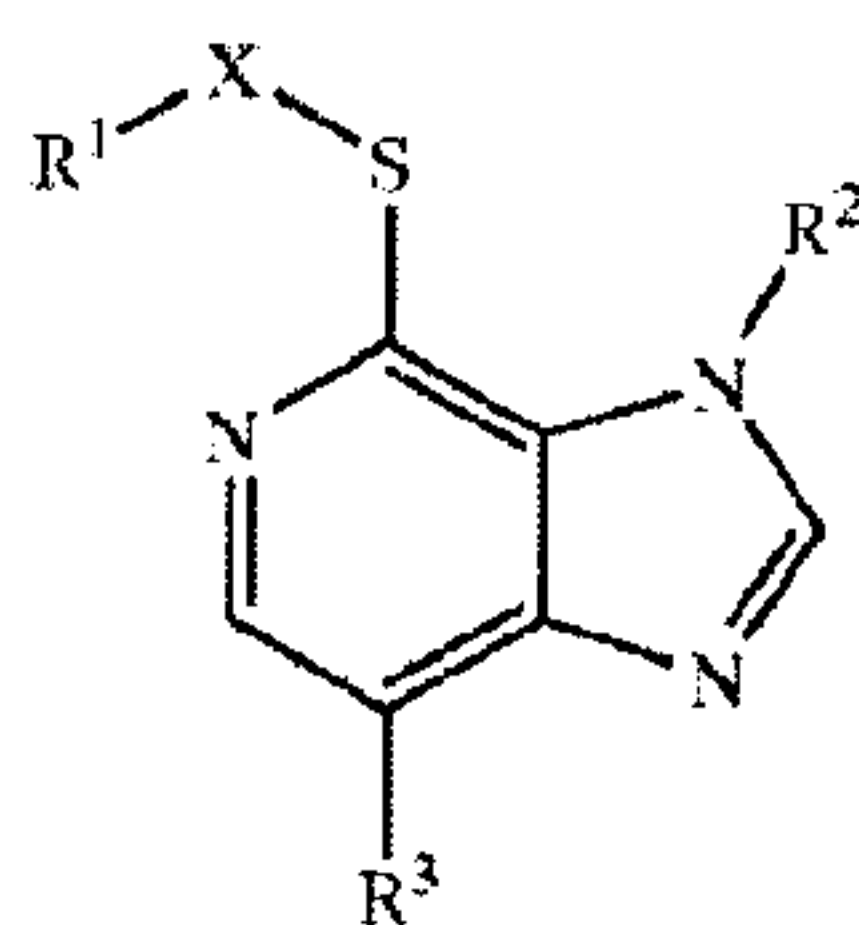
R3 is H or A,

R4 is A or NH2,

R5 is H, NH2, NHA or NA2,

A is alkyl having 1 to 10 carbon atoms, alkenyl, cycloalkyl or alkylencycloalkyl,

Hal is F, Cl, Br or I; and



(41)

wherein:

R1 is CONR4R5,

R2 is H or A,

R4 and R5 are each, independently of one another, H or A1,

R3 is Hal,

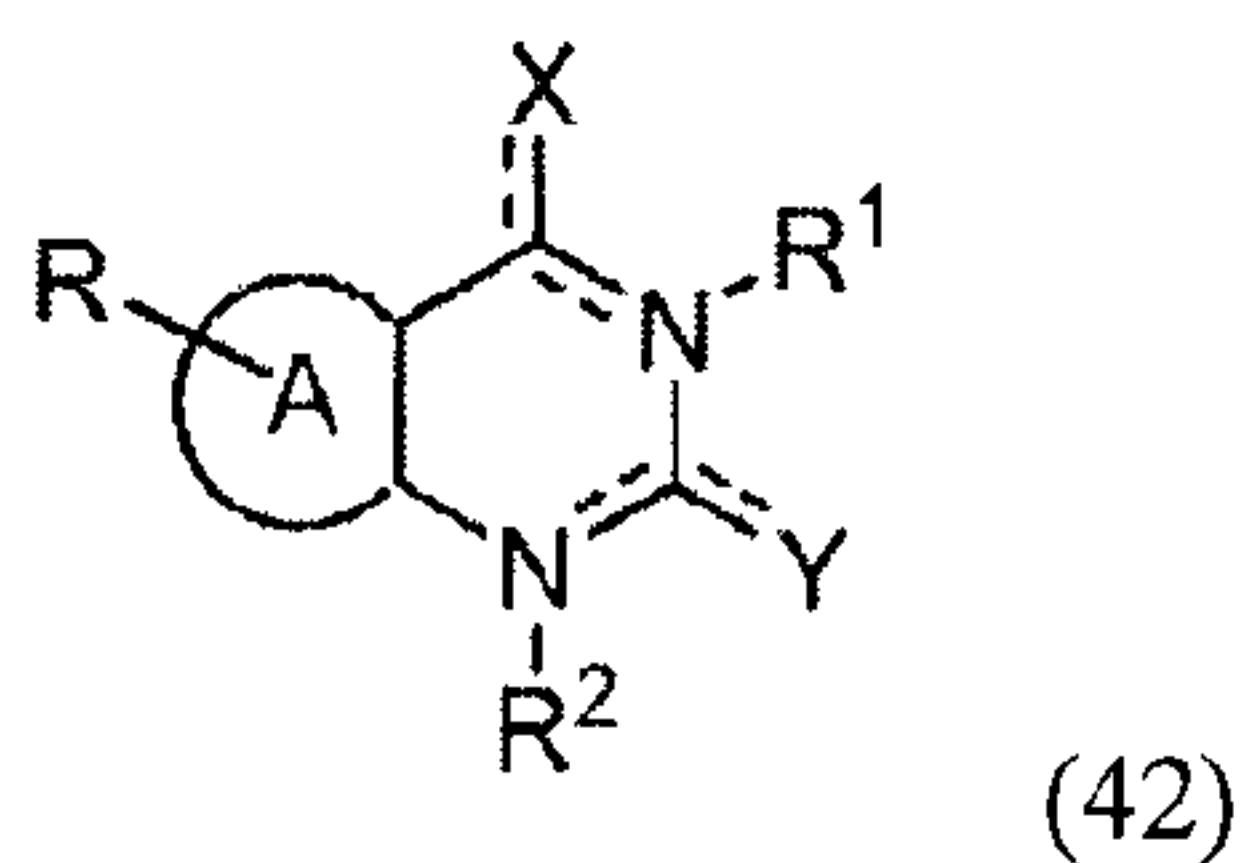
Hal is F, Cl, Br or I,

A is alkyl having 1-4 carbon atoms,

A1 is alkyl having 1-10 carbon atoms,

X is alkylene having 1-4 carbon atoms, in which an ethylene group may also be replaced by a double or triple bond, and their physiologically acceptable salts and/or solvates.

11. The use of Claim 1, wherein the PDE7 inhibitor is:



wherein:

A is fused carbocyclo or heterocyclo of 5, 6 or 7 members and may be saturated or unsaturated;

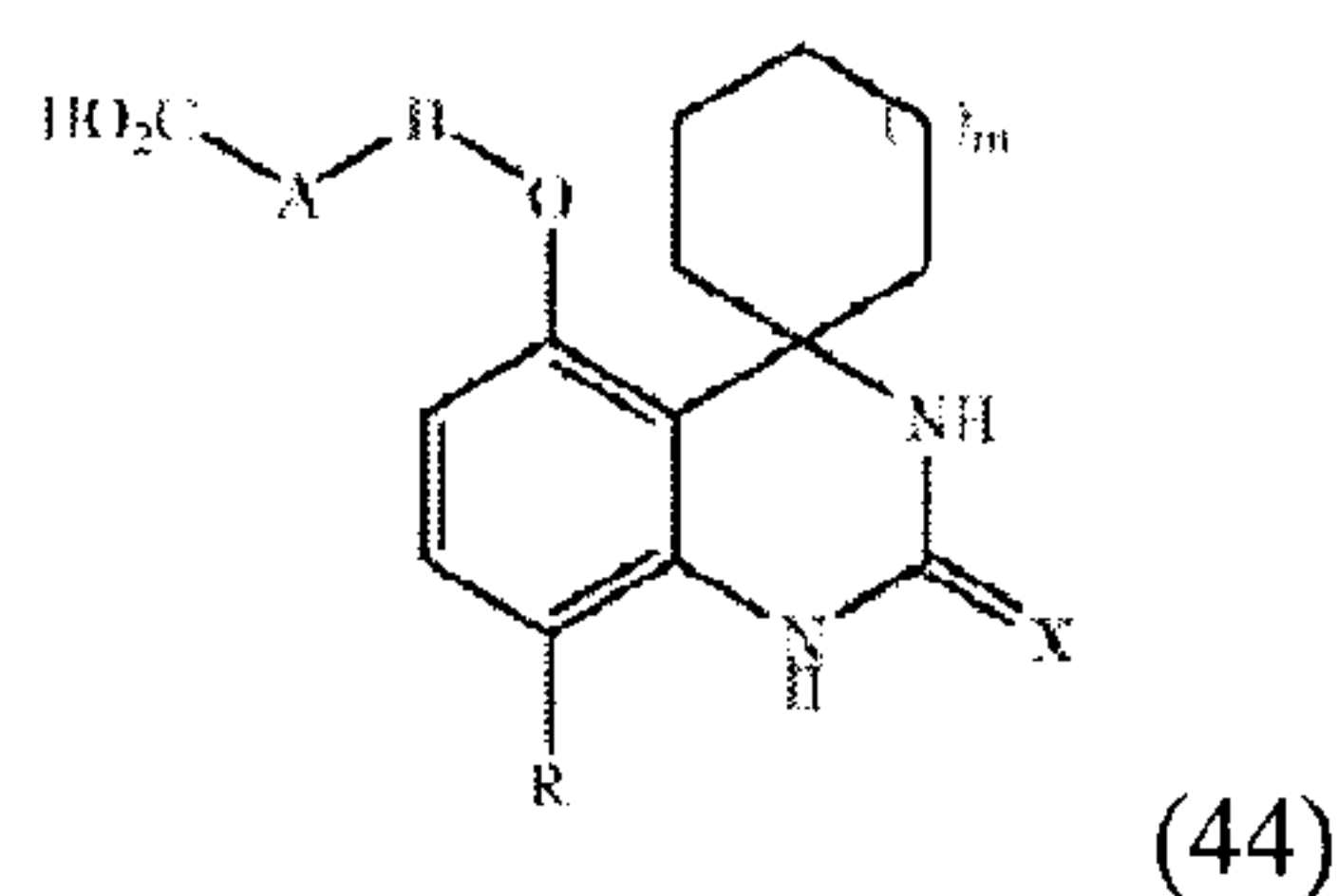
the dashed lines represent, independently, a single or double bond;

X and Y are chosen independently from the group consisting of alkyl, hydrogen, =O, =S, -N (alkyl), -N(aryl), aryl, O-alkyl, O-aryl, alkyl-S and -S-aryl; and

R1 and R2 are chosen independently from the group consisting of hydrogen, halogen, alkyl, halo alkyl, aryl, cycloalkyl, (Z)n-aryl, hetero aryl, -OR3; -C(O)OR3, -(Z)n-C(O)OR3 and -S(O), or a pharmaceutically acceptable salt, prodrug, solvate or stereoisomer of the same;

wherein, when A is unsubstituted benzene, X=O, Y=S, when A is unsubstituted benzene, X=O, Y=O, when A is unsubstituted benzene, X=O, Y=S-Me, when A is unsubstituted thiophene, X=O, Y=S, and when A is unsubstituted benzothiophene, X=O, Y=S.

12. The use of Claim 1, wherein the PDE7 inhibitor is selected from the following compounds:



wherein:

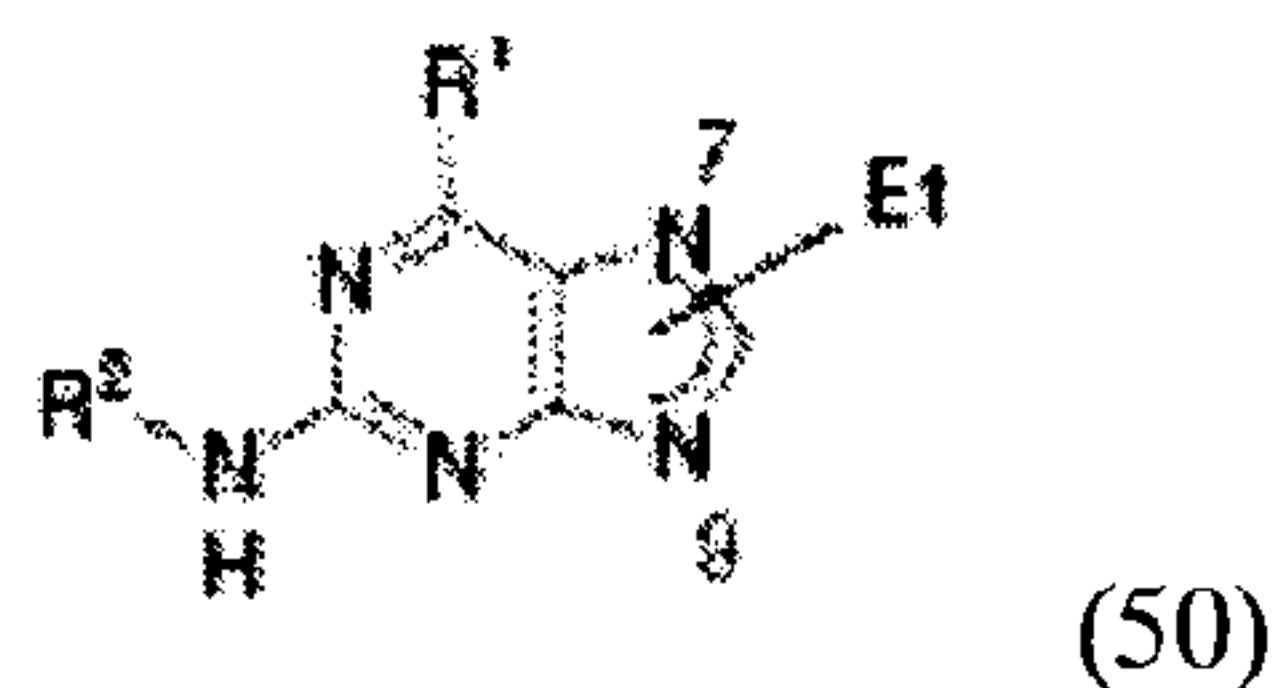
m is 0, 1 or 2;

X is O, S or N--CN;

R is F, Cl or CN;

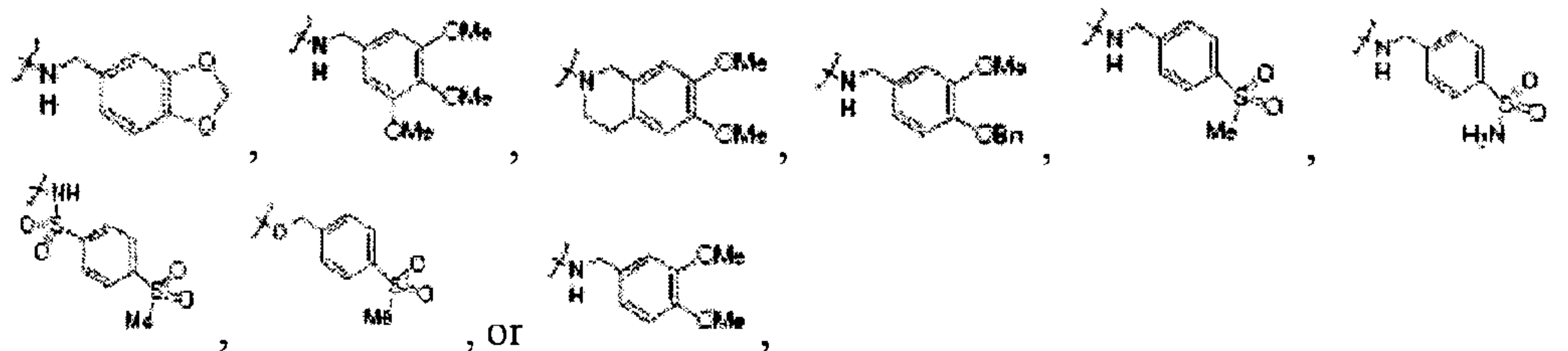
A is a C₃₋₆ cycloalkylene group optionally substituted with a C₁₋₄ alkyl group;
and

B is a single bond or a C₁₋₂ alkylene group;

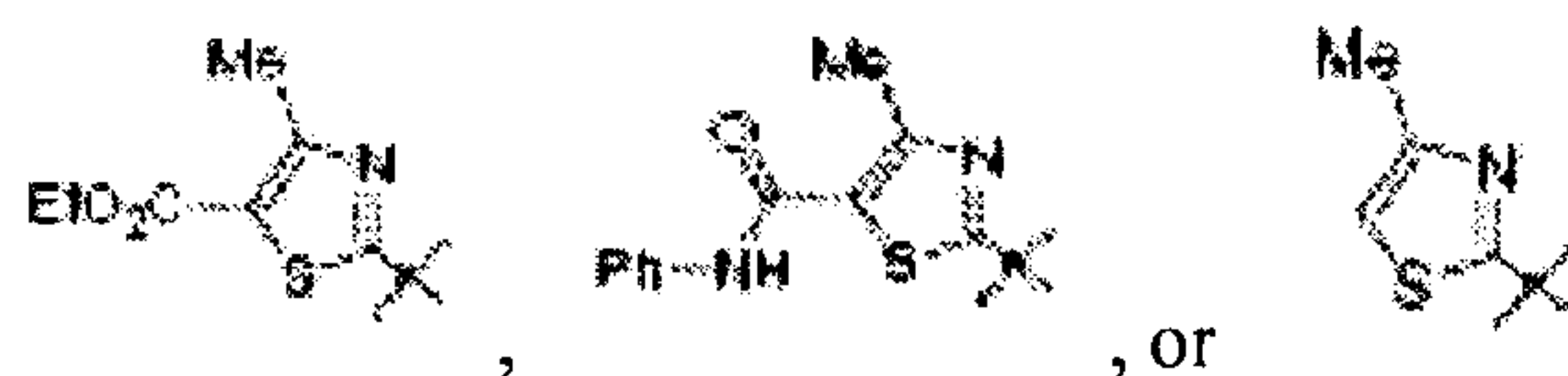


wherein:

R1 is:

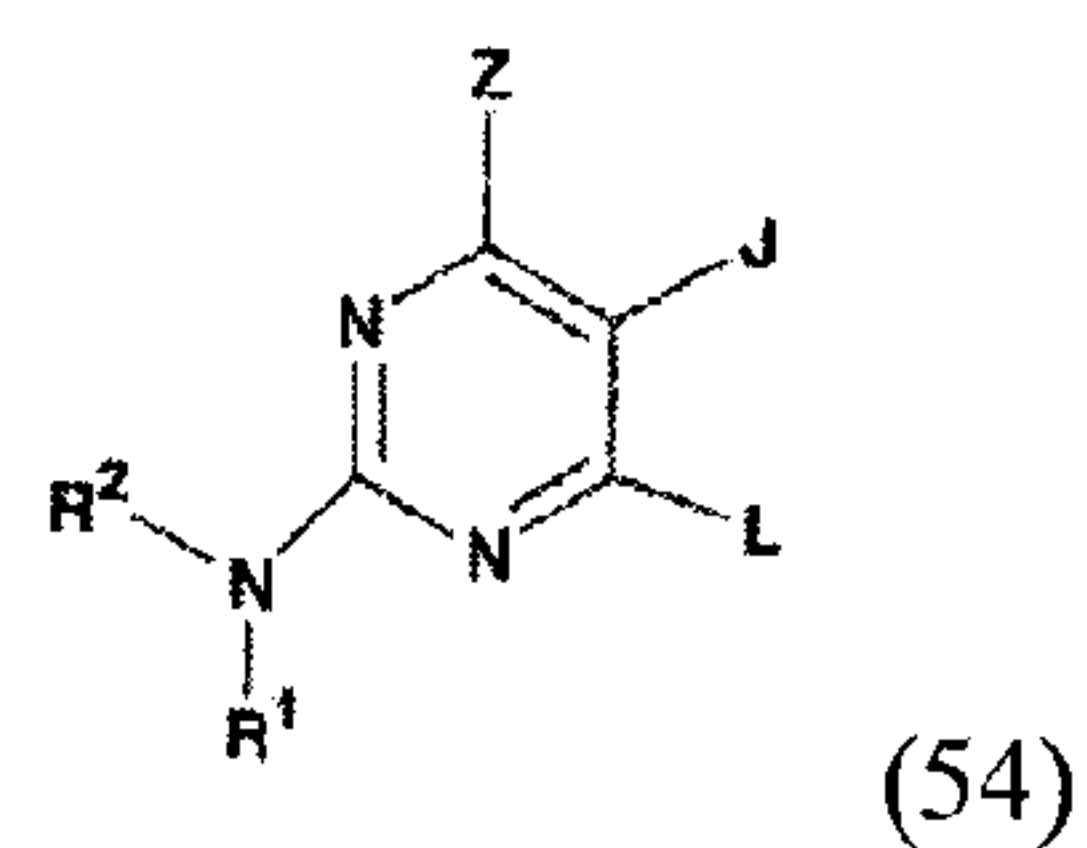


R2 is:



wherein the ethyl group may be attached to the 7 or 9 position.

13. The use of Claim 1, wherein the PDE7 inhibitor is:



wherein:

R1 is H or alkyl;

R2 is (a) heteroaryl, or heterocyclo, either of which may be optionally substituted with one to three groups T1, T2, T3; (b) aryl substituted with one to three groups T1, T2, T3 provided that at least one of T1, T2, T3 is other than H;

or (c) aryl fused to a heteroaryl or heterocyclo ring wherein the combined ring system may be optionally substituted with one to three groups T1, T2, T3;

Z is (a) -OR₄, -C(O)R₄, -C(O)OR₄, -SR₄, -NR₃R₄, -C(O)NR₃R₄, -NR₃S₀₂R_{4c}, halogen, nitro, halo alkyl; or (b) alkyl, aryl, hetero aryl, heterocyclo, or cycloalkyl any of which may be optionally substituted with one to three groups T1a, T2a T3a;

J is (a) hydrogen, halo, -OR_{4a}, or (b) alkyl, alkenyl, or alkynyl any of which may be optionally substituted with one to three groups T1b, T2b or T3b;

L is (a) hydrogen, -OR_{4b}, -C(O)R_{4b}, -C(O)OR_{4b}, -SR_{4b}, -NRSR₆, -C(O)NRSR₆, -NRSS₀₂R_{4d}, halogen, haloalkyl, nitro, or (b) alkyl, aryl, heteroaryl, heterocyclo, or cycloalkyl any of which may be optionally substituted with one to three groups T1c, T2c or T3c;

R₃ and R₄ are independently H, alkyl, alkenyl, aryl, (aryl)alkyl, hetero aryl, (heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocylo or (heterocyclo)alkyl any of which may be optionally substituted with one to three groups T1a, T2a or T3a; or

R₃ and R₄ together with the nitrogen atom to which they are attached may combine to form a 4 to 8 membered heterocyclo ring optionally substituted with one to three groups T1a, T2a or T3a;

R_{4a} is hydrogen, alkyl, alkenyl, aryl, heteroaryl, (aryl)alkyl, (heteroaryl)alkyl, heterocylo, (heterocyclo)alkyl, cycloalkyl or (cycloalkyl)alkyl any of which may be optionally substituted with one to three groups T1 b, T2b or T3b;

R4b is hydrogen, alkyl, alkenyl, aryl, heteroaryl, (aryl)alkyl, (heteroaryl)alkyl, heterocylo, (heterocyclo)alkyl, cycloalkyl or (cycloalkyl)alkyl any of which may be optionally substituted with one to three groups T1c, T2c or T3c;

R4c and R4d are independently alkyl, alkenyl, aryl, (aryl)alkyl, heteroaryl, (heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocylo or (heterocyclo)alkyl any of which may be optionally substituted with one to three groups T1a, T2a or T3a;

R5 and R6 are independently H, alkyl, alkenyl, aryl, (aryl)alkyl, heteroaryl, (heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocylo or (heterocyclo)alkyl any of which may be optionally independently substituted where valance allows with one to three groups T1c, T2c or T3c; or

R5 and R6 together with the nitrogen atom to which they are attached may combine to form a 4 to 8-membered heterocyclo ring optionally substituted with one to three groups T1c, T2c or T3c;

T1-1c, T2-2c, and T3-3c are each independently (1) hydrogen or T6, where T6 is (i) alkyl, (hydroxy)alkyl, (alkoxy)alkyl, alkenyl, alkynyl, cyclo alkyl, (cycloalkyl)alkyl, cycloalkenyl, (cycloalkenyl)alkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl, or (heteroaryl)alkyl; (ii) a group (i) which is itself substituted by one or more of the same or different groups (i); or (iii) a group (i) or (ii) which is independently substituted by one or more of the following groups (2) to (13) of the definition of T1-1c, T2-2c and T3-3c (2) -OH or -OT6, (3) -SH or -ST6, (4) -C(O)tH, -C(O)tT6, or -O-C(O)T6, where t is 1 or 2; (5)-SO₃H, -S(O)T6, or S(O)tN(T9)T6, (6) halo, (7) cyano, (8) nitro, (9) -T4-NT7T8, (10) -T4-N(T9)-T5-NT7T8, (11) -T4-N(T10)T5-T6, (12) -T4-N(T10)-T5-H, (13) oxo, T4 and T5 are each independently (1) a single bond, (2) -T11-S(O)t-T12-, (3) T11-C(O)-T12-, (4) -T11-C(S)-T12-, (5) -T11-O-T12-, (6) -

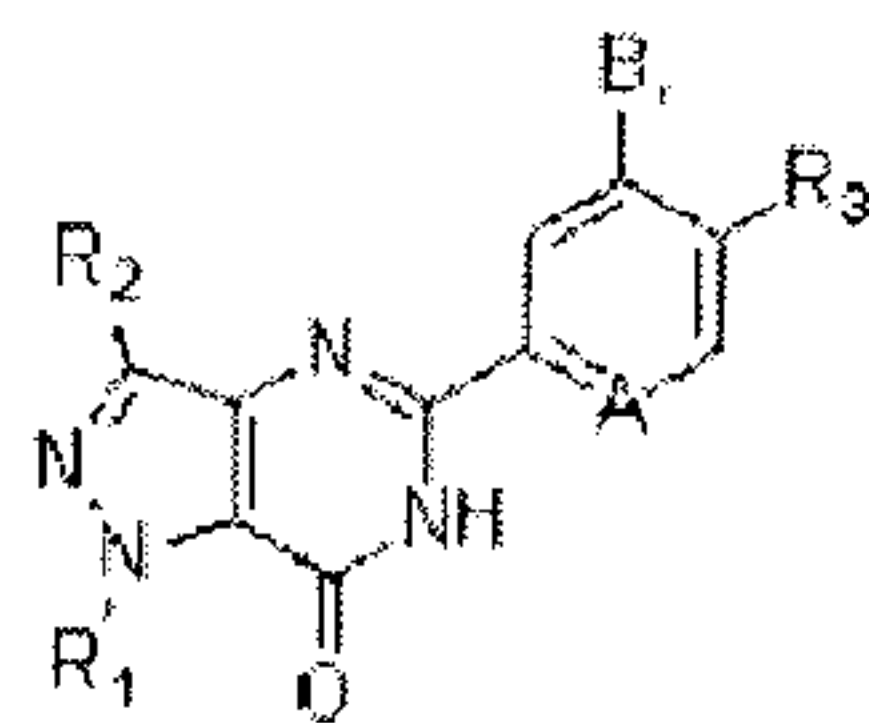
T11-S-T12-, (7) -T11-O-C(O)-T12-, (8) -T11-C(O)-O-T12-, (9) -T11-C(=NT9a)-T12-, or (10) -T11-C(O)-C(O)T12,

T7, T8, T9, T9a and T10 (1) are each independently hydrogen or a group provided in the definition of T6, or (2) T7 and T8 may together be alkylene or alkenylene, completing a 3-to 8- membered saturated or unsaturated ring together with the atoms to which they are attached, which ring is unsubstituted or substituted with one or more groups listed in the description of T1-1c, T2-2c and T3-3c, or (3) T7 or T8, together with T9, may be alkylene or alkenylene completing a 3-to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with one or more groups listed in the description of T1-1 c, T2-2c and T3-3c, or (4) T7 and T8 or T9 and T10 together with the nitrogen atom to which they are attached may combine to form a group-N=CT13T14 where T13 and T14 are each independently H or a group provided in the definition of T6; and

T11 and T12 are each independently (1) a single bond, (2) alkylene, (3) alkenylene, or (4) alkynylene.

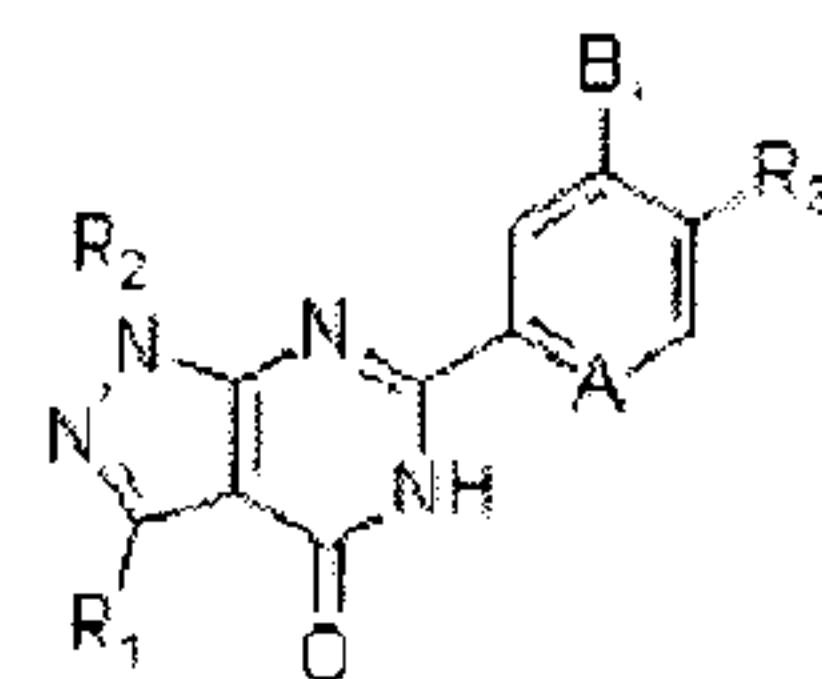
14. A combination comprising a phosphodiesterase 7 (PDE7) inhibitor that is selective for PDE7 relative to any other PDE enzyme from the PDE1-6 and PDE8-11 enzyme families and a dopamine receptor agonist for use to treat an addiction that is an addiction to an addictive substance or that is the practice of a compulsive behavior associated with a primary impulse-control disorder or an obsessive-compulsive disorder in a subject determined to have or to be at risk of developing an addiction, wherein each of the PDE7 inhibitor and the dopamine receptor agonist contribute to the effective treatment or reduction of use of the addictive agent or practice of the compulsive behavior.

15. The combination of Claim 14, wherein the subject is addicted to an addictive agent selected from the group consisting of: alcohol, nicotine, marijuana, a marijuana derivative, an opioid agonist, a benzodiazepine, a barbiturate, and a psychostimulant.
16. The combination of Claim 14, wherein the addiction is a compulsive behavior associated with a primary impulse-control disorder or an obsessive-compulsive disorder selected from the group consisting of: binge eating, food addiction, pathological gambling, pathological use of electronic devices, pathological use of electronic video games, pathological use of electronic communication devices, pathological use of cellular telephones, addiction to pornography, sex addiction, compulsive spending, anorexia, bulimia, intermittent explosive disorder, kleptomania, pyromania, trichotillomania, compulsive over-exercising, and compulsive overworking.
17. The combination of Claim 14, wherein the dopamine receptor agonist is selected from bromocriptine, pergolide, pramipexole, ropinirole, cabergoline, apomorphine, lisuride, rotigotine, quinagolide and fenoldopam.
18. The combination of Claim 14, wherein the selective PDE7 inhibitor has an IC_{50} for inhibiting PDE7A, PDE7B, or PDE7A and PDE7B for which the lesser of the IC_{50} for inhibiting PDE7A activity and the IC_{50} for inhibiting PDE7B activity is less than one-tenth the IC_{50} that the agent has for inhibiting the activity of any other PDE enzyme from the PDE1-6 and PDE8-11 enzyme families.
19. The combination of Claim 14, wherein the PDE7 inhibitor is:



(1A)

or



(1B)

wherein:

A is N or CR₄:

B is a hydrogen or a halogen atom;

R₁ is optionally substituted C₃₋₇ cycloalkyl or tert-butyl;

R₂ is hydrogen, methyl, or ethyl;

R₃ is hydrogen, nitro, cyano or halogen, NR₅R₆, C(=X)R₇, SO₂NR₅R₆, OR₈, NR₈CONR₅R₆, NR₈SO₂R₉, NR₈CO₂R₉, a heteroaryl group, optionally substituted C₁₋₃ alkyl, optionally substituted C₁₋₆ alkenyl, or optionally substituted saturated or unsaturated heterocycloalkyl;

R₄ is hydrogen, or C₁₋₃ alkoxy substituted by one or more fluorine atoms;

R₅ and R₆ are the same or different, and are a hydrogen atom, optionally substituted C₁₋₆ alkyl, optionally substituted heterocycloalkyl, or optionally substituted acyl or, together with the nitrogen atom which they are bound to, form azetidiny, pyrrolidiny, piperidiny, morpholino, thiomorpholino, piperaziny, or homopiperaziny, each of these groups being optionally substituted by optionally substituted C₁₋₄ alkyl, OH, C₁₋₃ alkoxy, CO₂H, NR₅R₆, an oxo group, NR₉COR₇, or C(=O)R₇;

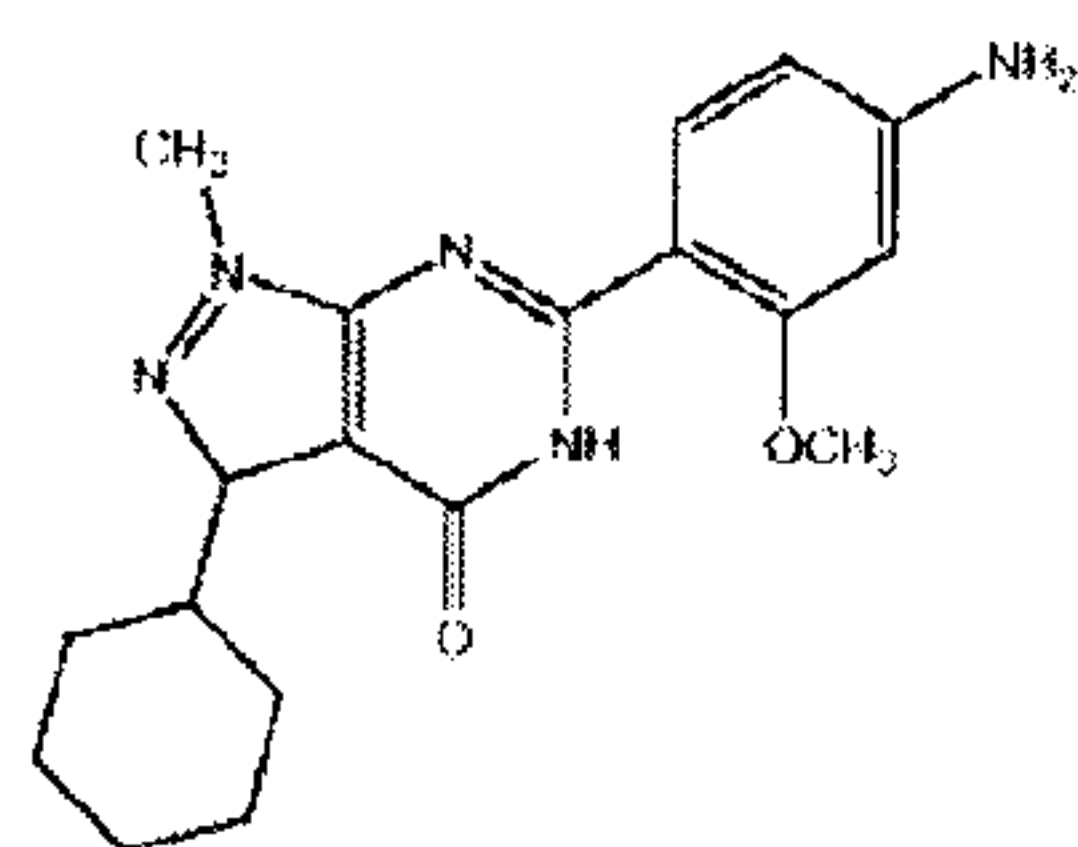
R₇ is optionally substituted C₁₋₆ alkyl, OH, OR₈, or NR₅R₆;

R₈ is hydrogen, an optionally substituted C₁₋₆ alkyl group, or optionally substituted heterocycloalkyl;

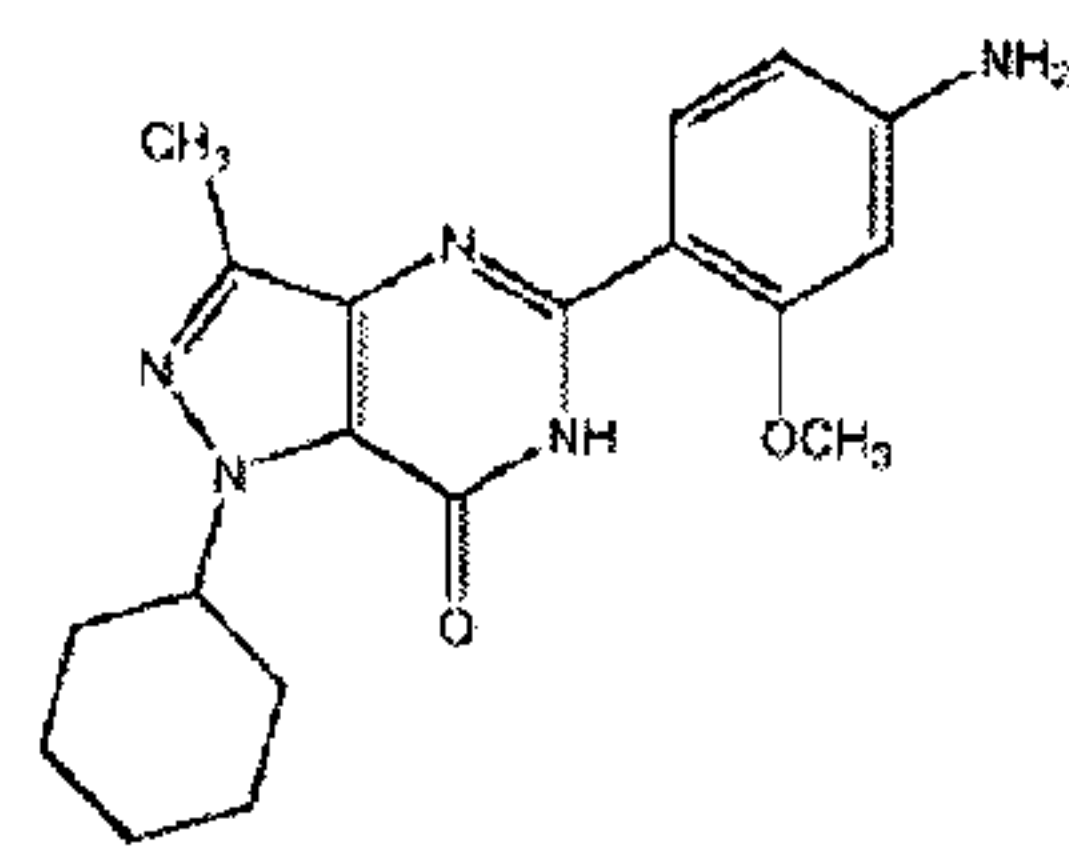
R₉ is an optionally substituted C₁₋₆ alkyl group; and

X represents O, S, or NH.

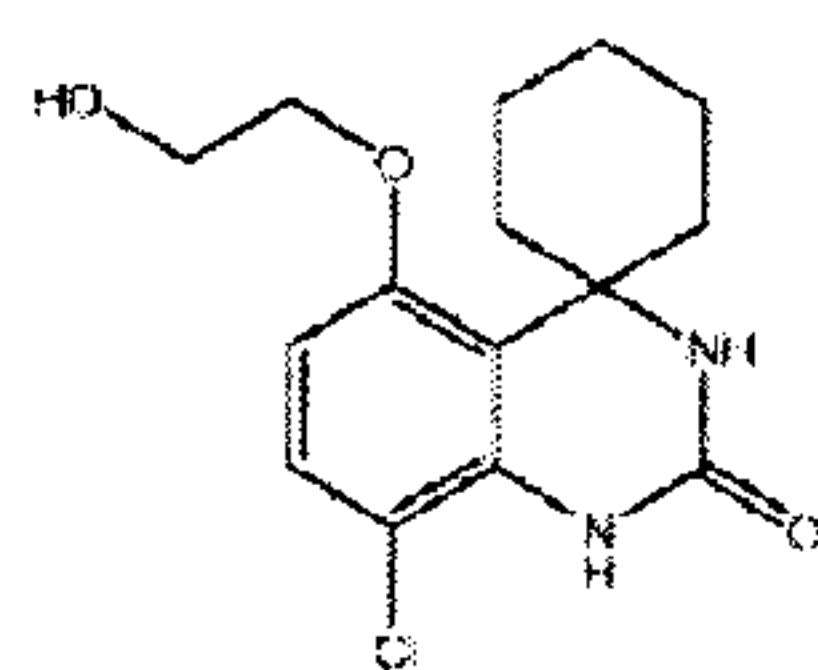
20. The combination of Claim 14, wherein the PDE7 inhibitor is selected from the following compounds:



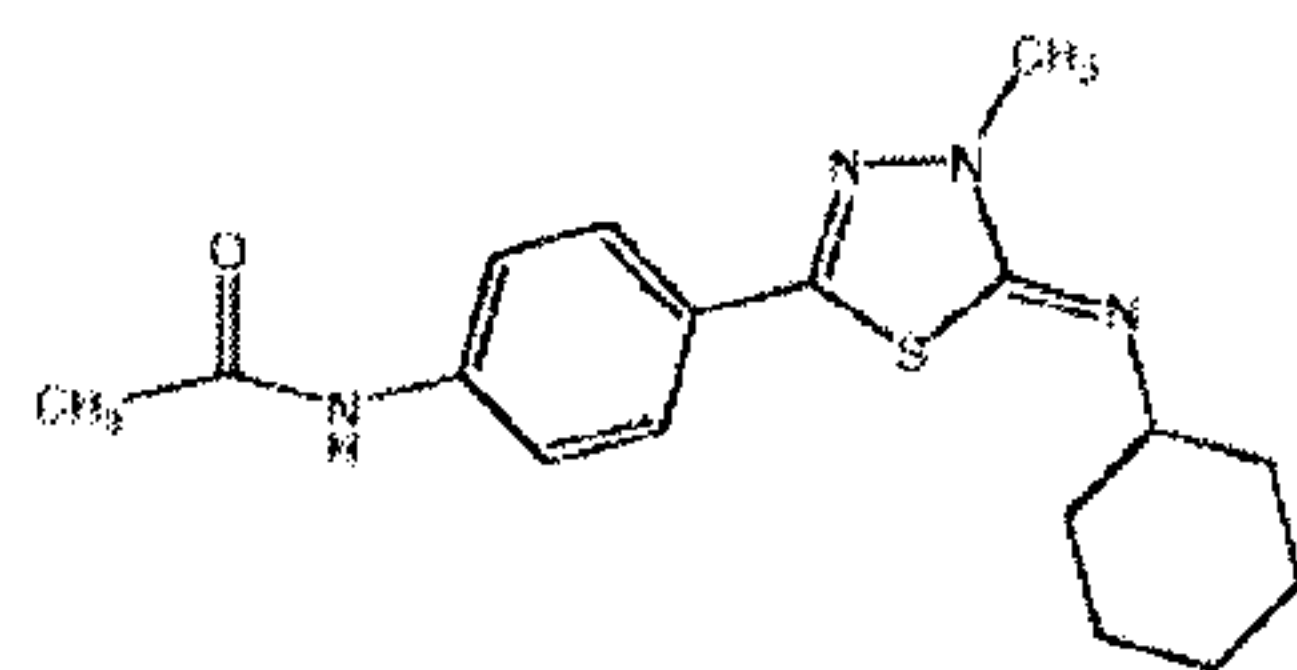
(1);



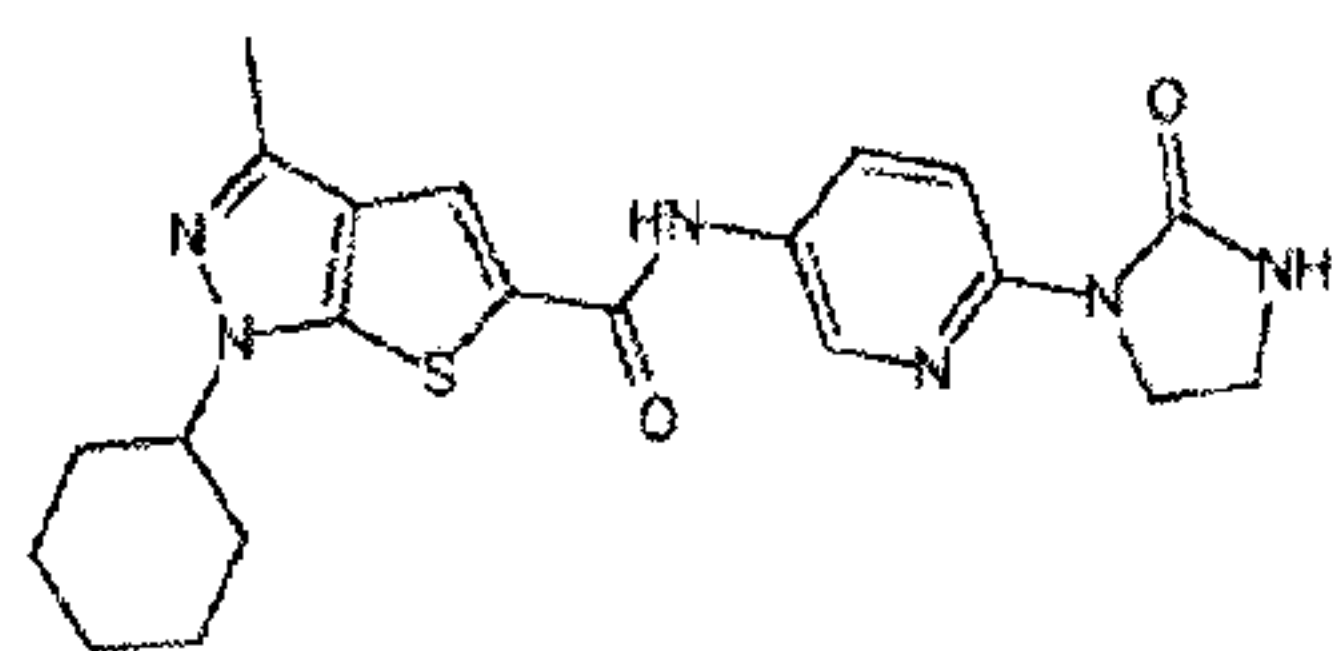
(2);



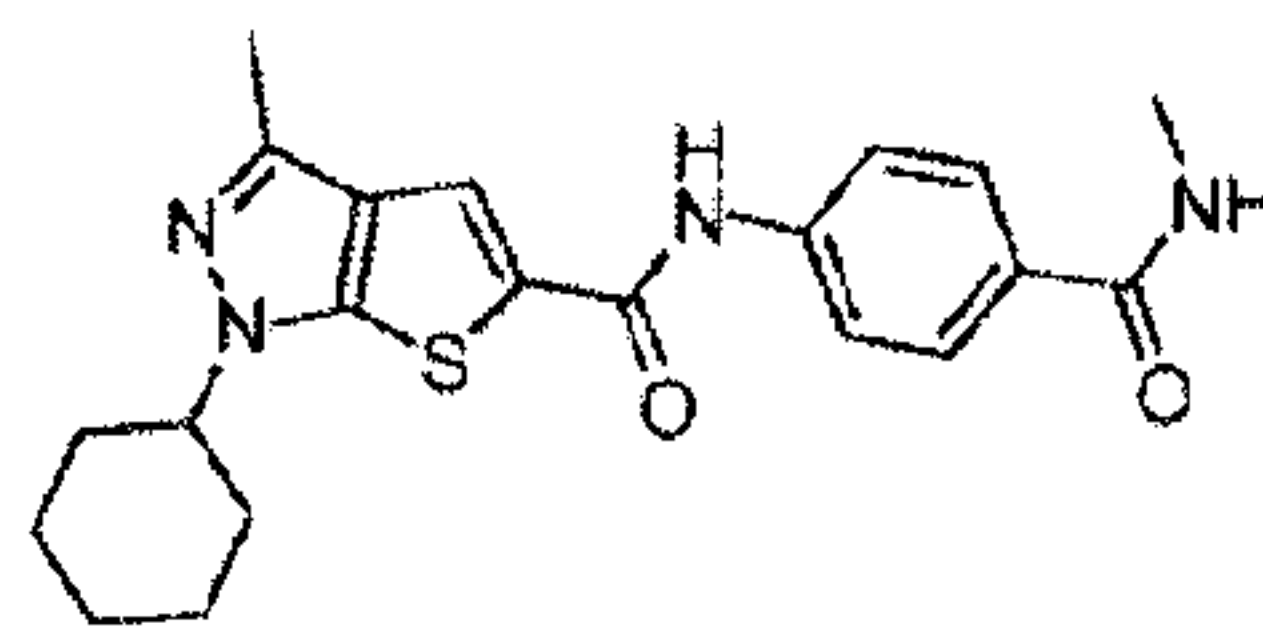
(3);



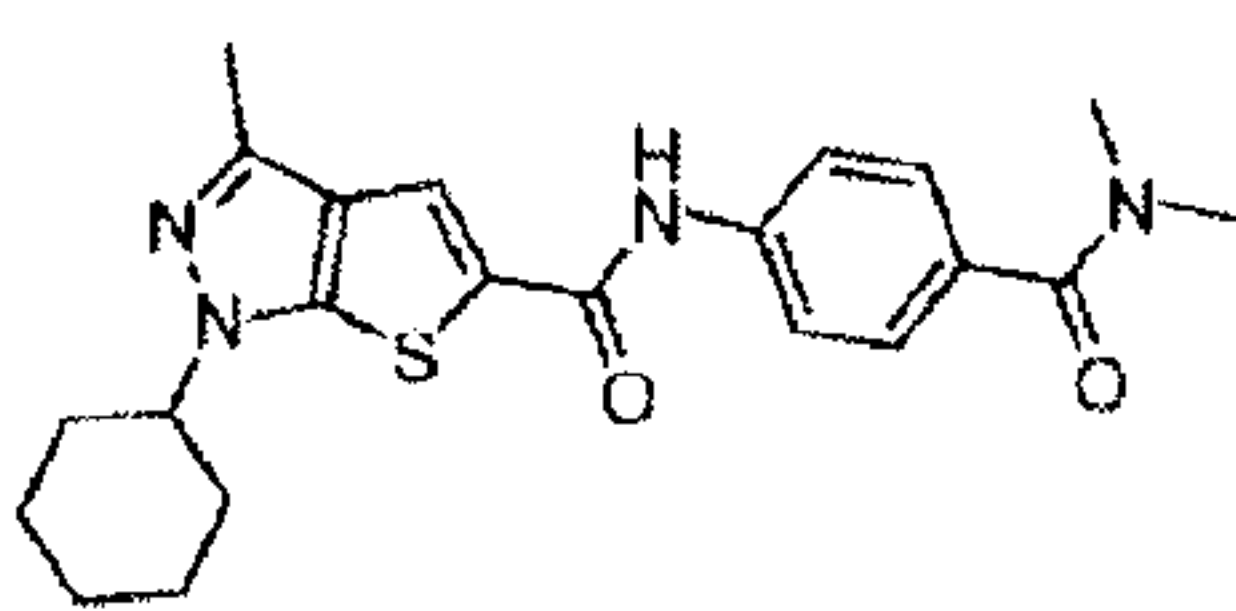
(4);



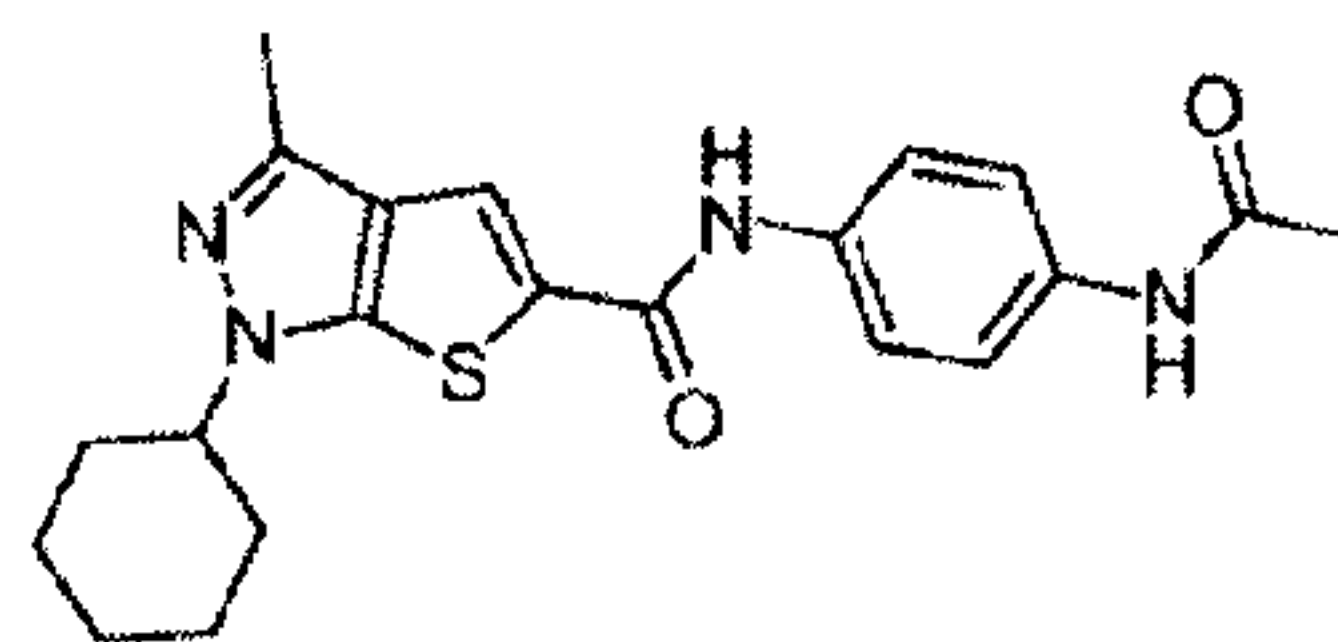
(6A);



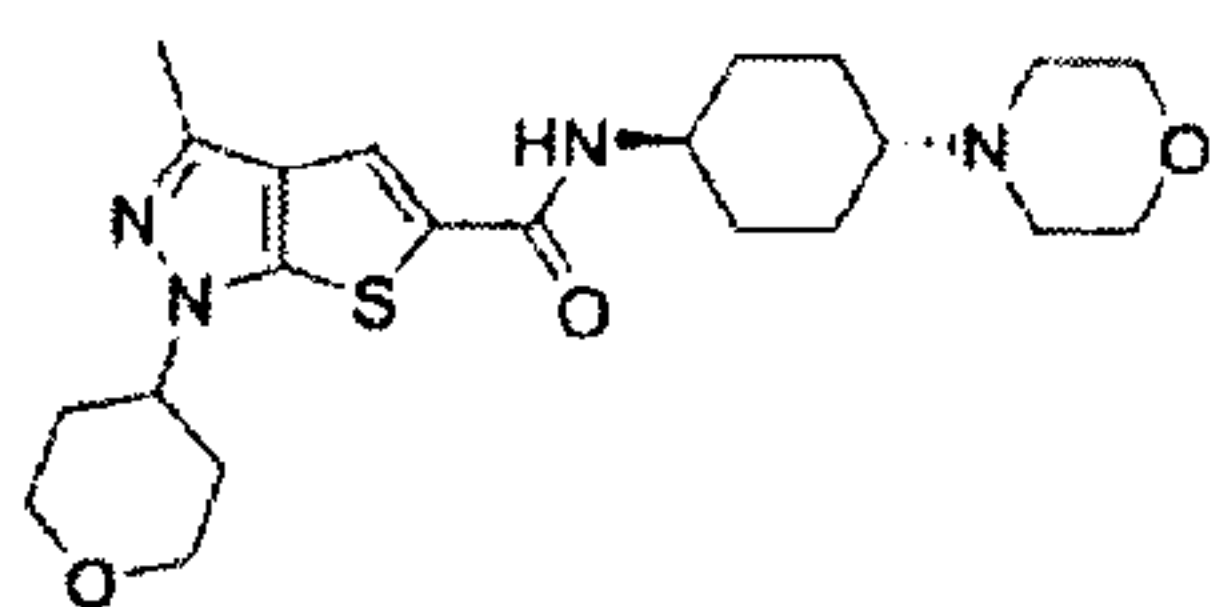
(6B);



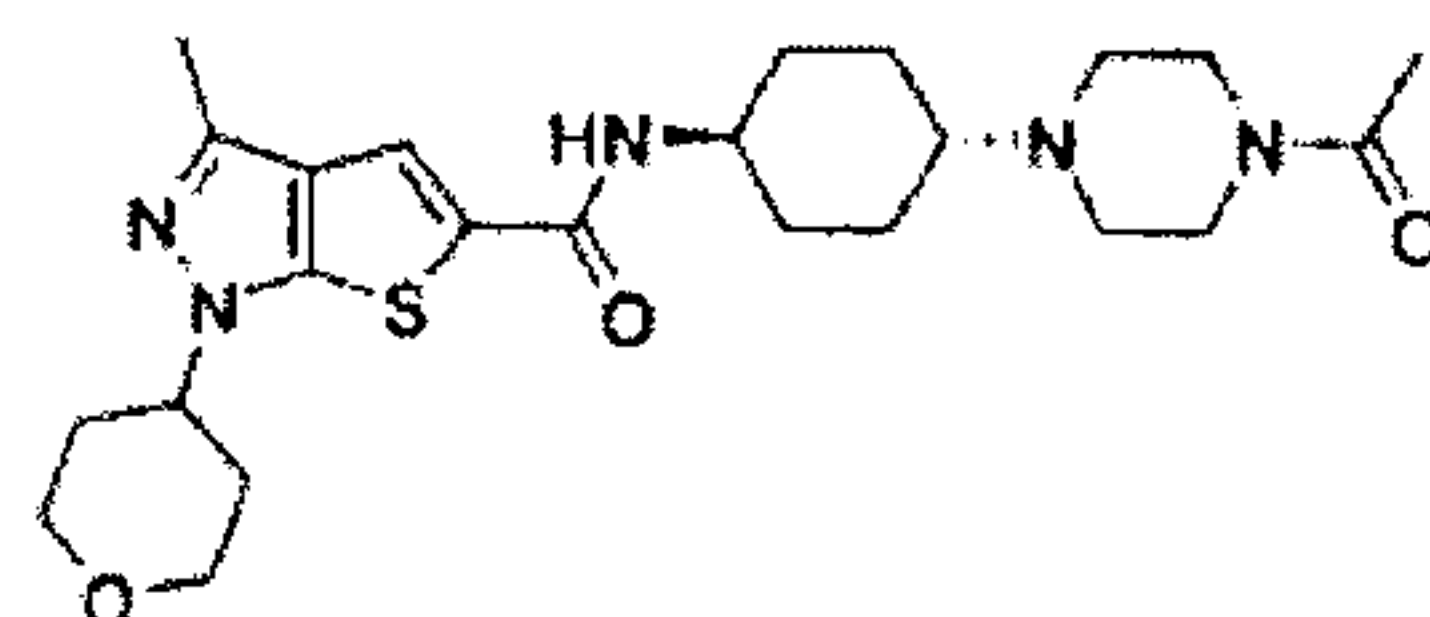
(6C);



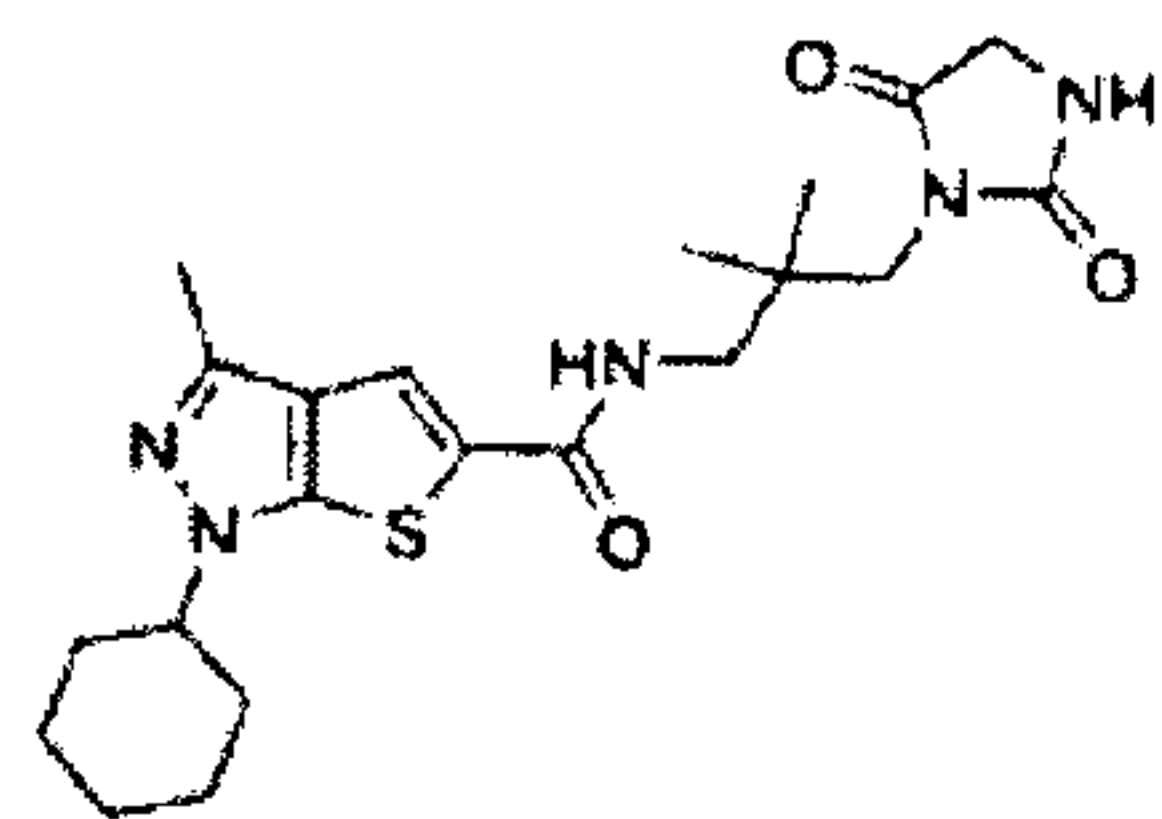
(6D);



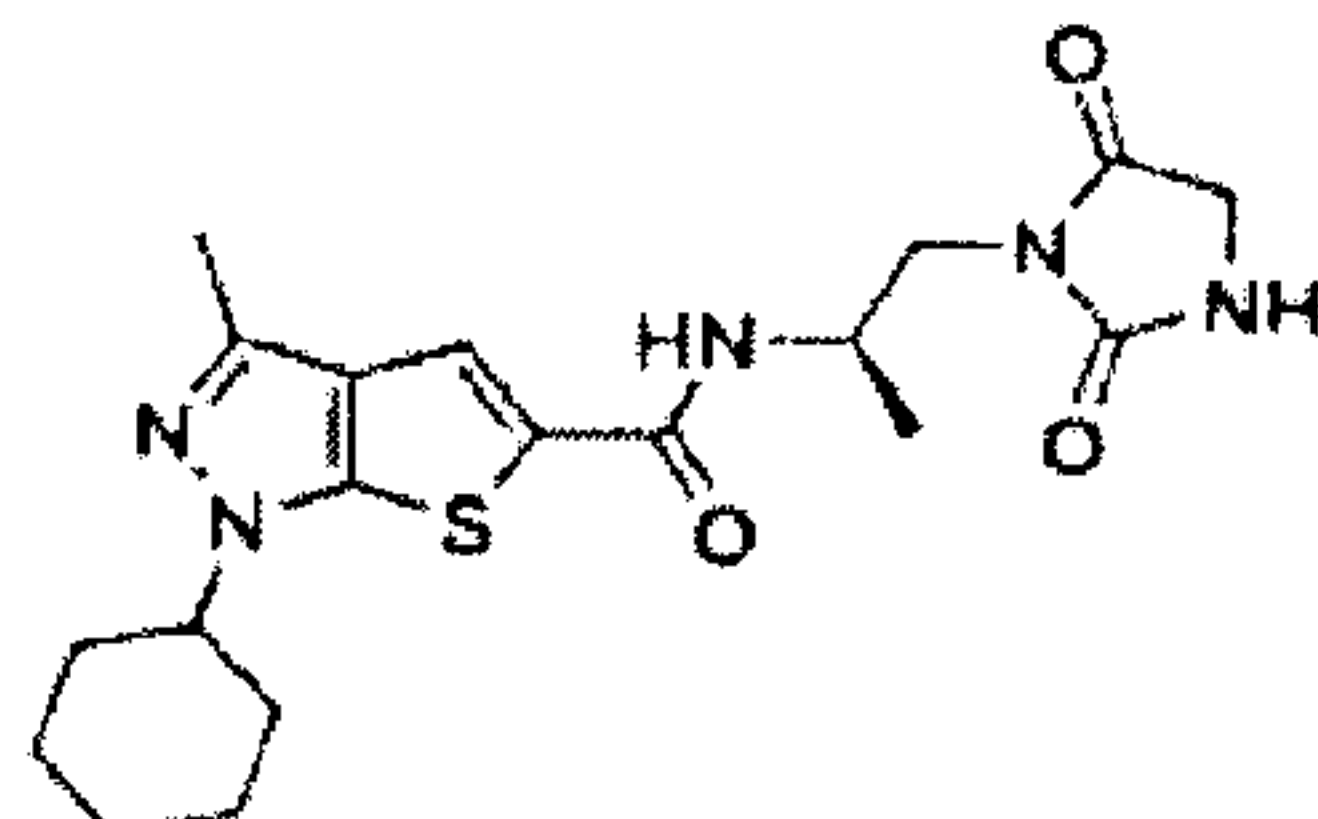
(6E);



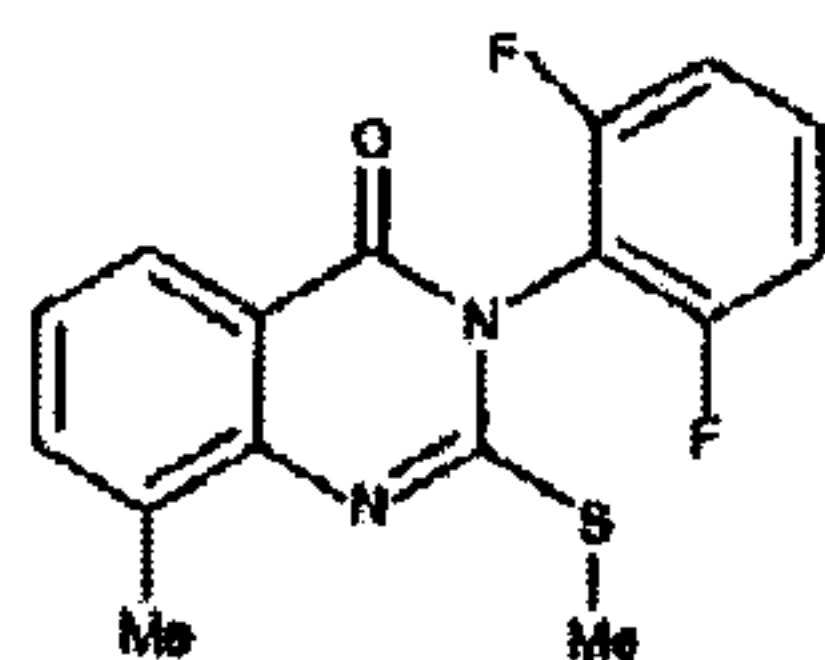
(6F);



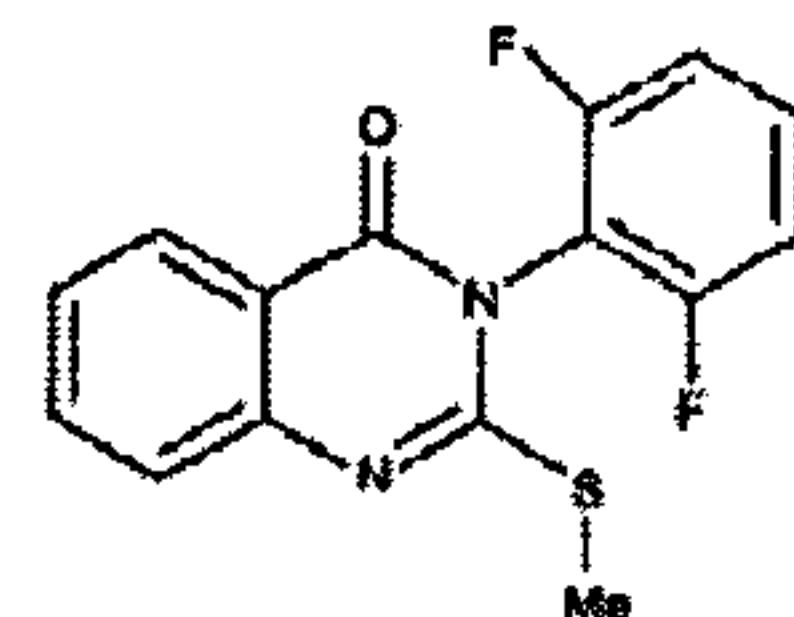
(6G);



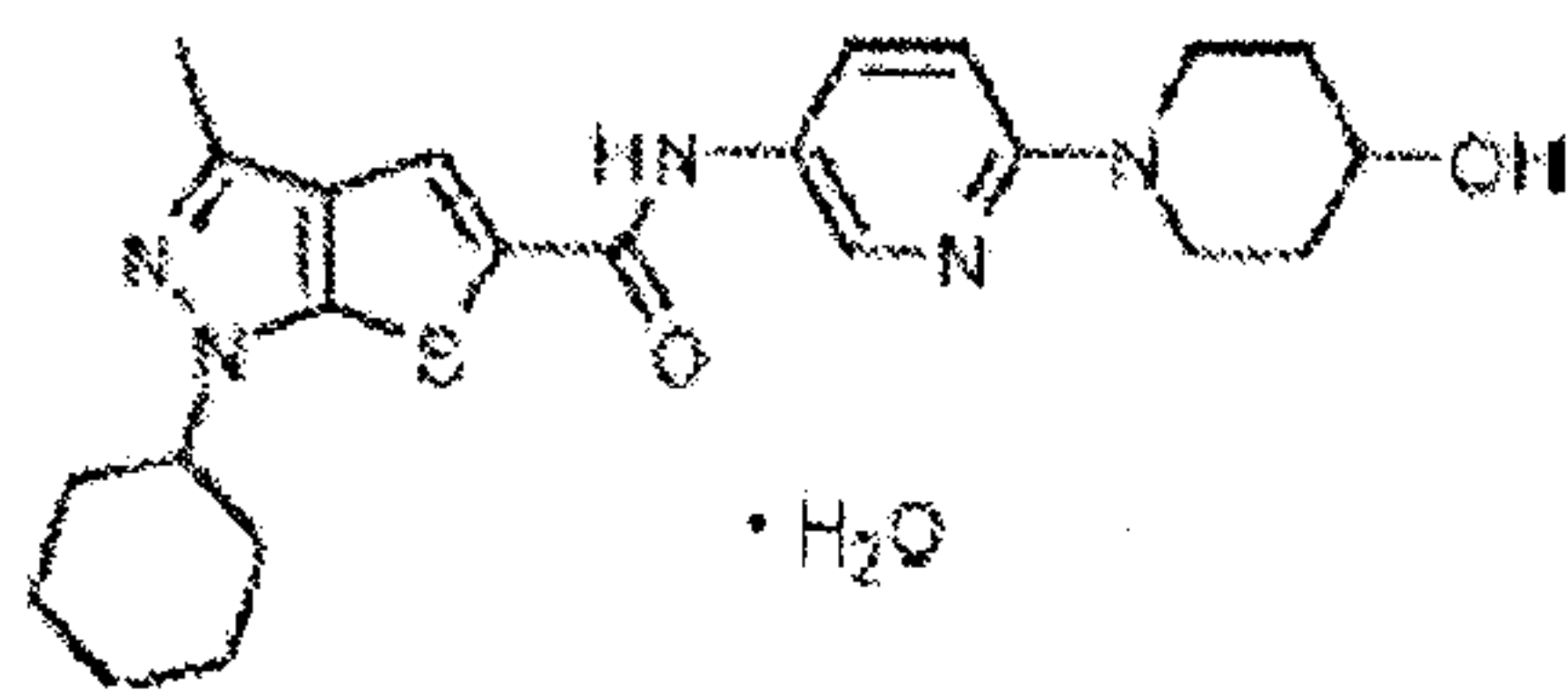
(6H);



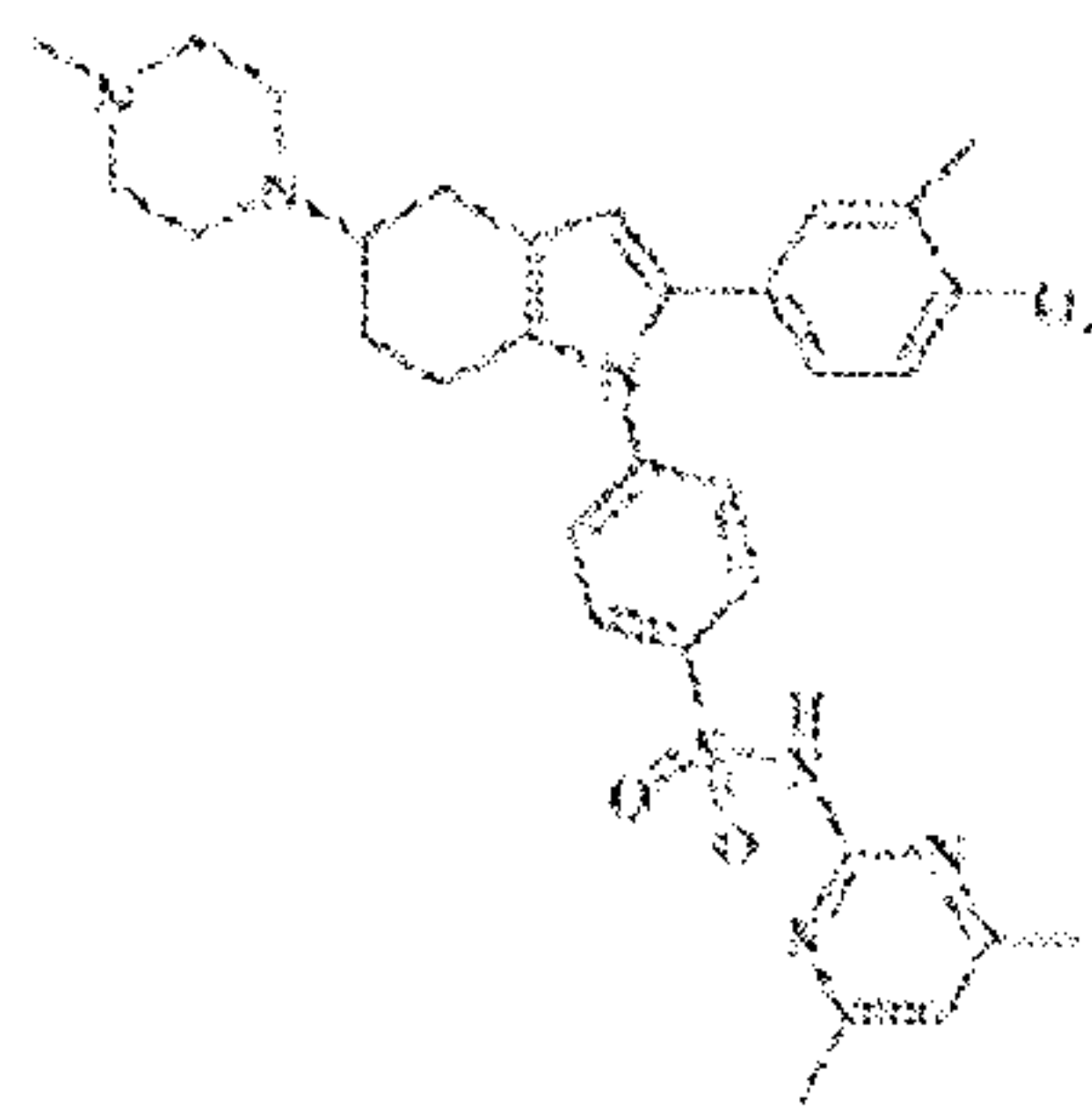
(43A);



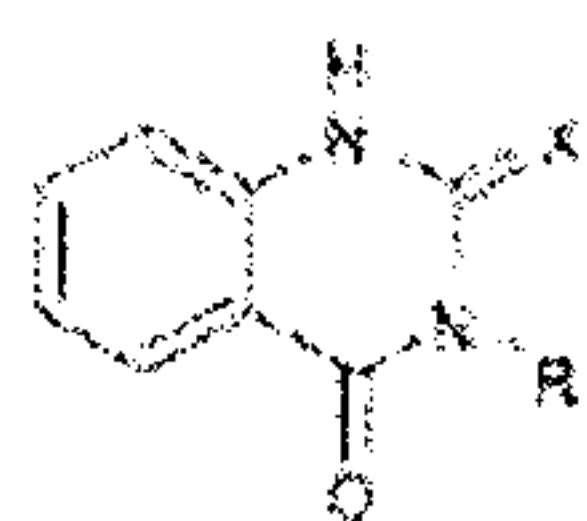
(43B);



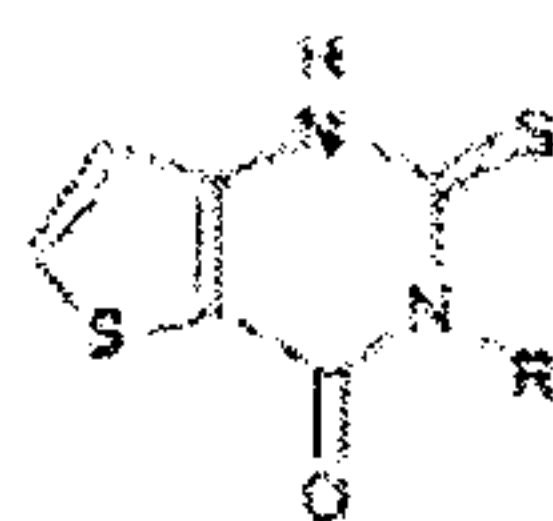
(45);



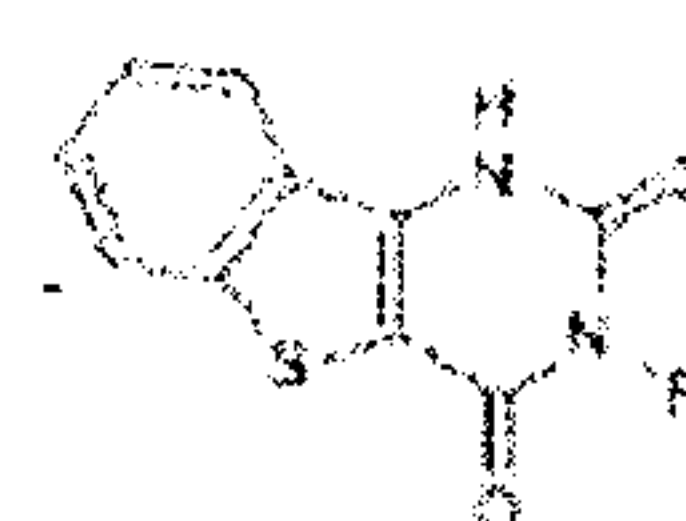
(46);



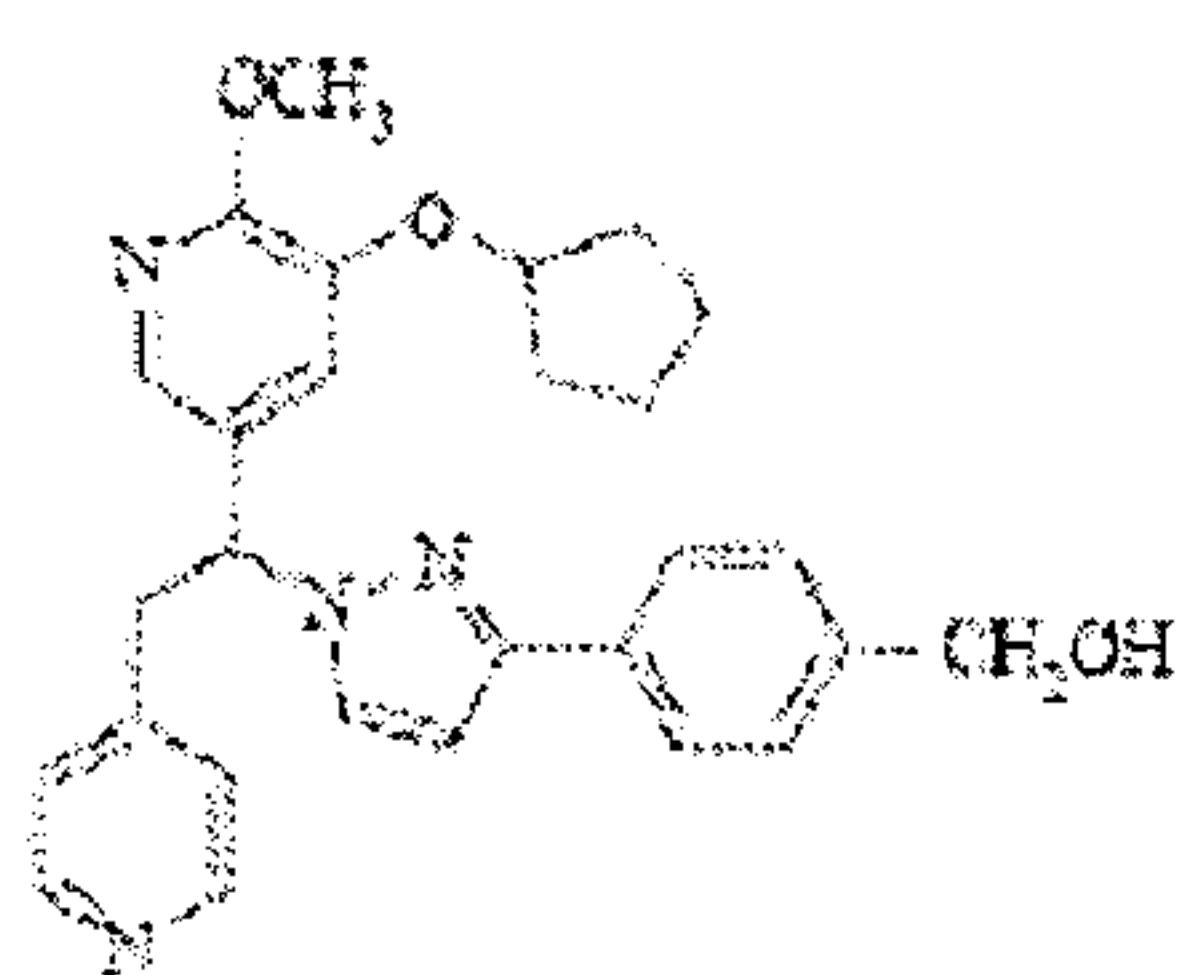
(47);



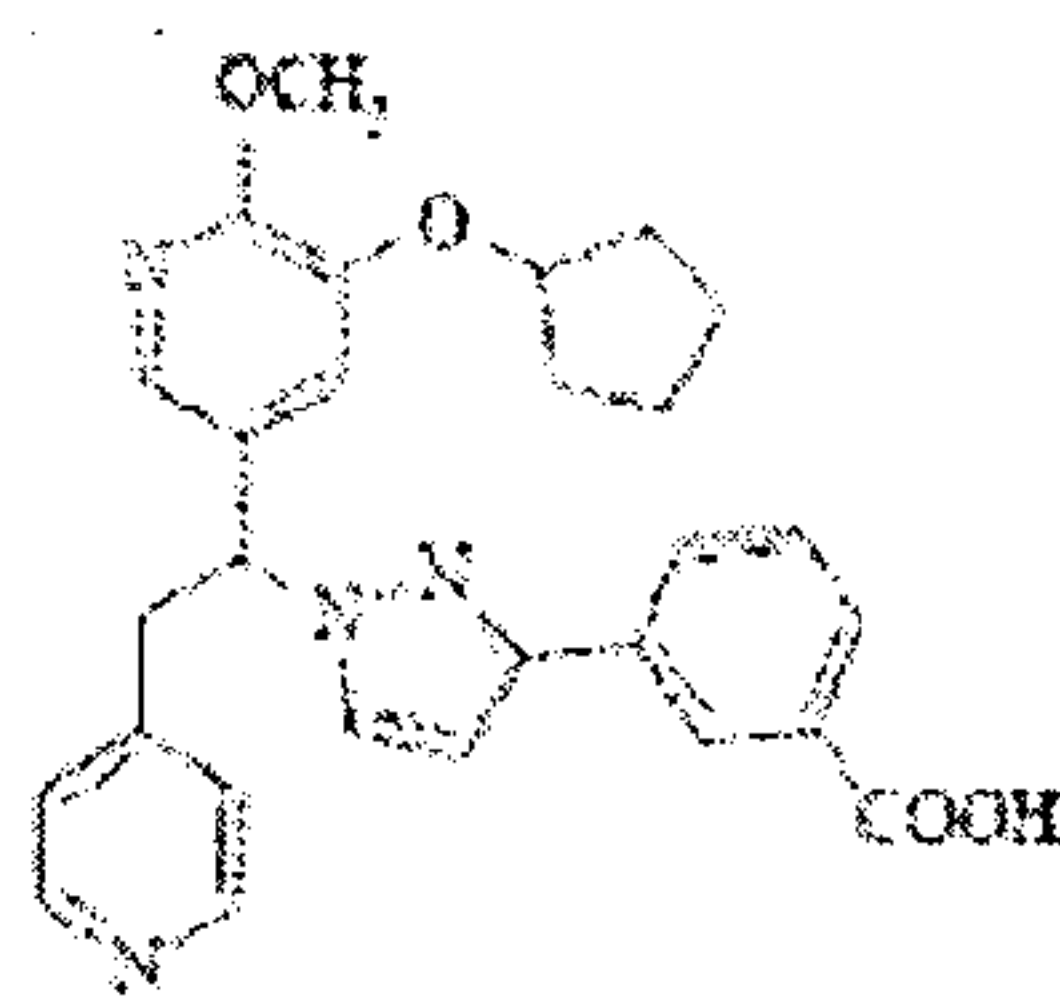
(48);



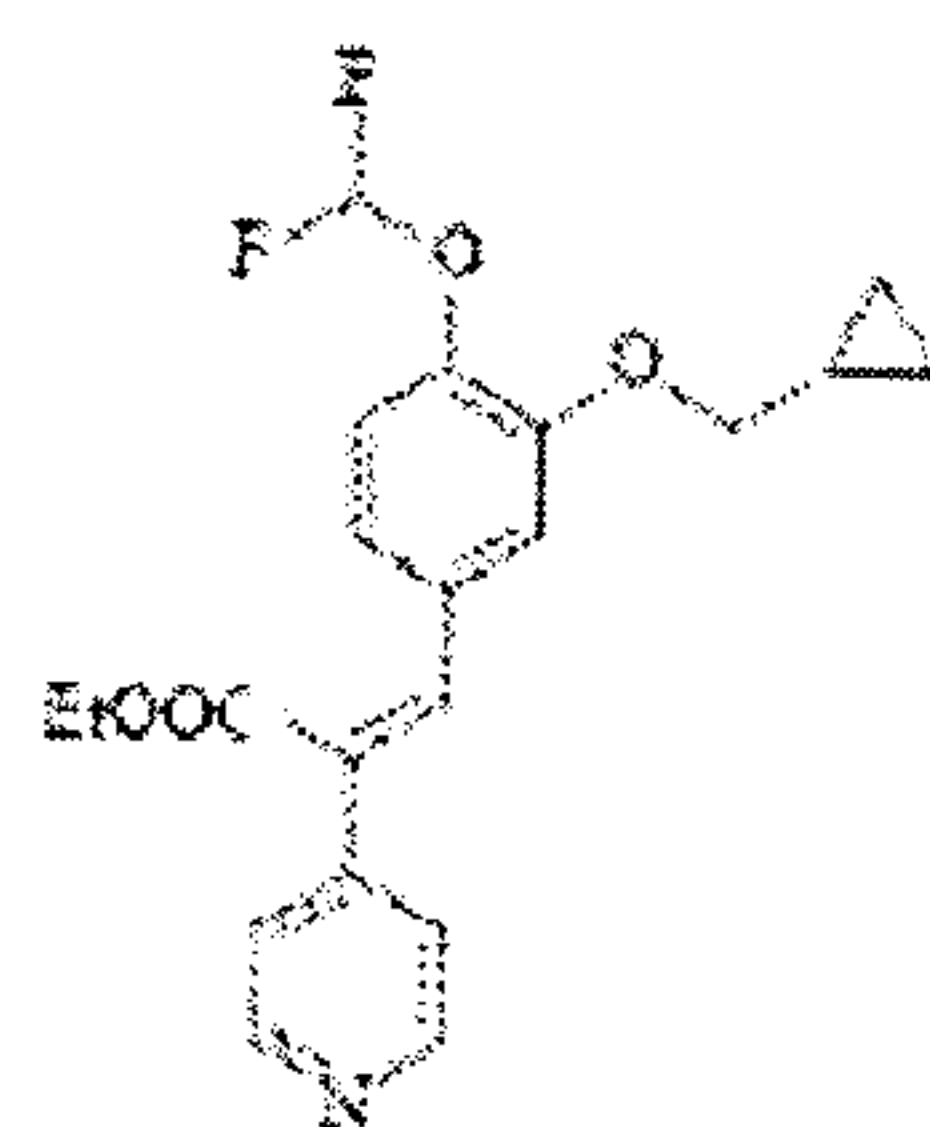
(49);



(51);

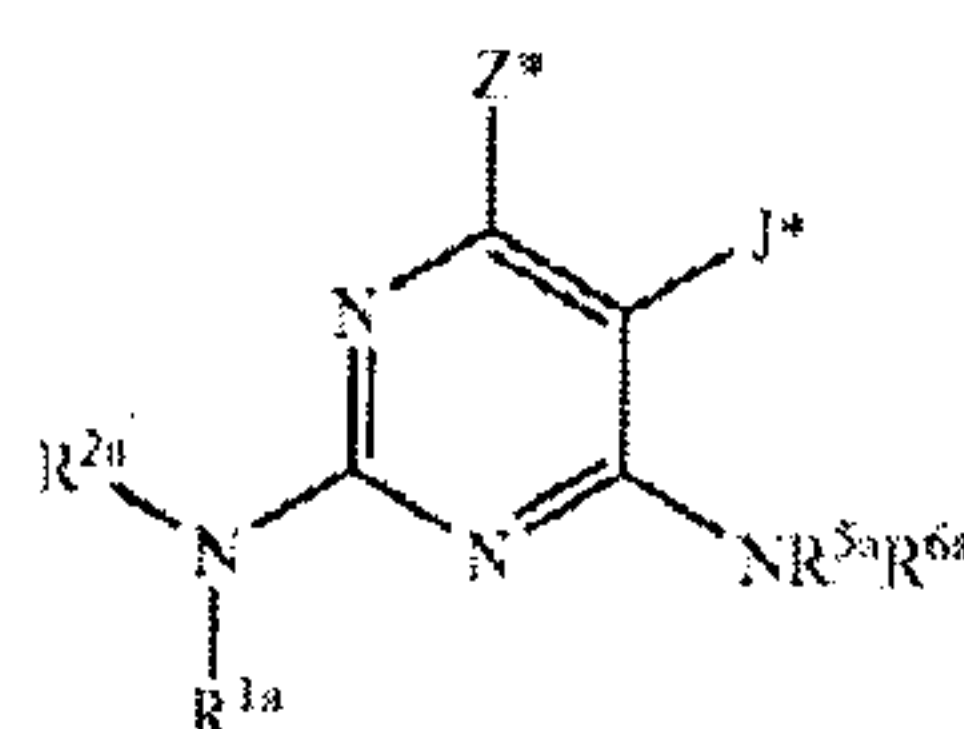


(52); and



(53).

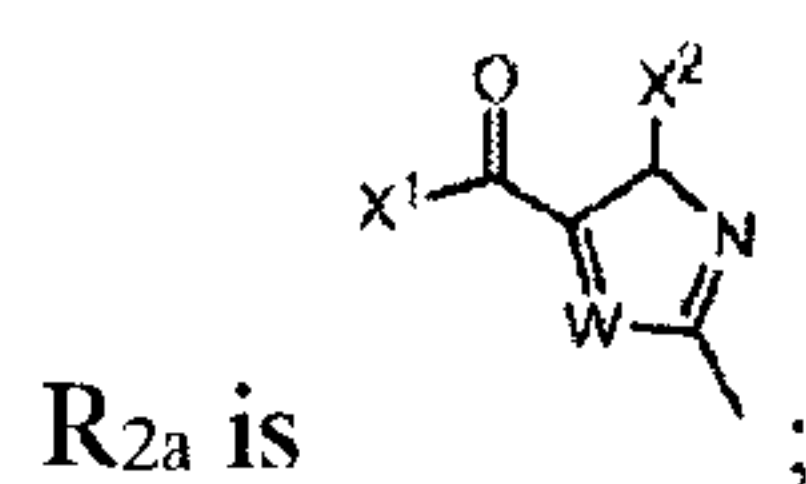
21. The combination of Claim 14, wherein the PDE7 inhibitor is:



(16A)

wherein:

R_{1a} is hydrogen or alkyl;



W is S;

X₁ is alkoxy;

X₂ is alkyl;

Z* is halogen, haloalkyl, oxazolyl, NR_{3a}R_{4a}, C(O)-N(H)-alkylene-COOH, or phenyl which is unsubstituted or substituted with heteroaryl, CO₂H, or CO₂T₆;

R_{3a} is hydrogen or alkyl;

R_{4a} is alkyl, alkoxy, unsubstituted or substituted (heteroaryl) alkyl, unsubstituted or substituted heterocyclo, unsubstituted or substituted (heterocyclo) alkyl, or (aryl) alkyl wherein the aryl group is substituted with one or two groups T₁ and/or T₂ and/or further substituted with a group T₃; or

R_{3a} and R_{4a} together with the nitrogen atom to which they are attached combine to form an unsubstituted or substituted heterocyclo ring;

R_{5a} is an unsubstituted or substituted (heteroaryl) alkyl, or (aryl) alkyl wherein the aryl group is substituted with one or two groups T₁ and/or T₂ and/or further substituted with a group T₃; or

R_{5a} and R_{6a} together with the nitrogen atom to which they are attached combine to form an unsubstituted or substituted heterocyclo ring;

R_{6a} is hydrogen or alkyl;

J* is hydrogen or alkyl;

T₁ and T₂ are independently alkoxy, alkoxycarbonyl, heteroaryl, SO₃H, or SO₂R_{8a} where R_{8a} is alkyl, amino, alkylamino or dialkylamino; or

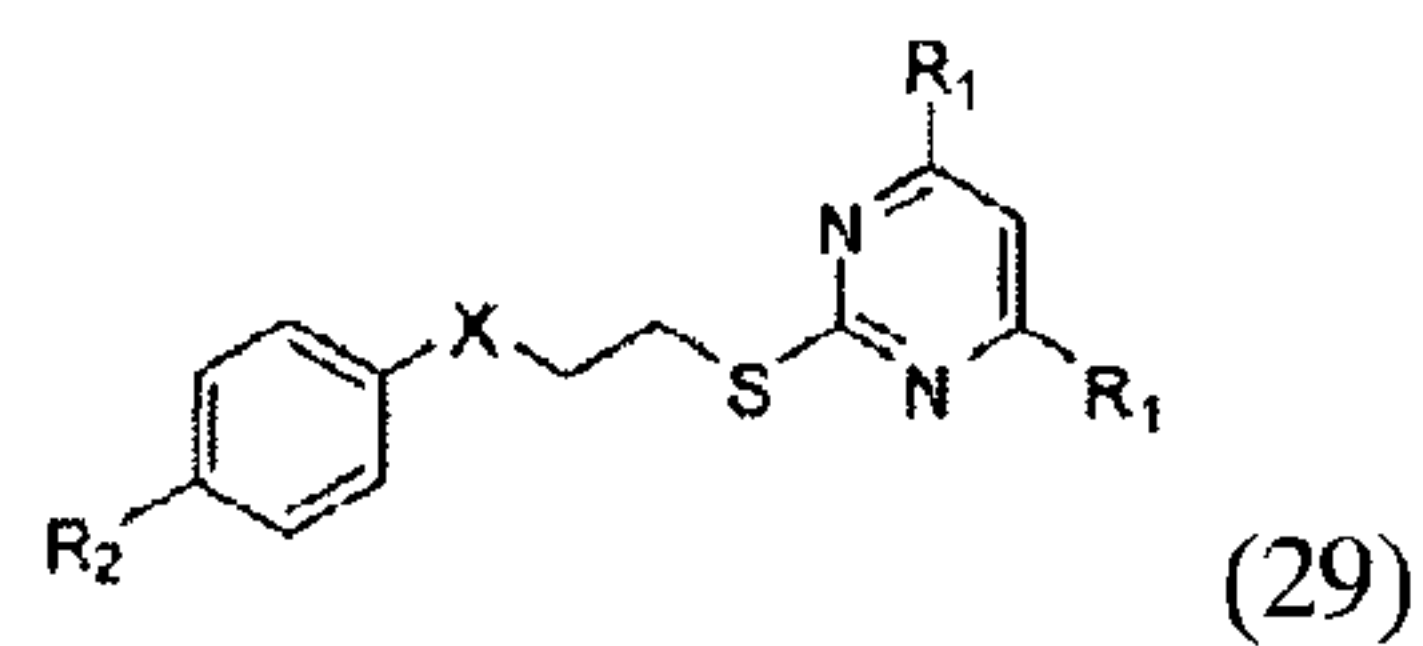
T₁ and T₂ together with the aryl ring to which they are attached combine to form a bicyclic ring;

T₃ is H, alkyl, halo, halo alkyl, or cyano;

t is 1 or 2; and

T₆ is alyl, halo alkyl, cycloalkyl, alkoxy, or heteroaryl.

22. The combination of Claim 14, wherein the PDE7 inhibitor is selected from the following compounds:

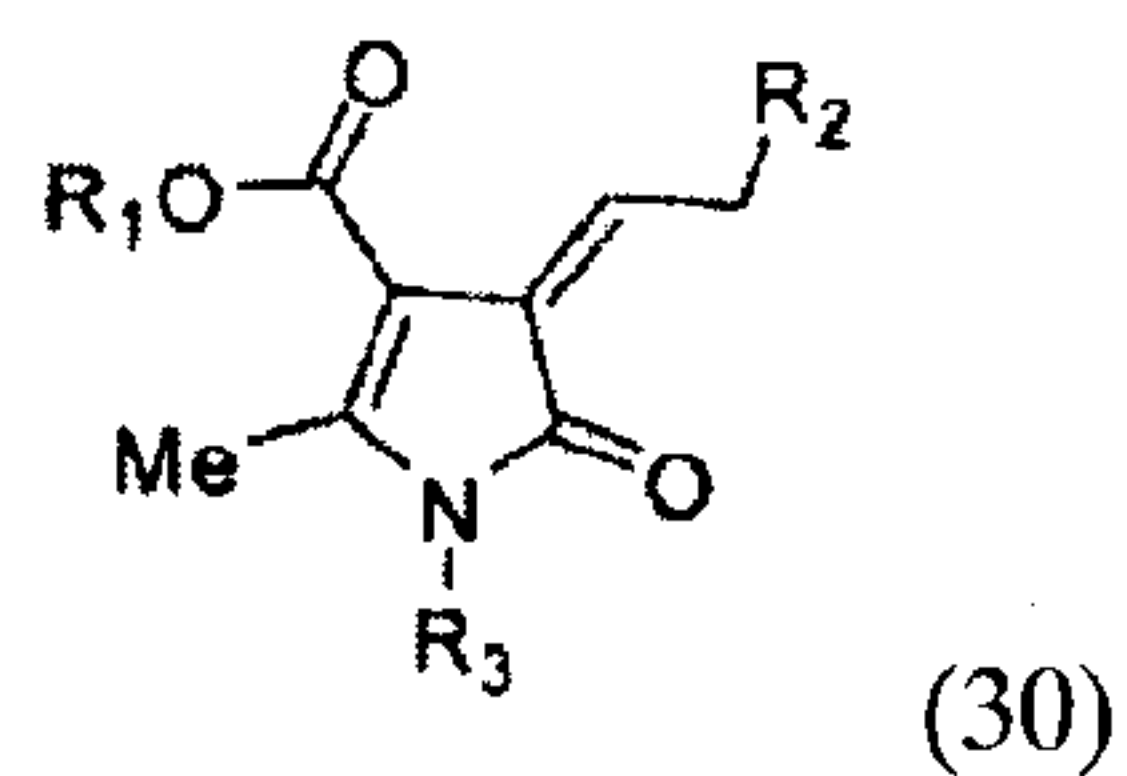


wherein:

X is SO, or SO₂,

R1 is H, or alkyl,

R2 is alkyl, or halogen;

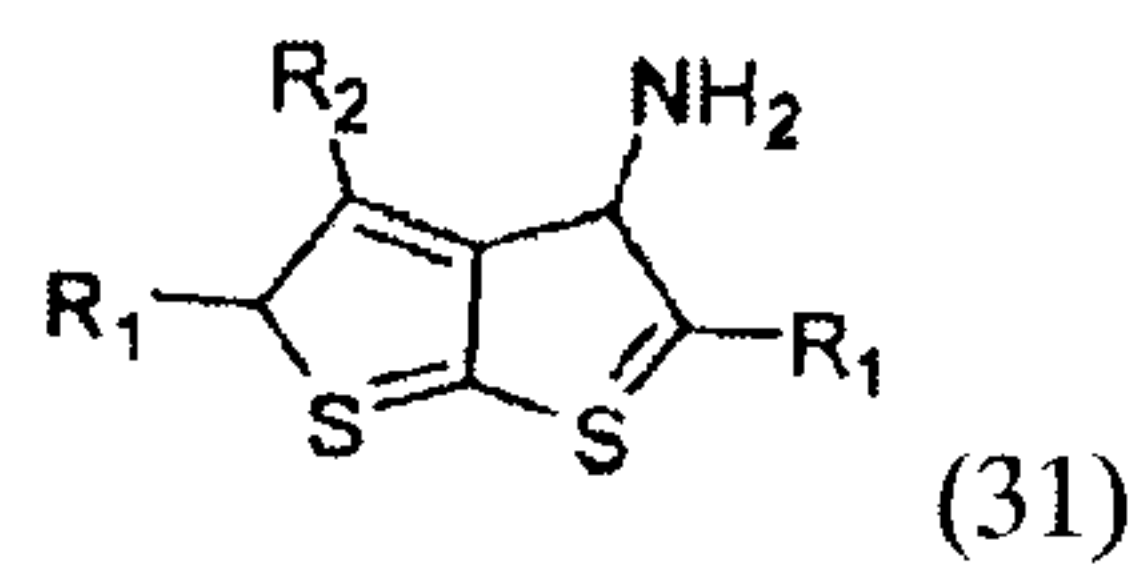


wherein:

R1 is alkyl,

R2 is aryl or heteroaryl,

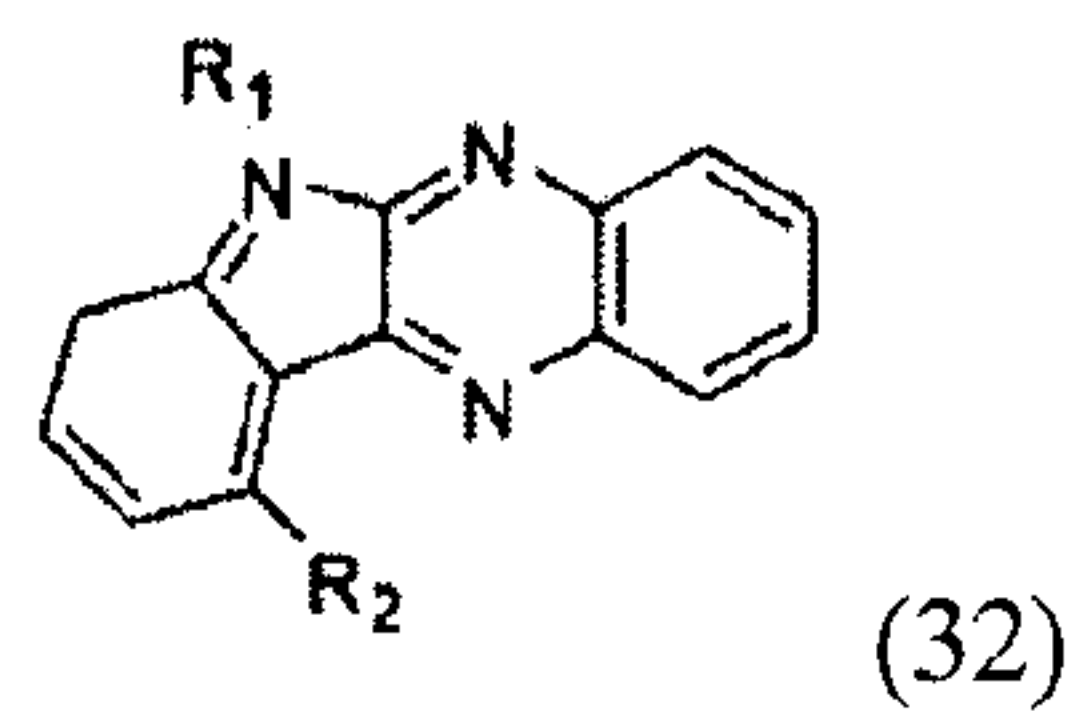
R3 is alkyl, aryl, cycloalkyl, or alkyl aryl;



wherein:

R1 is nitrile, or alkylcarboxylate,

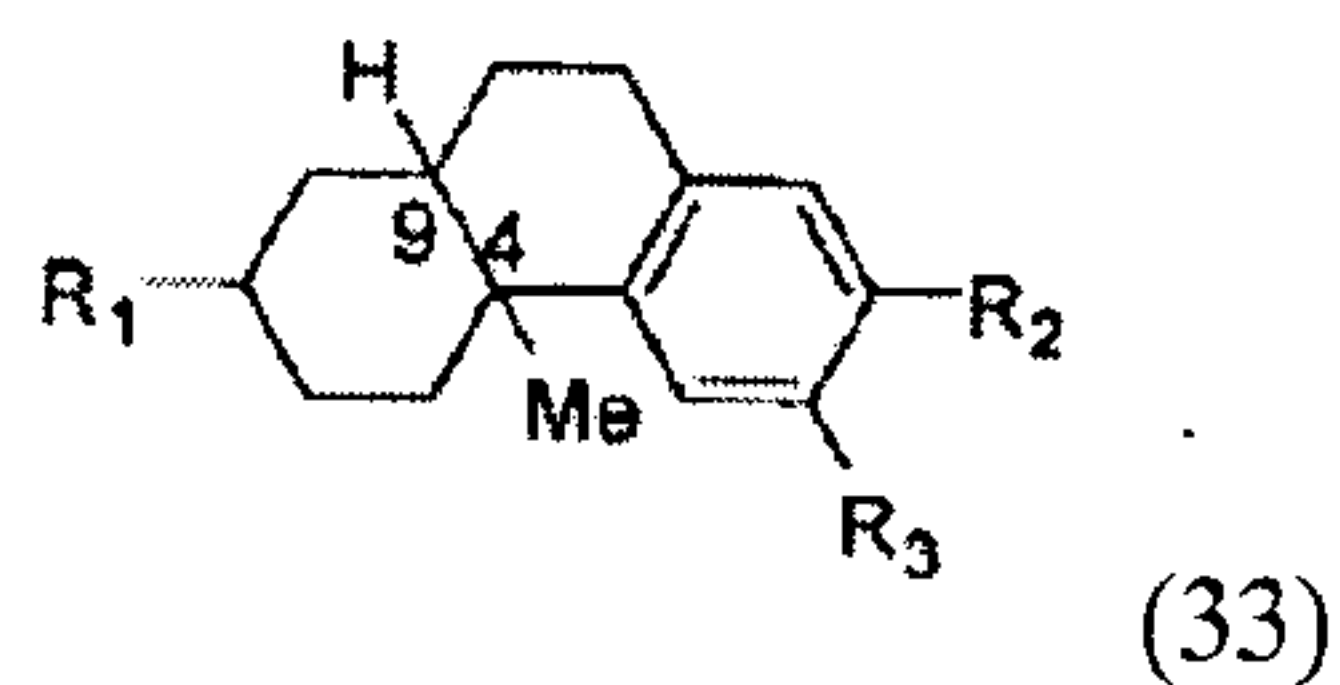
R2 is alkyl, aryl, or heteroaryl;



wherein:

R1 is alkyl, alkenyl, or alkylcarboxylic acid,

R2 is halogen;



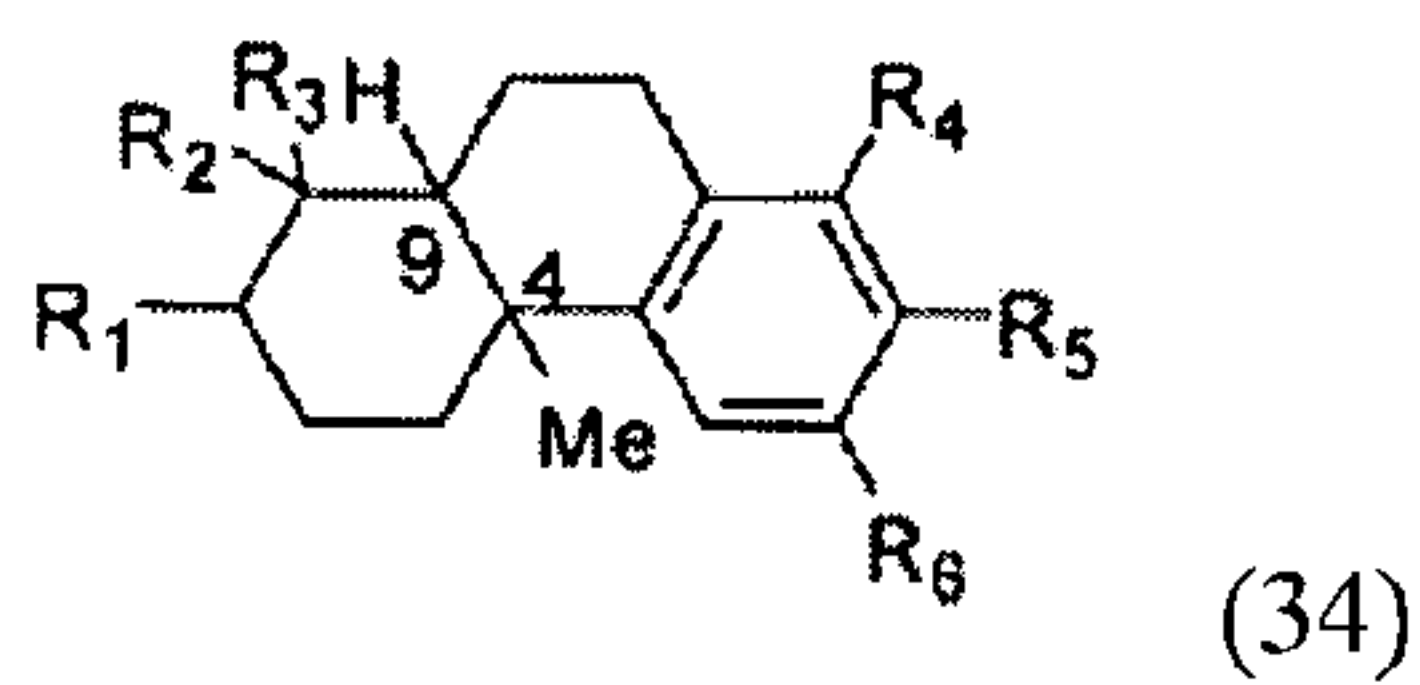
wherein:

R1 is CO, or alkylalcohol,

R2 is alkyl,

R3 is alkoxy, and

the C4 and C9 stereocenters are independently (R) or (S);



wherein:

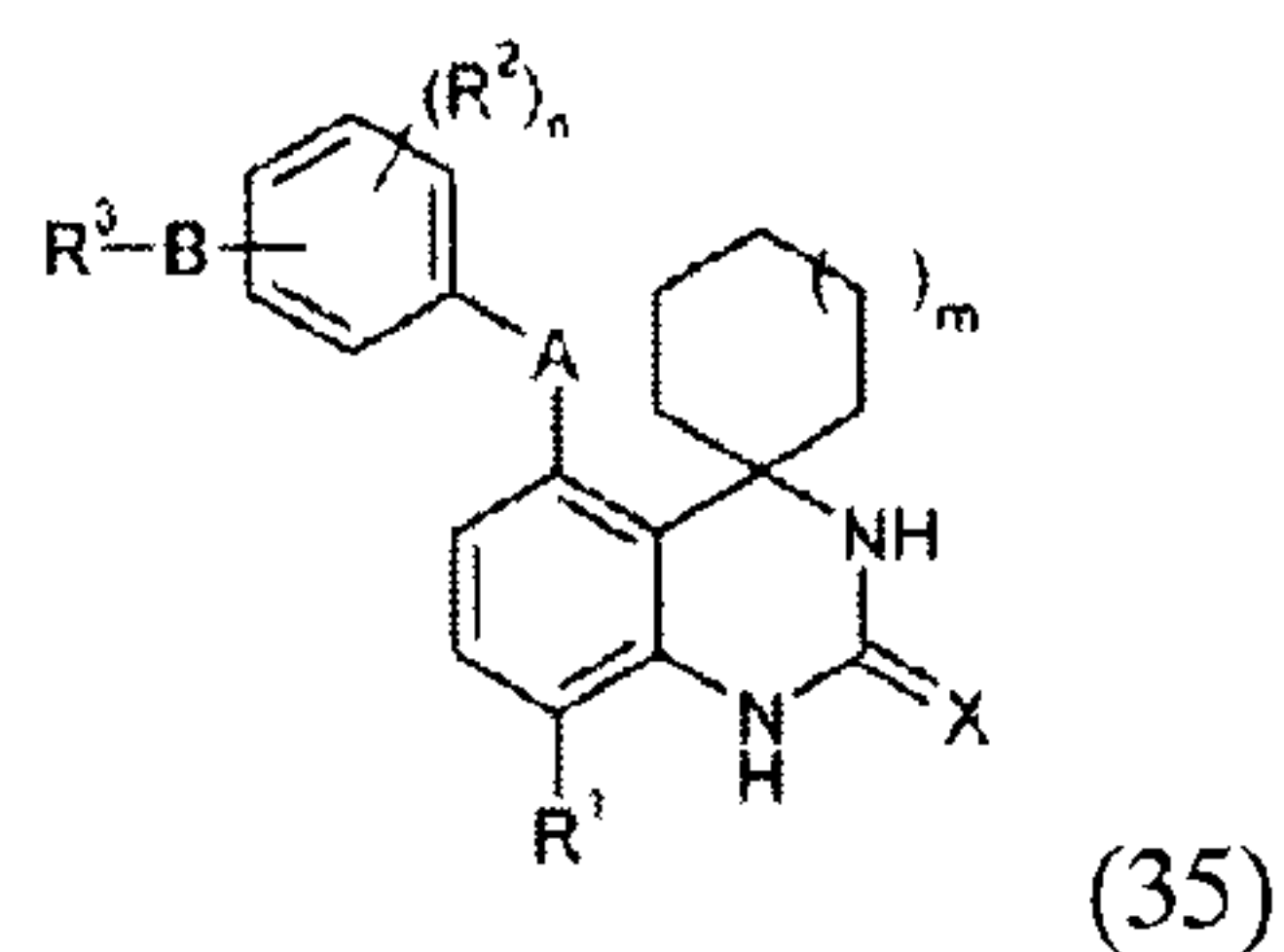
R1 is hydrogen, hydroxyl, carbonyl, or alkylalcohol,

R2 and R3 are independently selected from hydrogen, alkyl, alkylcarboxylate, and carboxylic acid,

R4 is hydrogen, or alkyl,

R5 is hydrogen, alkyl, hydroxyl, or acetate,

R6 is hydrogen, or alkoxy, and the C4 and C9 stereocenters are independently (R) or (S);



wherein:

m is 0, 1 or 2,

n is 0, 1, 2 or 3,

X is O, S or N-CN,

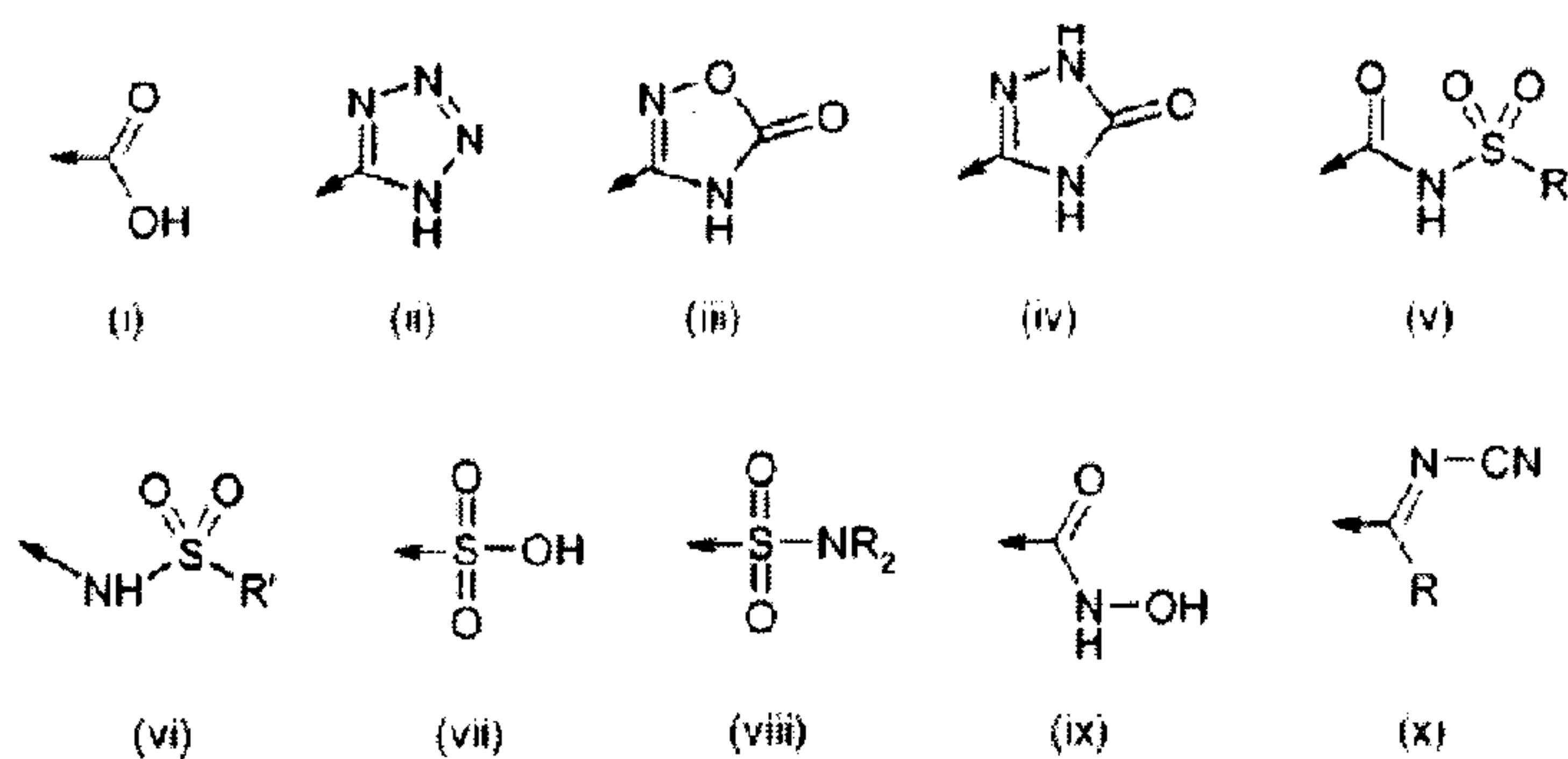
R¹ is halogen or CN,

A is a single bond, CH₂, O or S,

B is a single bond, CH₂ or OCH₂,

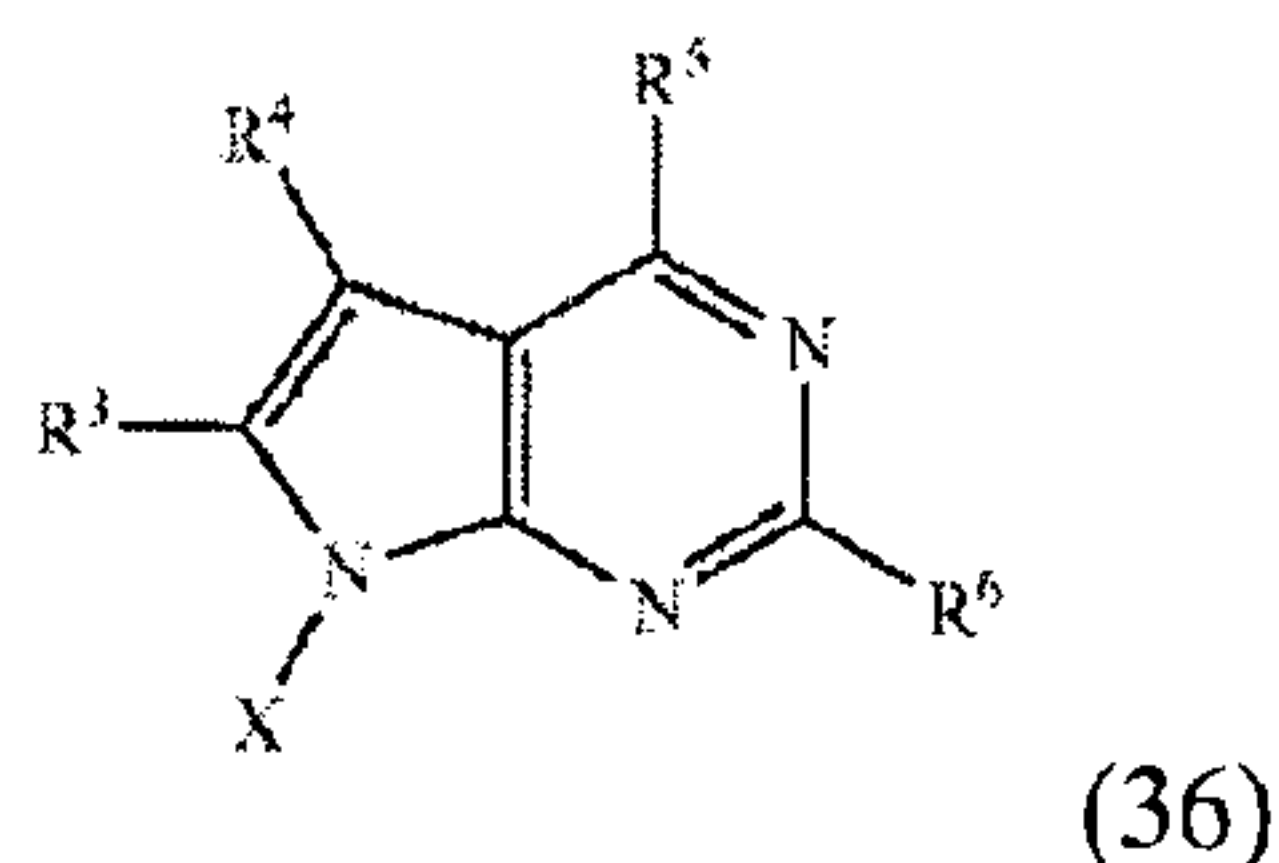
each R² is independently halogen, (C₁₋₆)alkyl optionally substituted by 1 to 3 fluorine atoms, OH, (C₁₋₆)alkylthio or CN,

R³ is selected from the following groups (i) to (x):



R is H or (C₁₋₆)alkyl optionally substituted by 1 to 3 fluorine atoms, R' is (C₁₋₆)alkyl optionally substituted by 1 to 3 fluorine atoms, or

a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof; and



wherein:

X is phenyl or Het, each of which is unsubstituted or monosubstituted or polysubstituted by R1 and/or R2,

R1 and R2 are each, independently of one another, A, OH, OA, SA, SOA, SO₂A, SO₂NH₂, SO₂NHA, SO₂AA', CN, NO₂, NH₂, NHA, NAA', NHCOA, NHCOOA, COOH, COOA, CONH₂, CONHA, CONAA' or Hal,

R1 and R2 together are alternatively -OCH₂O- or -OCH₂CH₂O-,

R3 is A, OH, OA, SA, SOA, SO₂A, SO₂NH₂, SO₂NHA, SO₂AA', CN, NO₂, NH₂, NHA, NHB, NAA', NHCOA, NHCOOA, NHCOB, NHCOOB, COOH, COOA, COOB, CONH₂, CONHA, CONHB, CONAA' or Hal,

R4 is branched or unbranched alkyl or alkenyl having up to 10 carbon atoms, which may be substituted by from 1 to 5 F and/or Cl atoms and/or in which one or more CH₂ groups may be replaced by O, S, SO, SO₂, NH, NA, NHCO, NACO, NHCOO or NACOO, or cycloalkyl or cycloalkenyl having from 3 to 7 carbon atoms, in which one or two CH₂ groups may be replaced by O, S, SO, SO₂, SO₂NH, SO₂NA, NH, NHA, NHCONH, NACONH, NACONA, NHCO, NACO, NHCOO or NACOO,

R5 is OH, OA, SA, SOA, SO2A, SO2NH2, SO2NHA, SO2AA', CN, NO2, NH2, NHA, NAA', NHCOA, NHCOOA, COOH, COOA, CONH2, CONHA, CONAA' or Hal,

R6 is H, OH, OA, SA, SOA, SO2A, SO2NH2, SO2NHA, SO2AA', CN, NO2, NH2, NHA, NAA', NHCOA, NHCOOA, COOH, COOA, CONH2, CONHA, CONAA' or Hal, A and A' are each, independently of one another, branched or unbranched alkyl or alkenyl having up to 10 carbon atoms, which may be substituted by from 1 to 5 F and/or Cl atoms and/or in which one or more CH2 groups may be replaced by O, S, SO, SO2, NH, NR7, NHCO, NR7CO, NHCOO or NR7COO,

A and A' together are alternatively alkylene having from 3 to 7 carbon atoms, in which one or two CH2 groups may be replaced by CHR7, CHR7R8, O, S, SO, SO2, NH, NR7, NHCO, NR7CO, NHCOO or NR7COO,

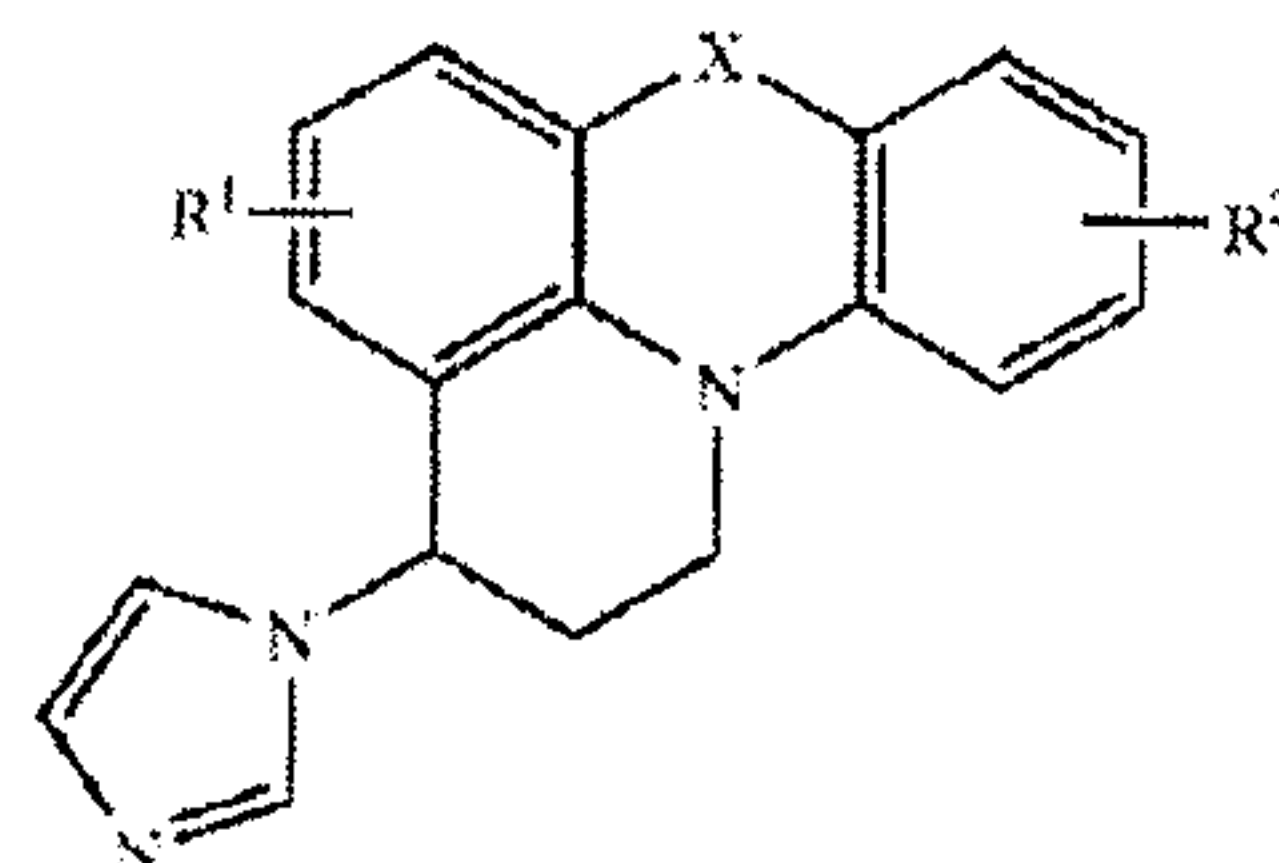
B is phenyl or Het, each of which is unsubstituted or monosubstituted or polysubstituted by R1 and/or R2, Het is an aromatic 5- or 6-membered heterocyclic ring having 1-3 N, O and/or S atoms which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A'', Hal or CF3,

R7 and R8 are each, independently of one another, branched or unbranched alkyl or alkenyl having up to 5 carbon atoms, which may be substituted by from 1 to 5 F and/or Cl atoms and/or in which one or more CH2 groups may be replaced by O, S, SO, SO2 or NH,

A'' is alkyl having from 1 to 6 carbon atoms, and

Hal is F, Cl, Br or I, and pharmaceutically acceptable salts, prodrugs, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

23. The combination of Claim 14, wherein the PDE7 inhibitor is selected from the following compounds:



(37)

wherein:

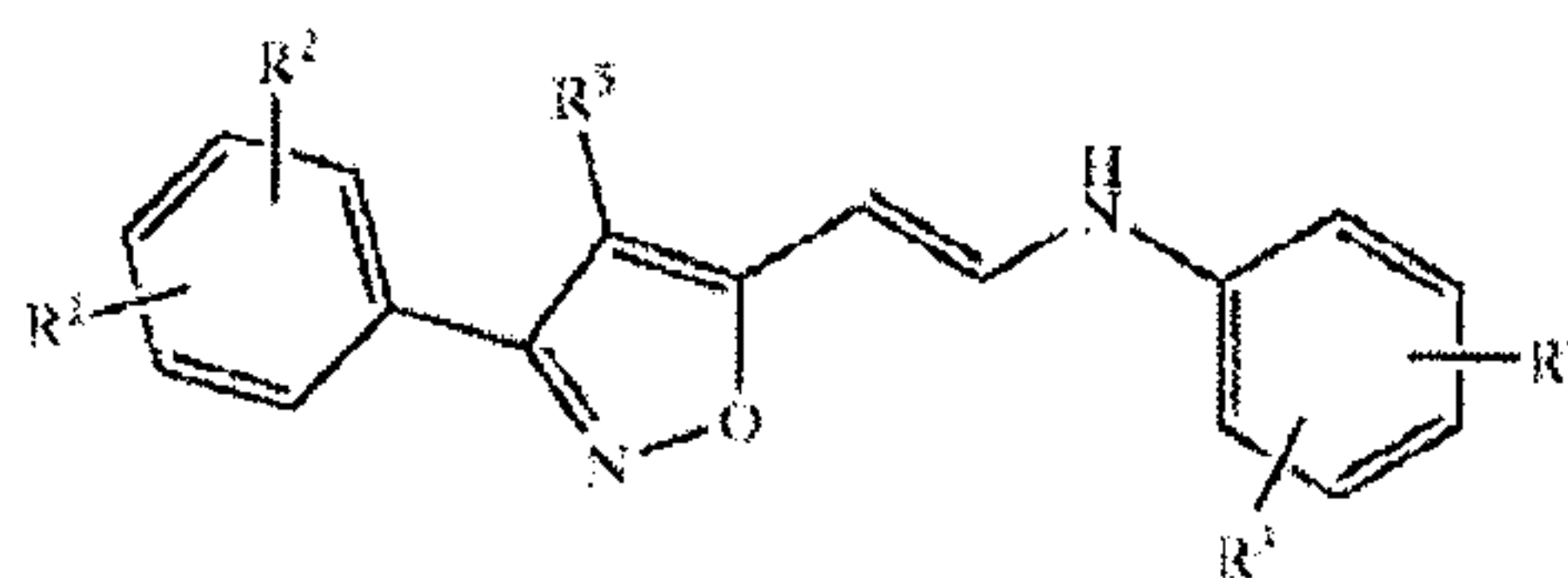
R₁ and R₂ are each, independently of one another, A₁, OA₁, SA₁ or Hal,

A₁ is H, A, alkenyl, cycloalkyl or alkylencycloalkyl,

A is alkyl having 1-10 carbon atoms,

Hal is F, Cl, Br or I, and

x is O, S, SO or SO₂;



(38)

wherein:

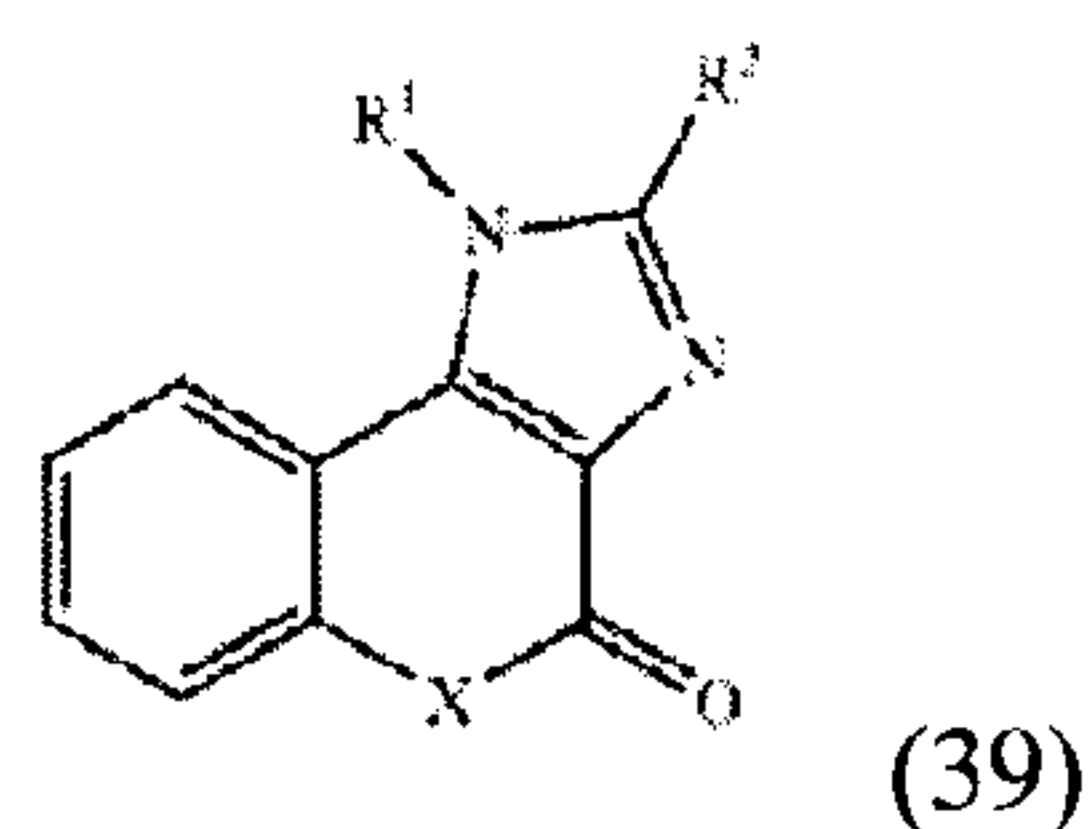
R₁, R₂, R₃, R₄ are each, independently of one another, Hal, OA₁, SA₁, A, H, COOA₁, CN or CONA₁A₂,

R₅ is COOA₁, CN or CONA₁A₂,

A₁, A₂ are each, independently of one another, H, A, alkenyl, cycloalkyl or alkylencycloalkyl,

A is alkyl having 1 to 10 C atoms,

Hal is F, Cl, Br or I;



wherein:

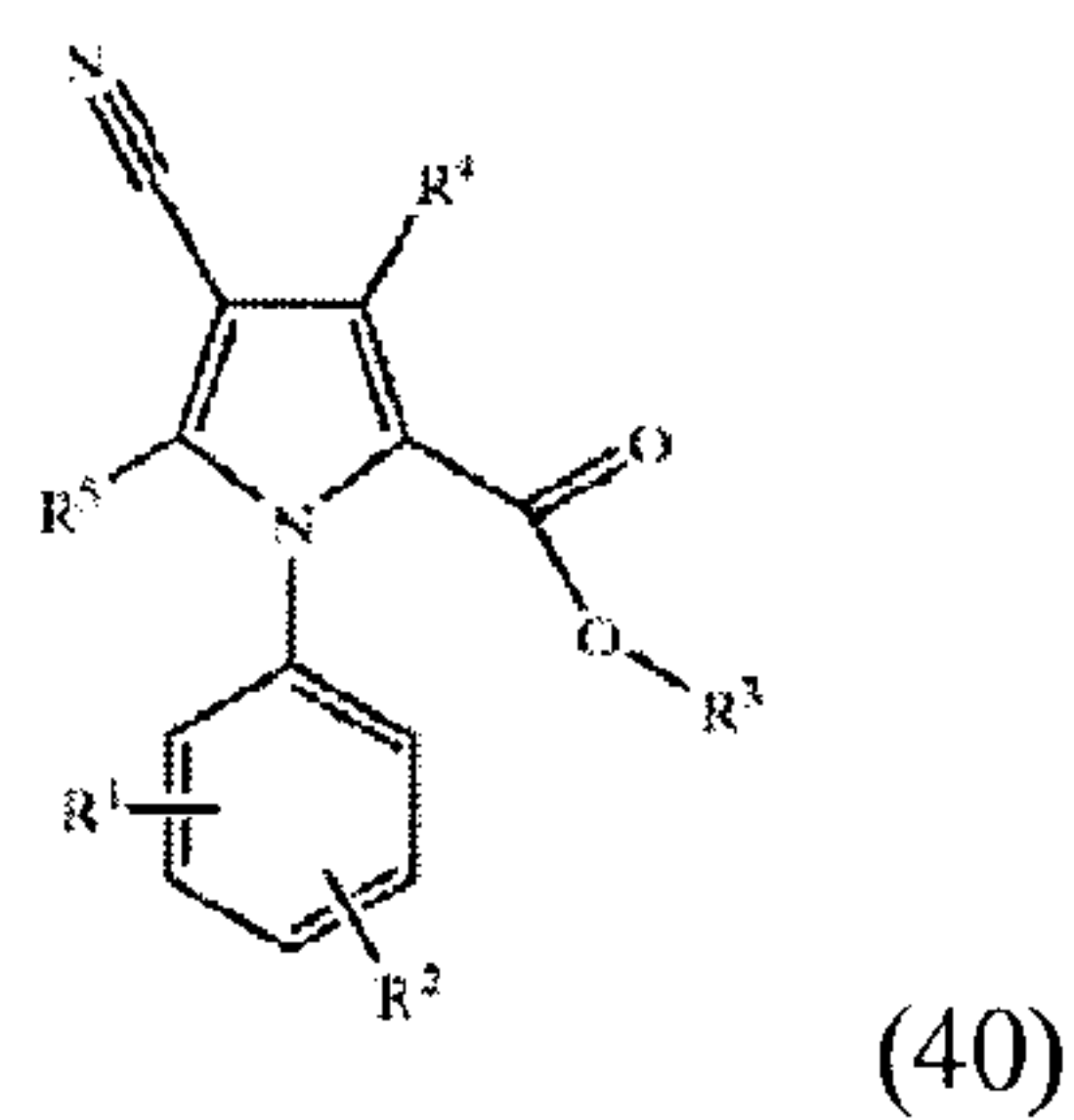
R1 is H, A, benzyl, indan-5-yl, 1,2,3,4-tetrahydronaphthalen-5-yl, dibenzothien-2-yl, or phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal, A, A- CONH, benzyloxy, alkoxy, COOH or COOA,

R2 is H or A,

X is O or S,

Hal is F, Cl, Br or I,

A is alkyl with 1 to 6 C atoms;



wherein:

R1 and R2 are each, independently of one another H, A, OA, SA or Hal,

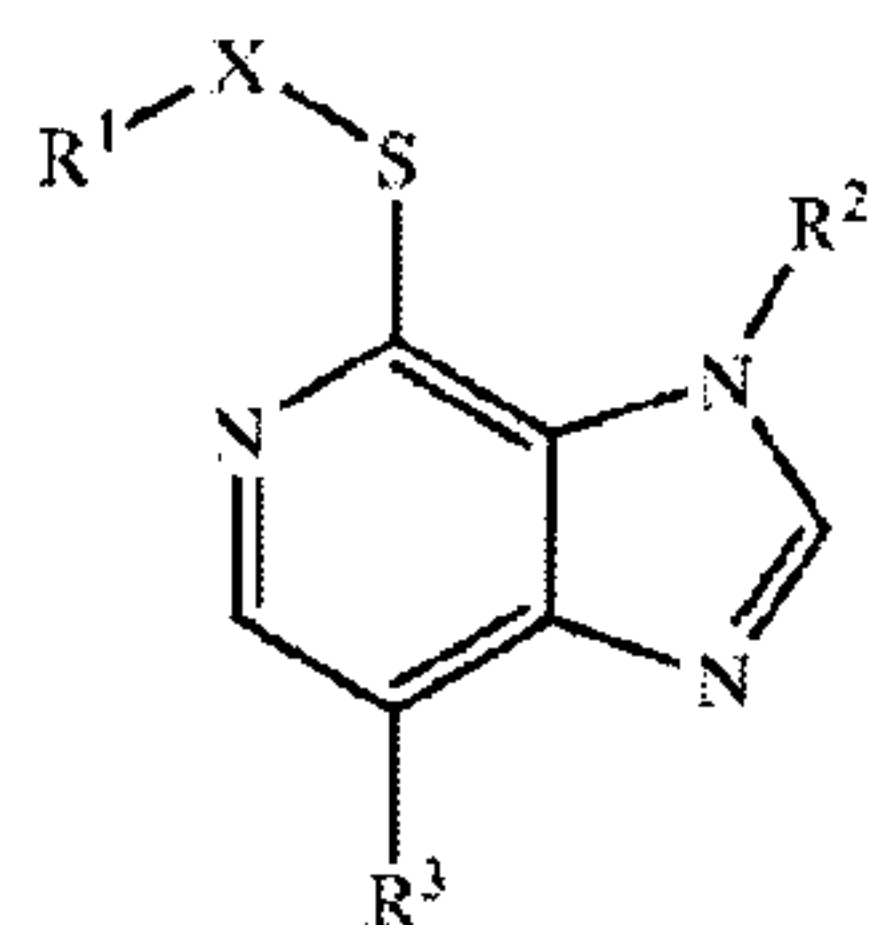
R3 is H or A,

R4 is A or NH₂,

R5 is H, NH₂, NHA or NA₂,

A is alkyl having 1 to 10 carbon atoms, alkenyl, cycloalkyl or alkylenecycloalkyl,

Hal is F, Cl, Br or I; and



(41)

wherein:

R1 is CONR₄R₅,

R2 is H or A,

R4 and R5 are each, independently of one another, H or A₁,

R3 is Hal,

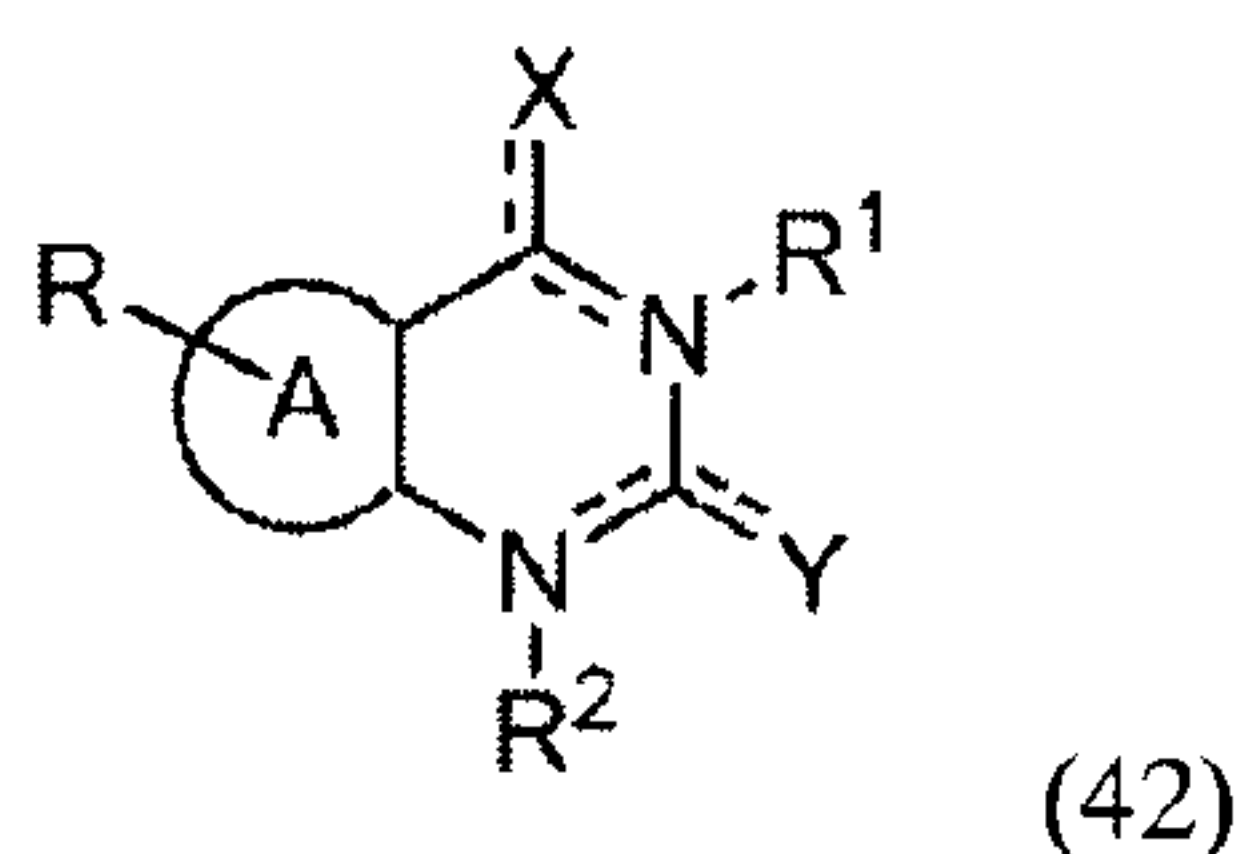
Hal is F, Cl, Br or I,

A is alkyl having 1-4 carbon atoms,

A₁ is alkyl having 1-10 carbon atoms,

X is alkylene having 1-4 carbon atoms, in which an ethylene group may also be replaced by a double or triple bond, and their physiologically acceptable salts and/or solvates.

24. The combination of Claim 14, wherein the PDE7 inhibitor is:



wherein:

A is fused carbocyclo or heterocyclo of 5, 6 or 7 members and may be saturated or unsaturated;

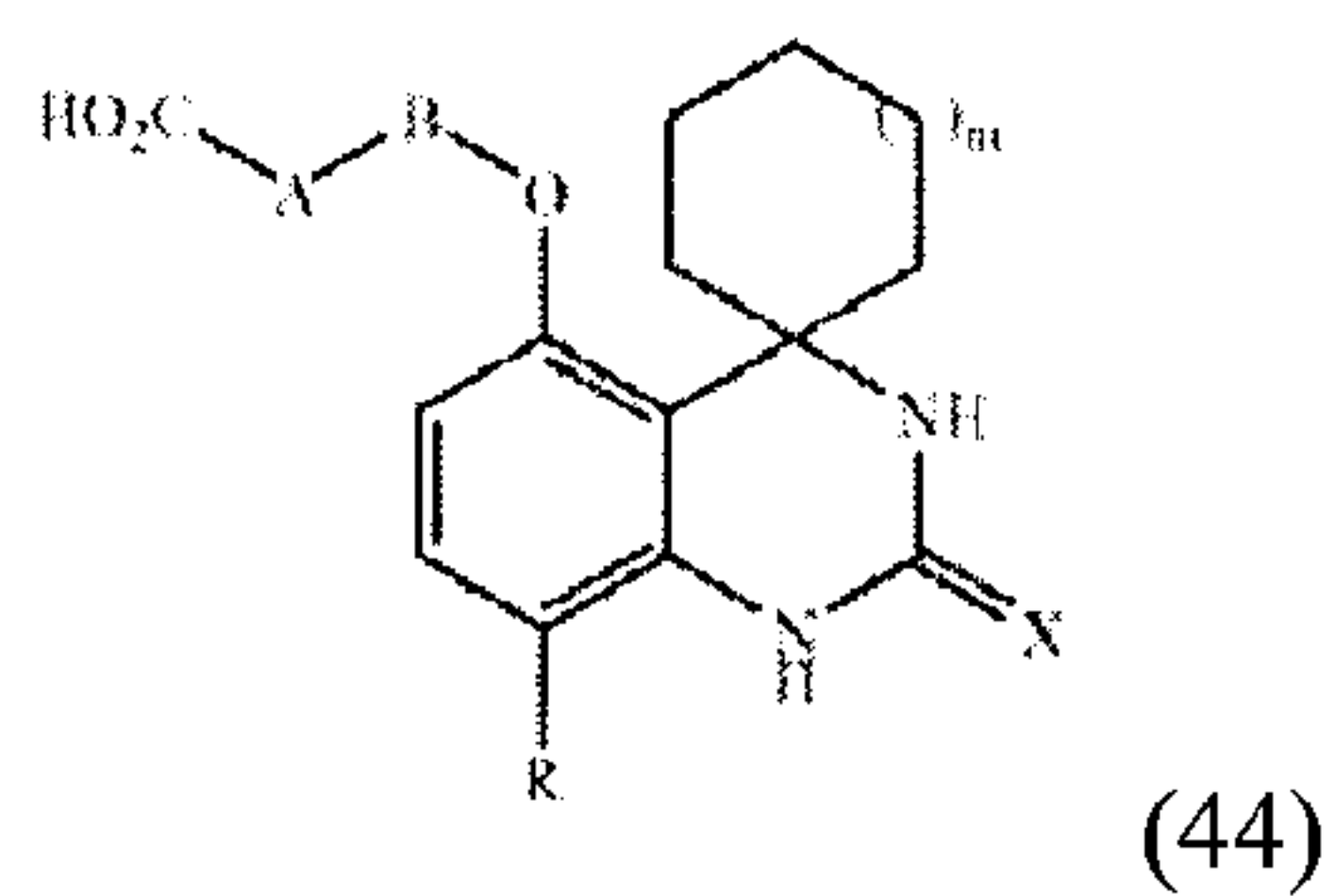
the dashed lines represent, independently, a single or double bond;

X and Y are chosen independently from the group consisting of alkyl, hydrogen, =O, =S, -N (alkyl), -N(aryl), aryl, O-alkyl, O-aryl, alkyl-S and -S-aryl; and

R1 and R2 are chosen independently from the group consisting of hydrogen, halogen, alkyl, halo alkyl, aryl, cycloalkyl, (Z)n-aryl, hetero aryl, -OR3; -C(O)OR3, -(Z)n-C(O)OR3 and -S(O), or a pharmaceutically acceptable salt, prodrug, solvate or stereoisomer of the same;

wherein, when A is unsubstituted benzene, X=O, Y=S, when A is unsubstituted benzene, X=O, Y=O, when A is unsubstituted benzene, X=O, Y=S-Me, when A is unsubstituted thiophene, X=O, Y=S, and when A is unsubstituted benzothiophene, X=O, Y=S.

25. The combination of Claim 14, wherein the PDE7 inhibitor is selected from the following compounds:



wherein:

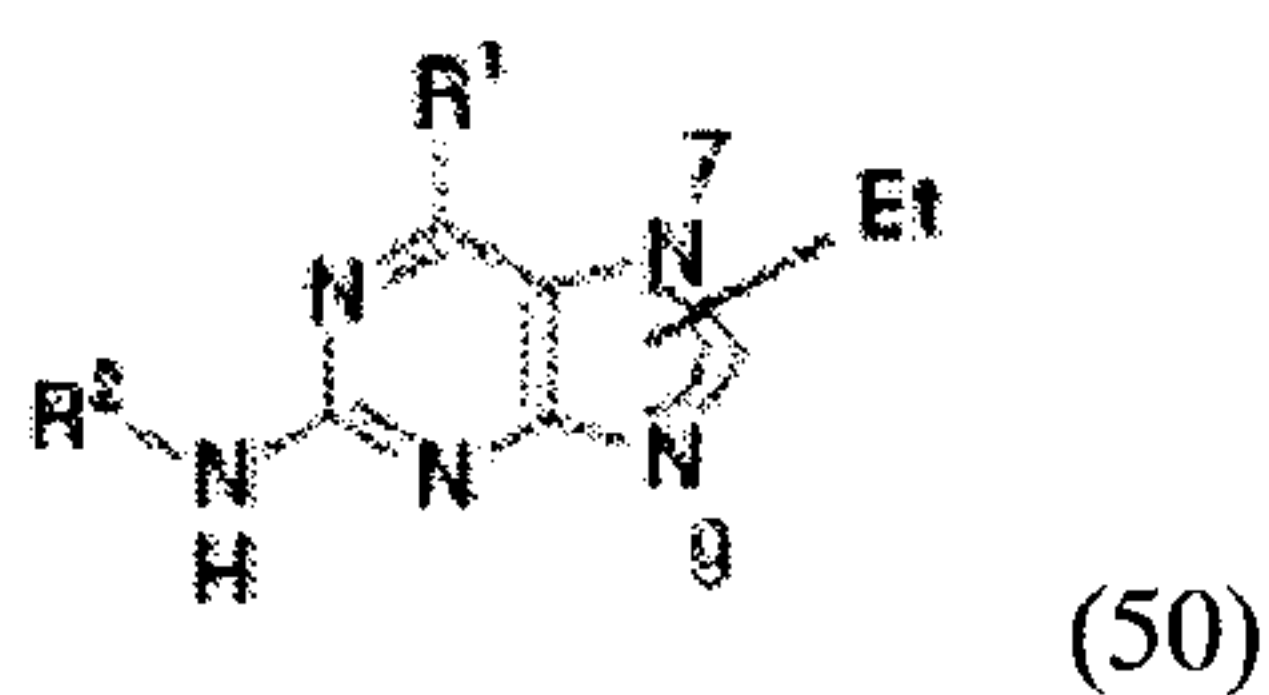
m is 0, 1 or 2;

X is O, S or N--CN;

R is F, Cl or CN;

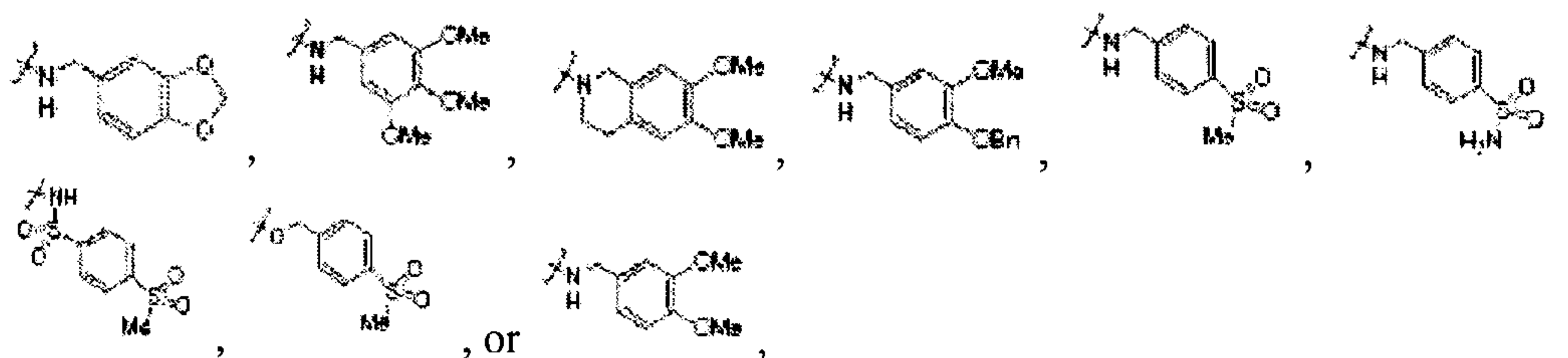
A is a C₃₋₆ cycloalkylene group optionally substituted with a C₁₋₄ alkyl group;
and

B is a single bond or a C₁₋₂ alkylene group;

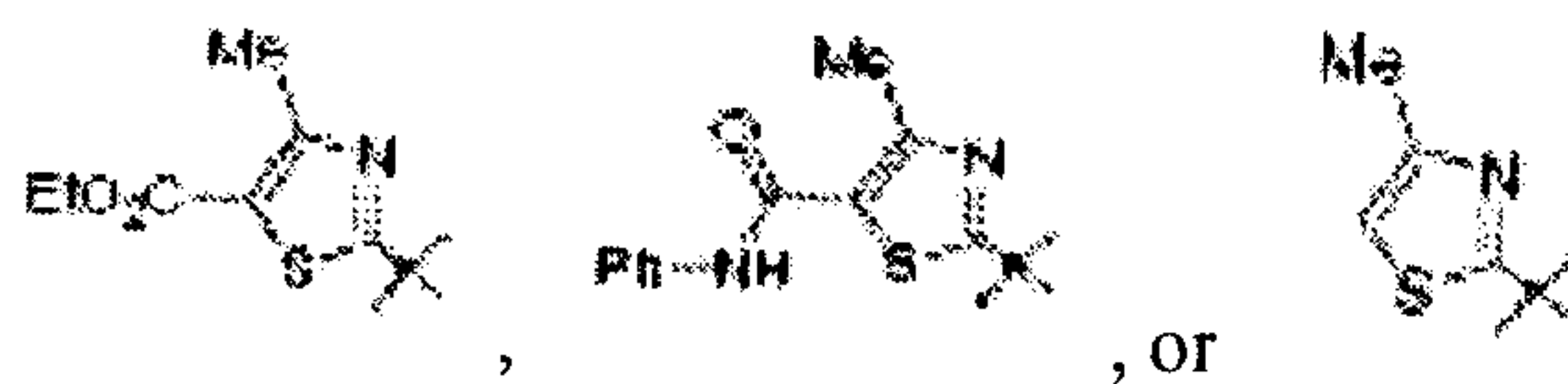


wherein:

R1 is:

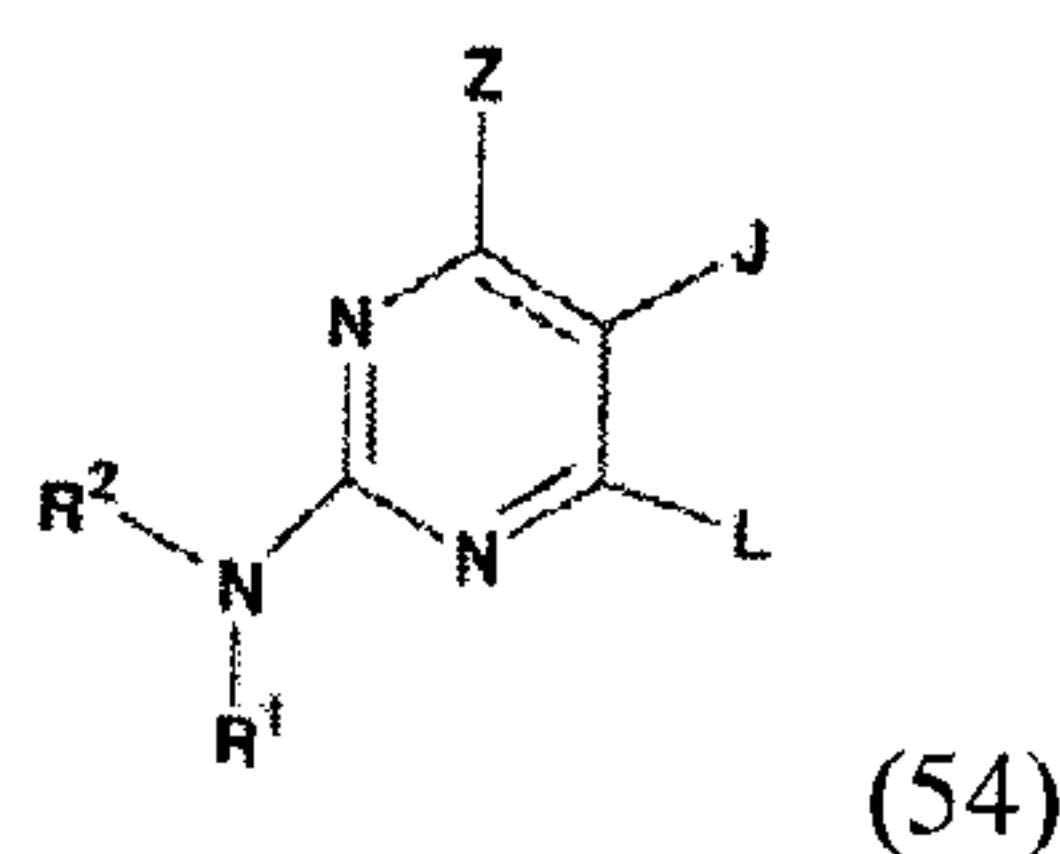


R2 is:



wherein the ethyl group may be attached to the 7 or 9 position.

26. The combination of Claim 14, wherein the PDE7 inhibitor is:



wherein:

R1 is H or alkyl;

R2 is (a) heteroaryl, or heterocyclo, either of which may be optionally substituted with one to three groups T1, T2, T3; (b) aryl substituted with one to three groups T1, T2, T3 provided that at least one of T1, T2, T3 is other than H; or (c) aryl fused to a heteroaryl or heterocyclo ring wherein the combined ring system may be optionally substituted with one to three groups T1, T2, T3;

Z is (a) -OR₄, -C(O)R₄, -C(O)OR₄, -SR₄, -NR₃R₄, -C(O)NR₃R₄, -NR₃SO₂R_{4c}, halogen, nitro, halo alkyl; or (b) alkyl, aryl, hetero aryl, heterocyclo, or cycloalkyl any of which may be optionally substituted with one to three groups T1a, T2a T3a;

J is (a) hydrogen, halo, -OR_{4a}, or (b) alkyl, alkenyl, or alkynyl any of which may be optionally substituted with one to three groups T1b, T2b or T3b;

L is (a) hydrogen, -OR_{4b}, -C(O)R_{4b}, -C(O)OR_{4b}, -SR_{4b}, -NRSR₆, -C(O)NRSR₆, -NRSSO₂R_{4d}, halogen, haloalkyl, nitro, or (b) alkyl, aryl, heteroaryl, heterocyclo, or cycloalkyl any of which may be optionally substituted with one to three groups T_{1c}, T_{2c} or T_{3c};

R₃ and R₄ are independently H, alkyl, alkenyl, aryl, (aryl)alkyl, hetero aryl, (heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocylo or (heterocyclo)alkyl any of which may be optionally substituted with one to three groups T_{1a}, T_{2a} or T_{3a}; or

R₃ and R₄ together with the nitrogen atom to which they are attached may combine to form a 4 to 8 membered heterocyclo ring optionally substituted with one to three groups T_{1a}, T_{2a} or T_{3a};

R_{4a} is hydrogen, alkyl, alkenyl, aryl, heteroaryl, (aryl)alkyl, (heteroaryl)alkyl, heterocylo, (heterocyclo)alkyl, cycloalkyl or (cycloalkyl)alkyl any of which may be optionally substituted with one to three groups T_{1 b}, T_{2b} or T_{3b};

R_{4b} is hydrogen, alkyl, alkenyl, aryl, heteroaryl, (aryl)alkyl, (heteroaryl)alkyl, heterocylo, (heterocyclo)alkyl, cycloalkyl or (cycloalkyl)alkyl any of which may be optionally substituted with one to three groups T_{1c}, T_{2c} or T_{3c};

R_{4c} and R_{4d} are independently alkyl, alkenyl, aryl, (aryl)alkyl, heteroaryl, (heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocylo or (heterocyclo)alkyl any of which may be optionally substituted with one to three groups T_{1a}, T_{2a} or T_{3a};

R₅ and R₆ are independently H, alkyl, alkenyl, aryl, (aryl)alkyl, heteroaryl, (heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocylo or (heterocyclo)alkyl any of which may be optionally independently substituted where valance allows with one to three groups T_{1c}, T_{2c} or T_{3c}; or

R5 and R6 together with the nitrogen atom to which they are attached may combine to form a 4 to 8-membered heterocyclo ring optionally substituted with one to three groups T1c, T2c or T3c;

T1-1c, T2-2c, and T3-3c are each independently (1) hydrogen or T6, where T6 is (i) alkyl, (hydroxy)alkyl, (alkoxy)alkyl, alkenyl, alkynyl, cyclo alkyl, (cycloalkyl)alkyl, cycloalkenyl, (cycloalkenyl)alkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl, or (heteroaryl)alkyl; (ii) a group (i) which is itself substituted by one or more of the same or different groups (i); or (iii) a group (i) or (ii) which is independently substituted by one or more of the following groups (2) to (13) of the definition of T1-1c, T2-2c and T3-3c (2) -OH or -OT6, (3) -SH or -ST6, (4) -C(O)tH, -C(O)tT6, or -O-C(O)T6, where t is 1 or 2; (5) -SO₃H, -S(O)T6, or S(O)tN(T9)T6, (6) halo, (7) cyano, (8) nitro, (9) -T4-NT7T8, (10) -T4-N(T9)-T5-NT7T8, (11) -T4-N(T10)T5-T6, (12) -T4-N(T10)-T5-H, (13) oxo, T4 and T5 are each independently (1) a single bond, (2) -T11-S(O)t-T12-, (3) T11-C(O)-T12-, (4) -T11-C(S)-T12-, (5) -T11-O-T12-, (6) -T11-S-T12-, (7) -T11-O-C(O)-T12-, (8) -T11-C(O)-O-T12-, (9) -T11-C(=NT9a)-T12-, or (10) -T11-C(O)-C(O)T12,

T7, T8, T9, T9a and T10 (1) are each independently hydrogen or a group provided in the definition of T6, or (2) T7 and T8 may together be alkylene or alkenylene, completing a 3-to 8- membered saturated or unsaturated ring together with the atoms to which they are attached, which ring is unsubstituted or substituted with one or more groups listed in the description of T1-1c, T2-2c and T3-3c, or (3) T7 or T8, together with T9, may be alkylene or alkenylene completing a 3-to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with one or more groups listed in the description of T1-1 c, T2-2c and T3-3c, or (4) T7 and T8 or T9 and T10 together with the nitrogen atom to which they are attached may combine to form a group-N=CT13T14 where T13

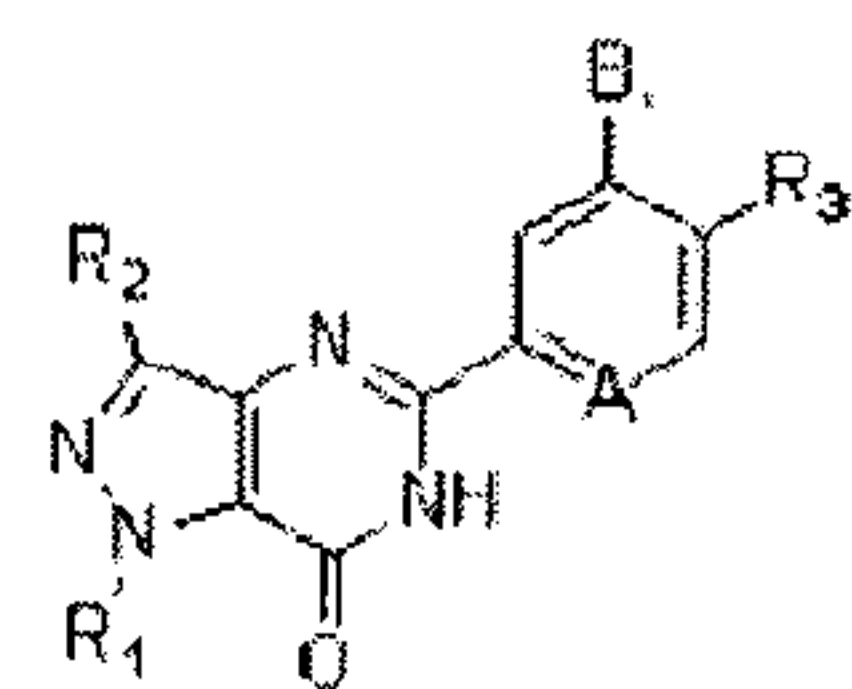
and T14 are each independently H or a group provided in the definition of T6;
and

T11 and T12 are each independently (1) a single bond, (2) alkylene, (3)
alkenylene, or (4) alkynylene.

27. A pharmaceutical composition, comprising a phosphodiesterase 7 (PDE7) inhibitor that
is selective for PDE7 relative to any other PDE enzyme from the PDE1-6 and PDE8-11 enzyme
families and a dopamine receptor agonist, wherein each of the PDE7 inhibitor and the
dopamine receptor agonist is included in an amount effective to contribute to the treatment or
reduction of use of an addictive agent or practice of a compulsive behavior.

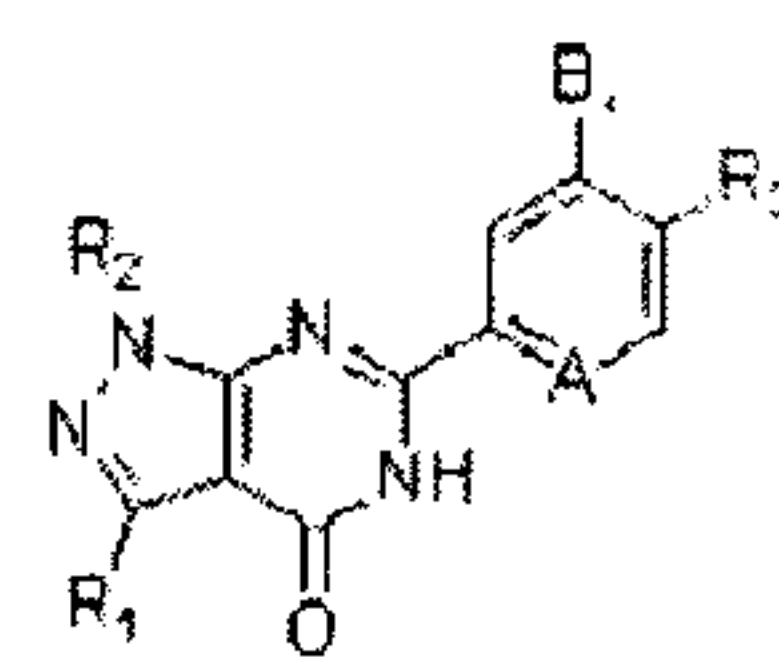
28. The pharmaceutical composition of Claim 27, wherein the dopamine receptor agonist is
selected from bromocriptine, pergolide, pramipexole, ropinirole, cabergoline, apomorphine,
lisuride, rotigotine, quinagolide and fenoldopam.

29. The pharmaceutical composition of Claim 27, wherein the PDE7 inhibitory agent is:



(1A)

or



(1B)

wherein:

A is N or CR₄;

B is a hydrogen or a halogen atom;

R₁ is optionally substituted C₃₋₇ cycloalkyl or tert-butyl;

R₂ is hydrogen, methyl, or ethyl;

R₃ is hydrogen, nitro, cyano or halogen, NR₅R₆, C(=X)R₇, SO₂NR₅R₆, OR₈, NR₈CONR₅R₆, NR₈SO₂R₉, NR₈CO₂R₉, a heteroaryl group, optionally substituted C₁₋₃ alkyl, optionally substituted C₁₋₆ alkenyl, or optionally substituted saturated or unsaturated heterocycloalkyl;

R₄ is hydrogen, or C₁₋₃ alkoxy substituted by one or more fluorine atoms;

R₅ and R₆ are the same or different, and are a hydrogen atom, optionally substituted C₁₋₆ alkyl, optionally substituted heterocycloalkyl, or optionally substituted acyl or, together with the nitrogen atom which they are bound to, form azetidiny, pyrrolidiny, piperidiny, morpholino, thiomorpholino, piperaziny, or homopiperaziny, each of these groups being optionally substituted by optionally substituted C₁₋₄ alkyl, OH, C₁₋₃ alkoxy, CO₂H, NR₅R₆, an oxo group, NR₉COR₇, or C(=O)R₇;

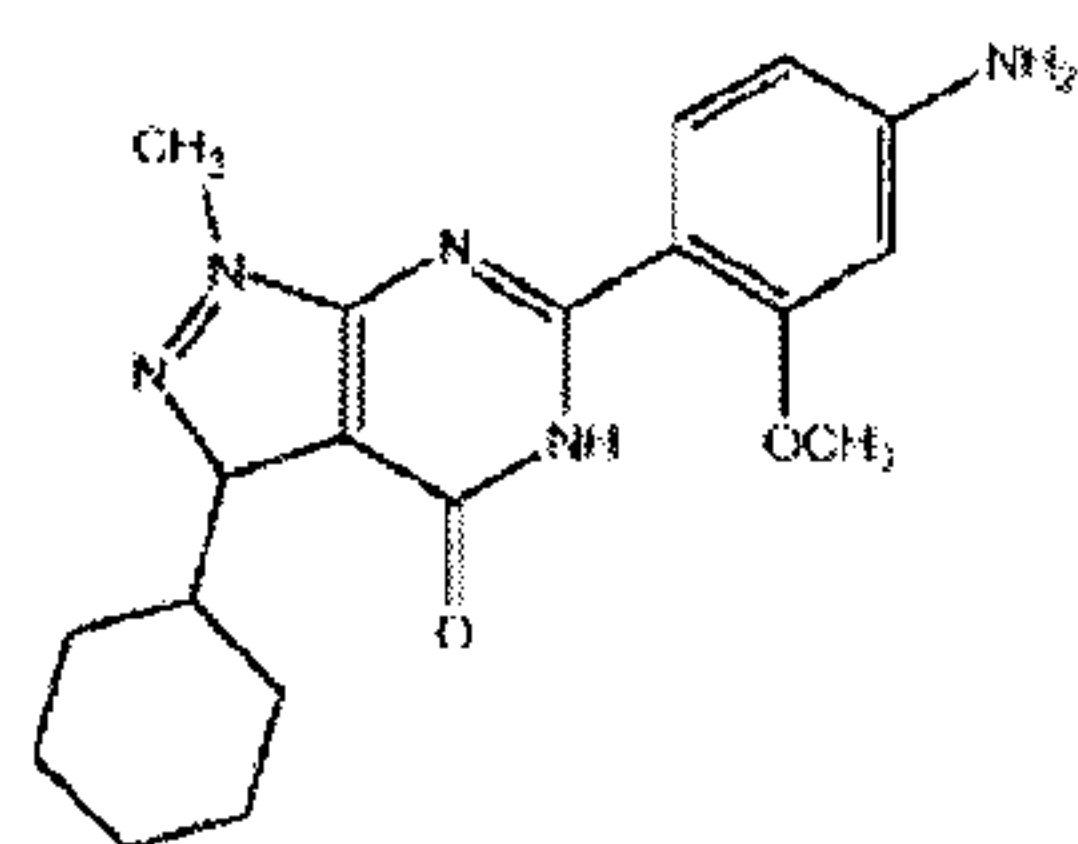
R₇ is optionally substituted C₁₋₆ alkyl, OH, OR₈, or NR₅R₆;

R₈ is hydrogen, an optionally substituted C₁₋₆ alkyl group, or optionally substituted heterocycloalkyl;

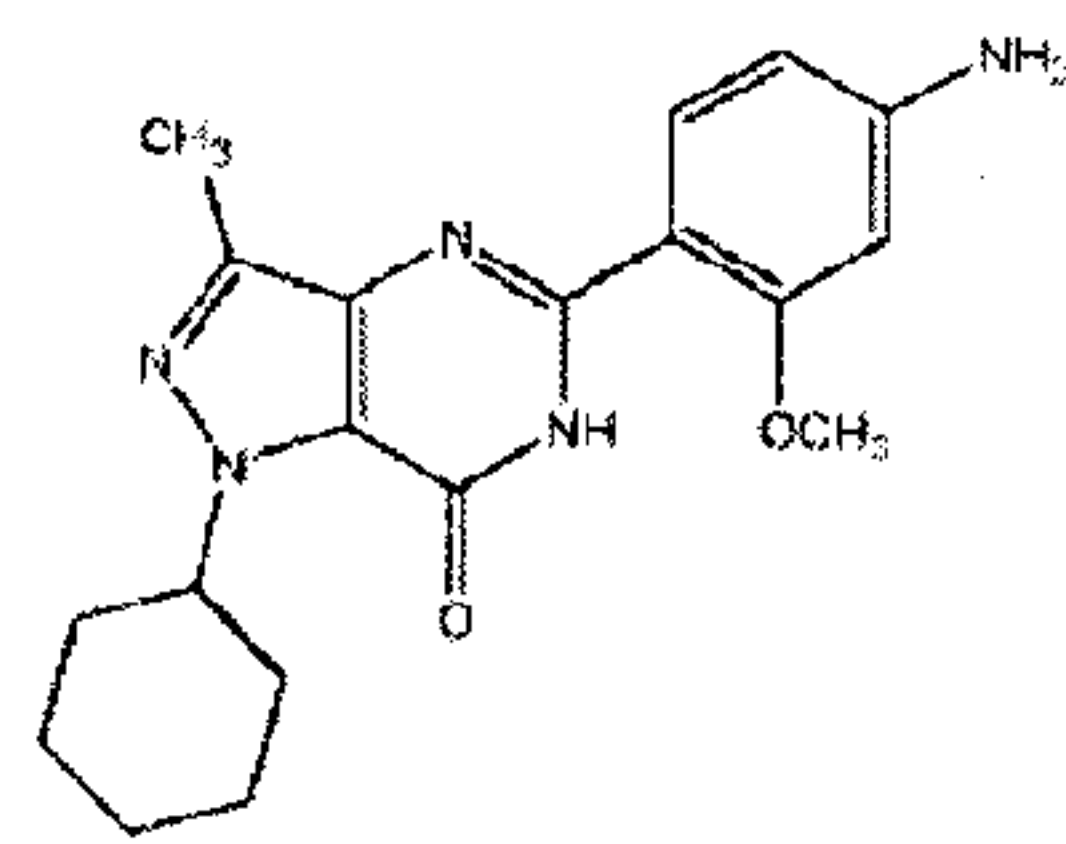
R₉ is an optionally substituted C₁₋₆ alkyl group; and

X represents O, S, or NH.

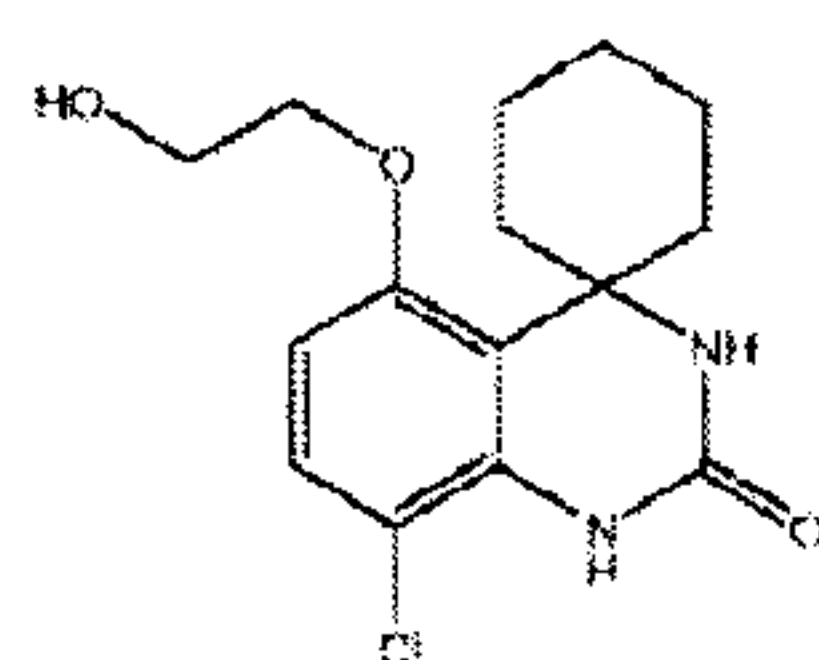
30. The pharmaceutical composition of Claim 27, wherein the PDE7 inhibitor is selected from the following compounds:



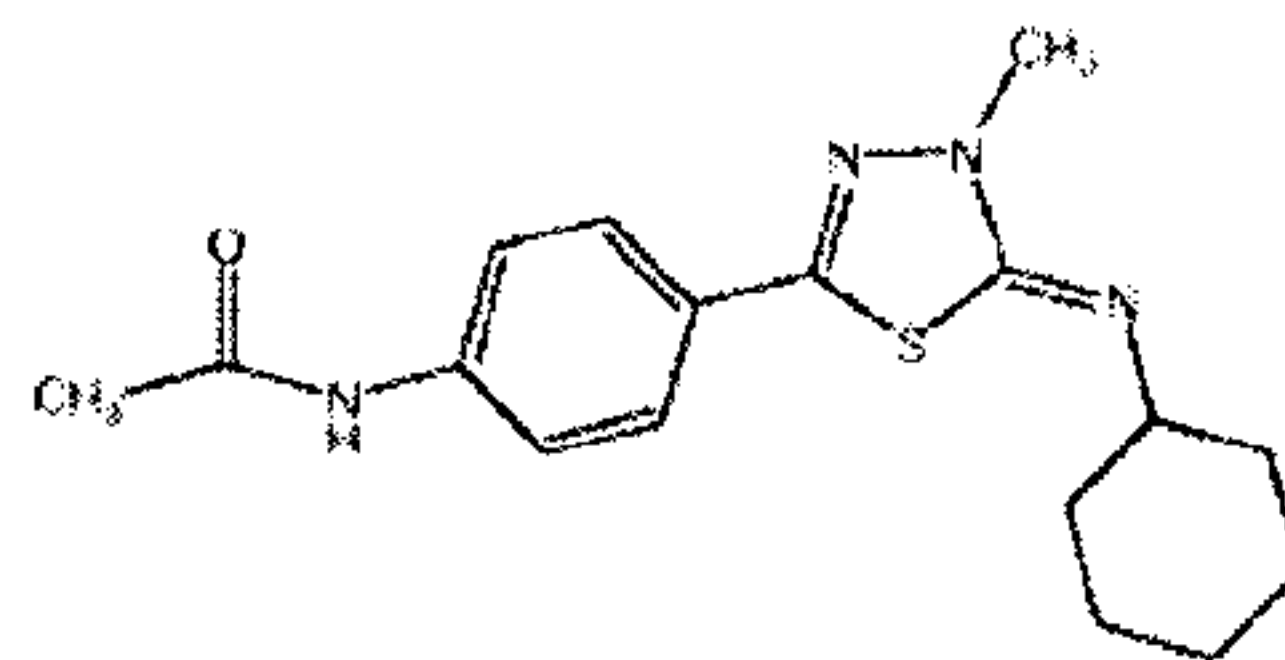
(1);



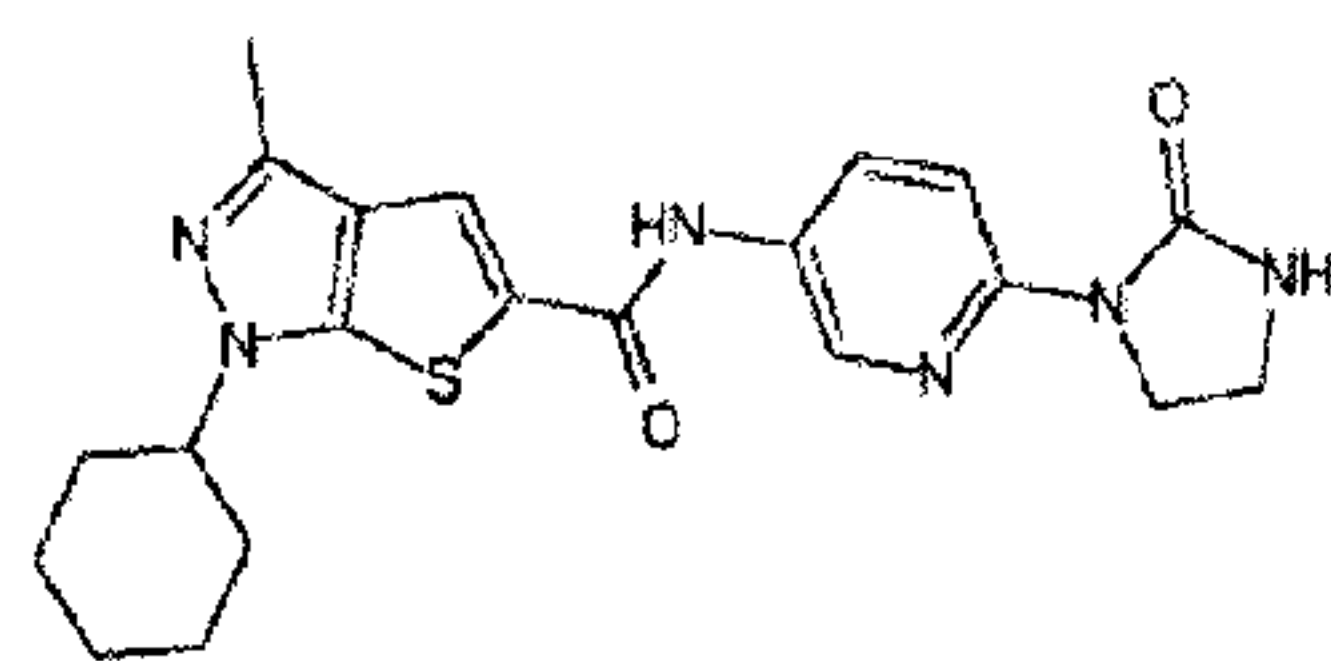
(2);



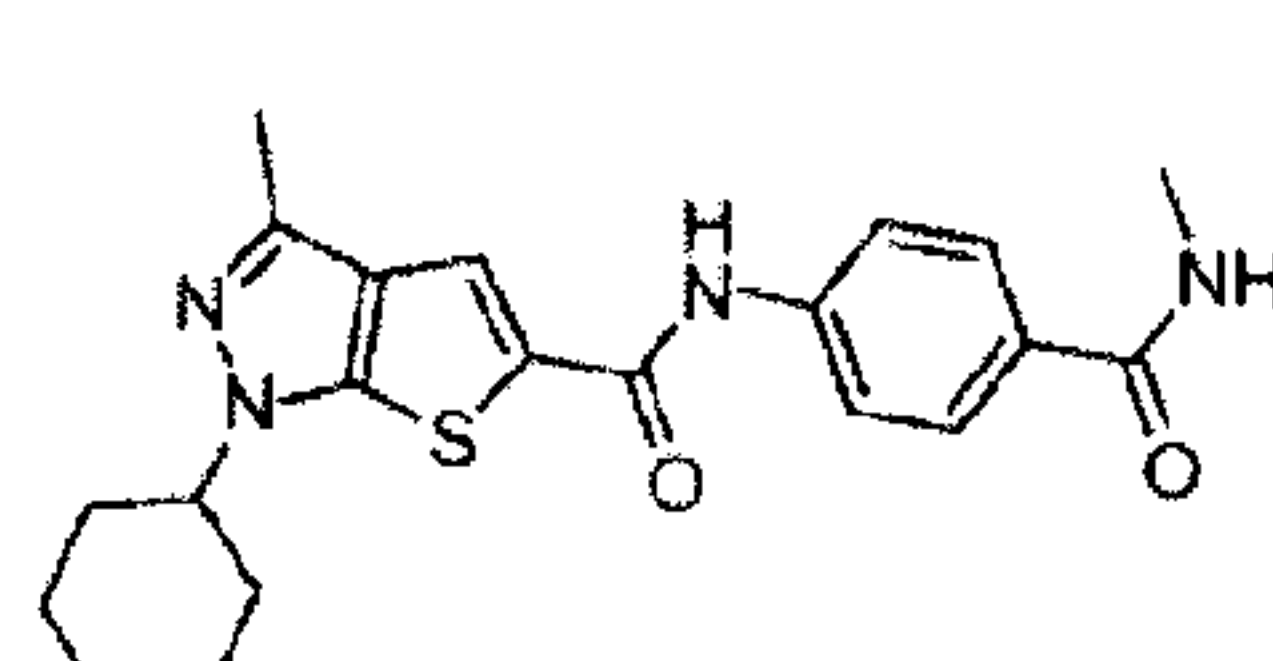
(3);



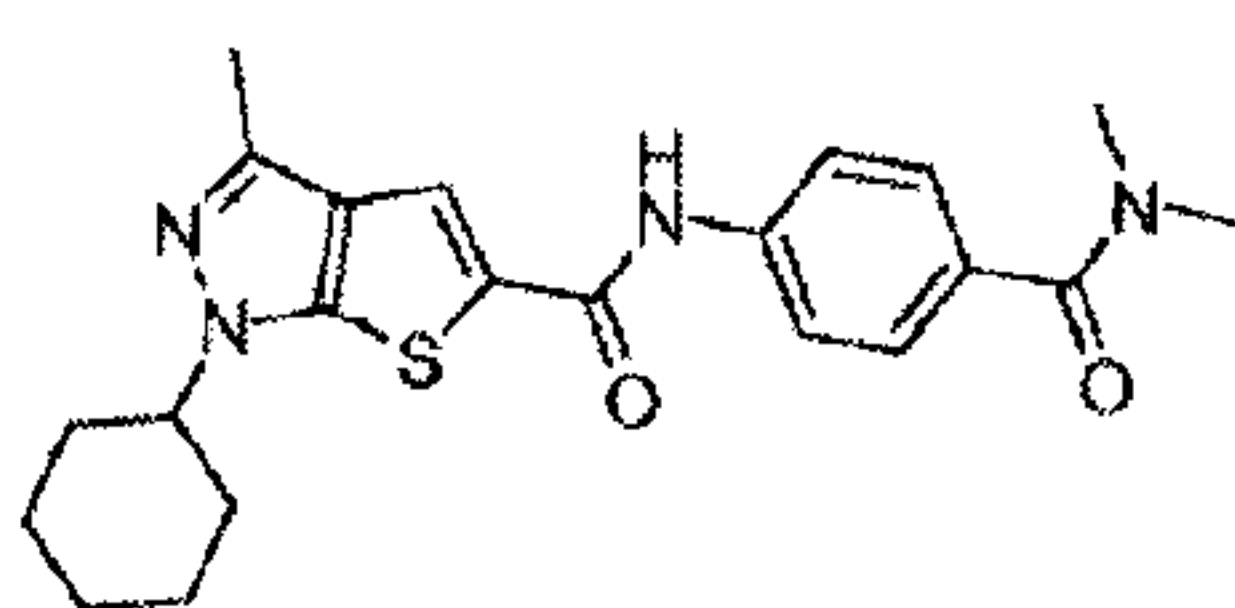
(4);



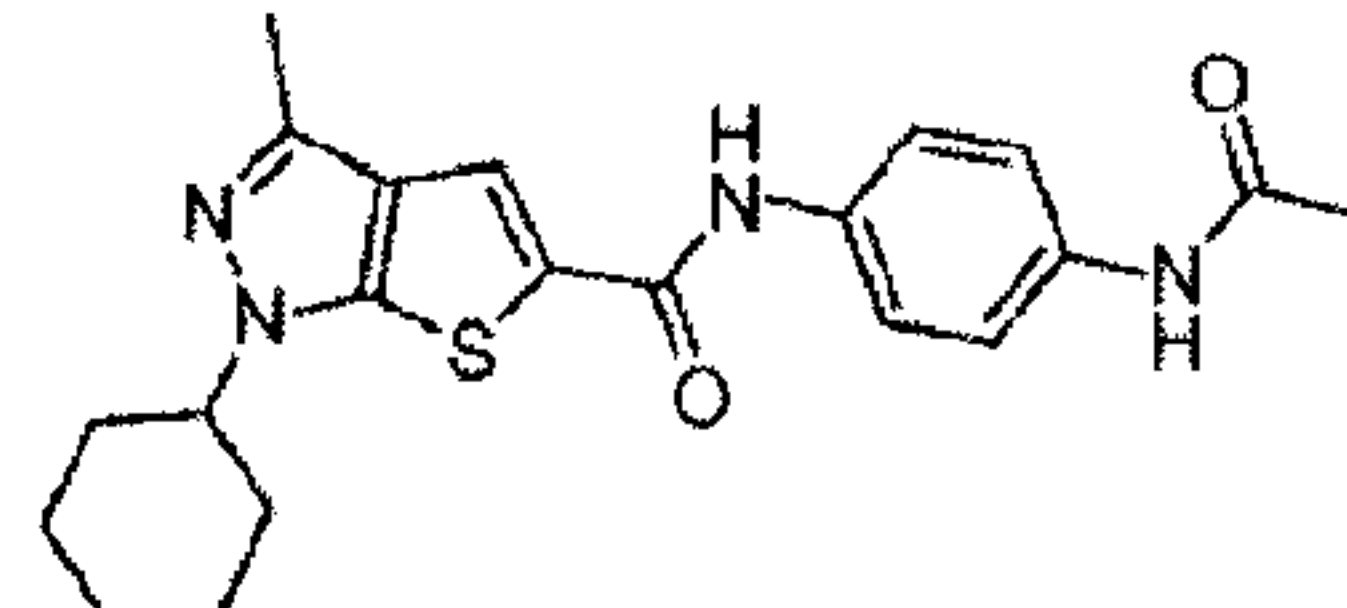
(6A);



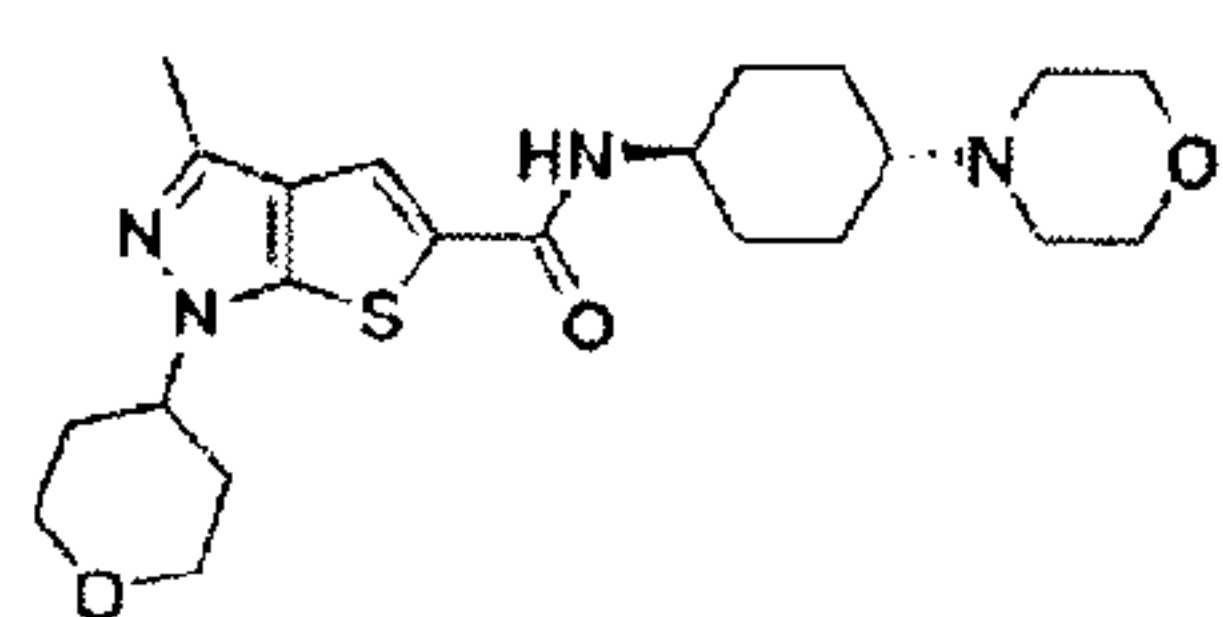
(6B);



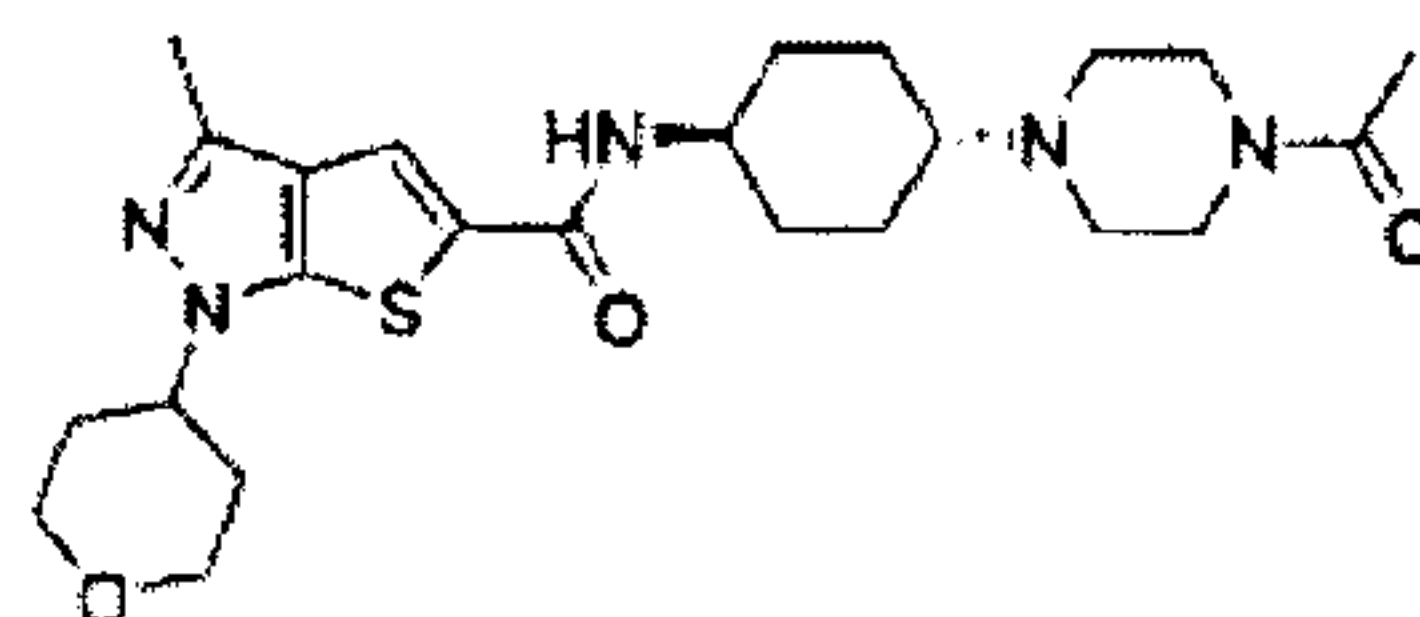
(6C);



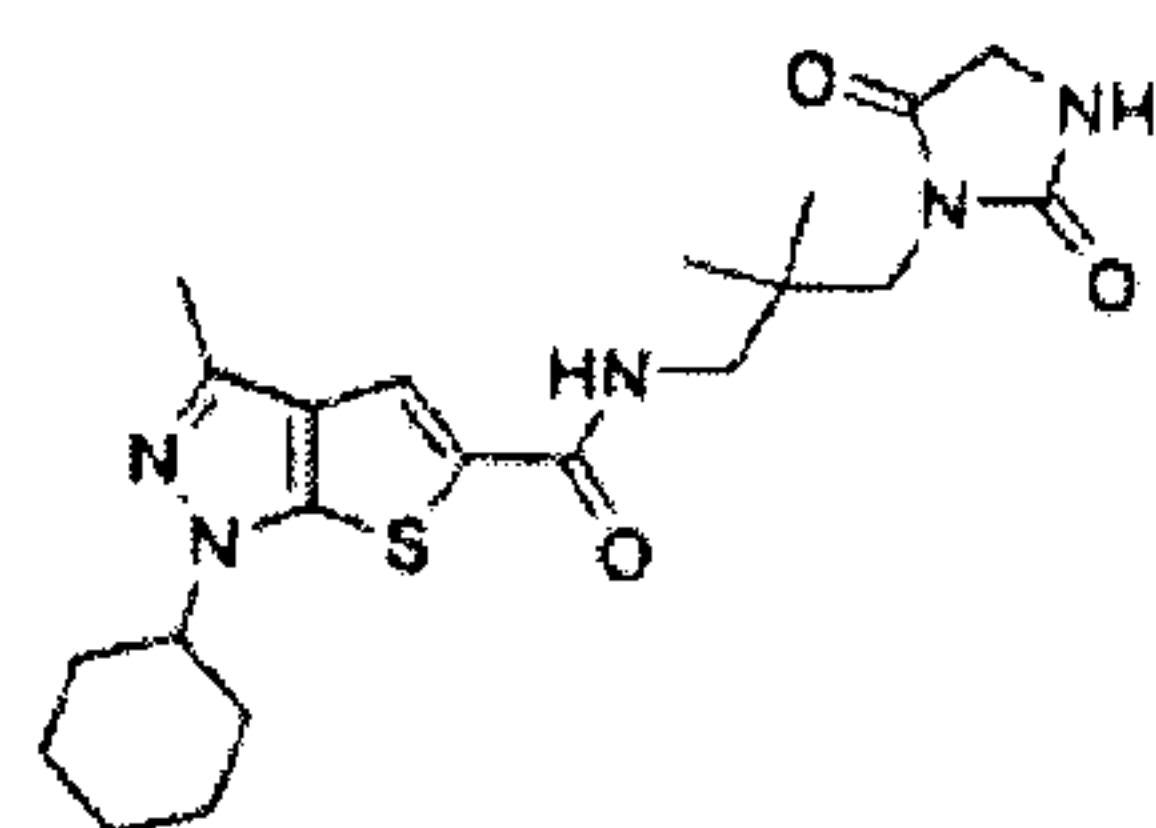
(6D);



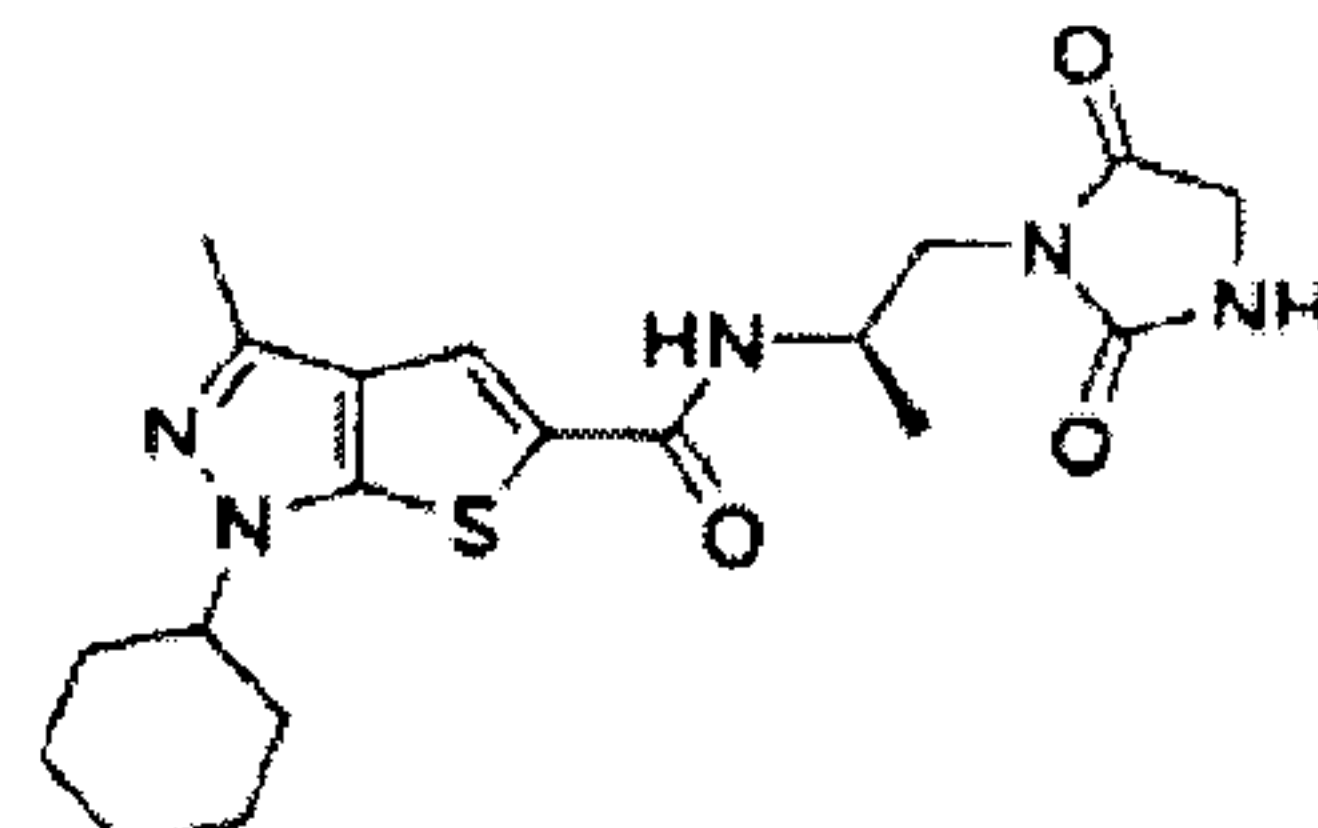
(6E);



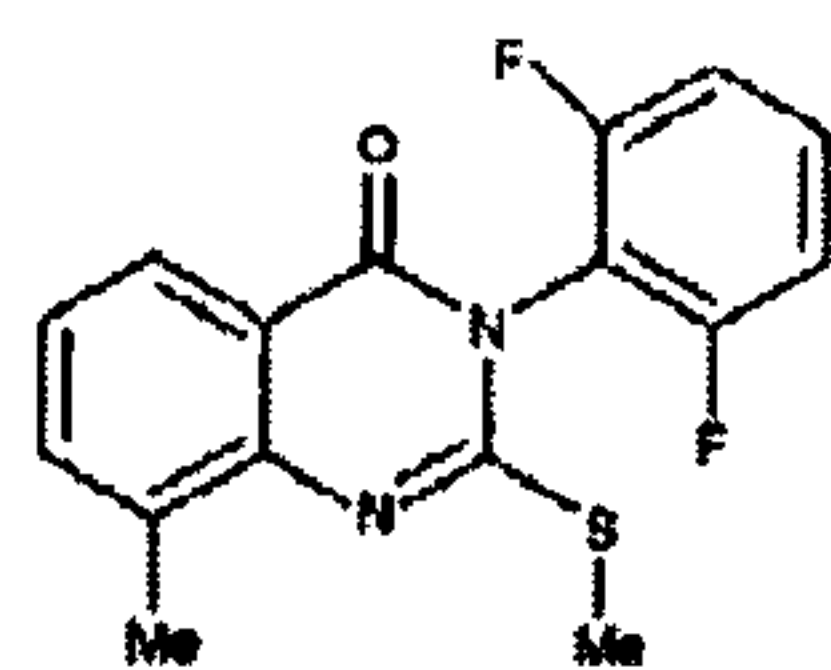
(6F);



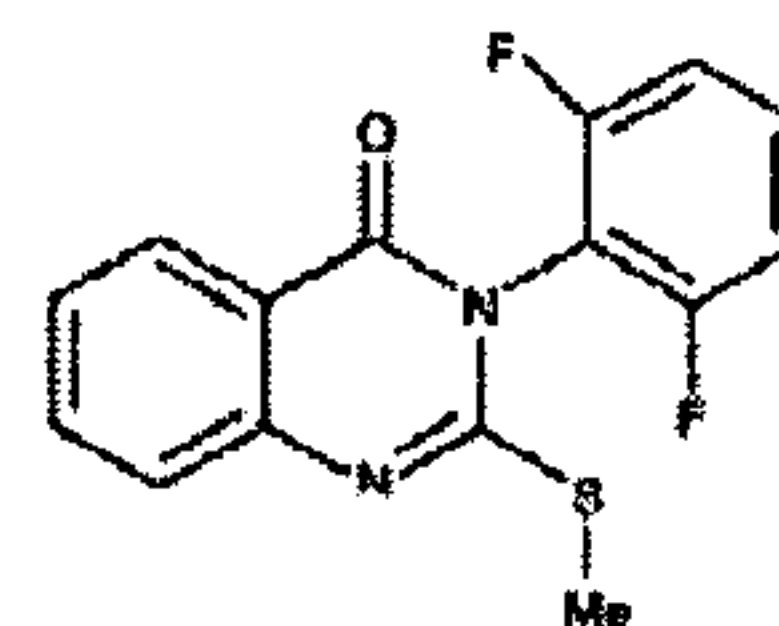
(6G);



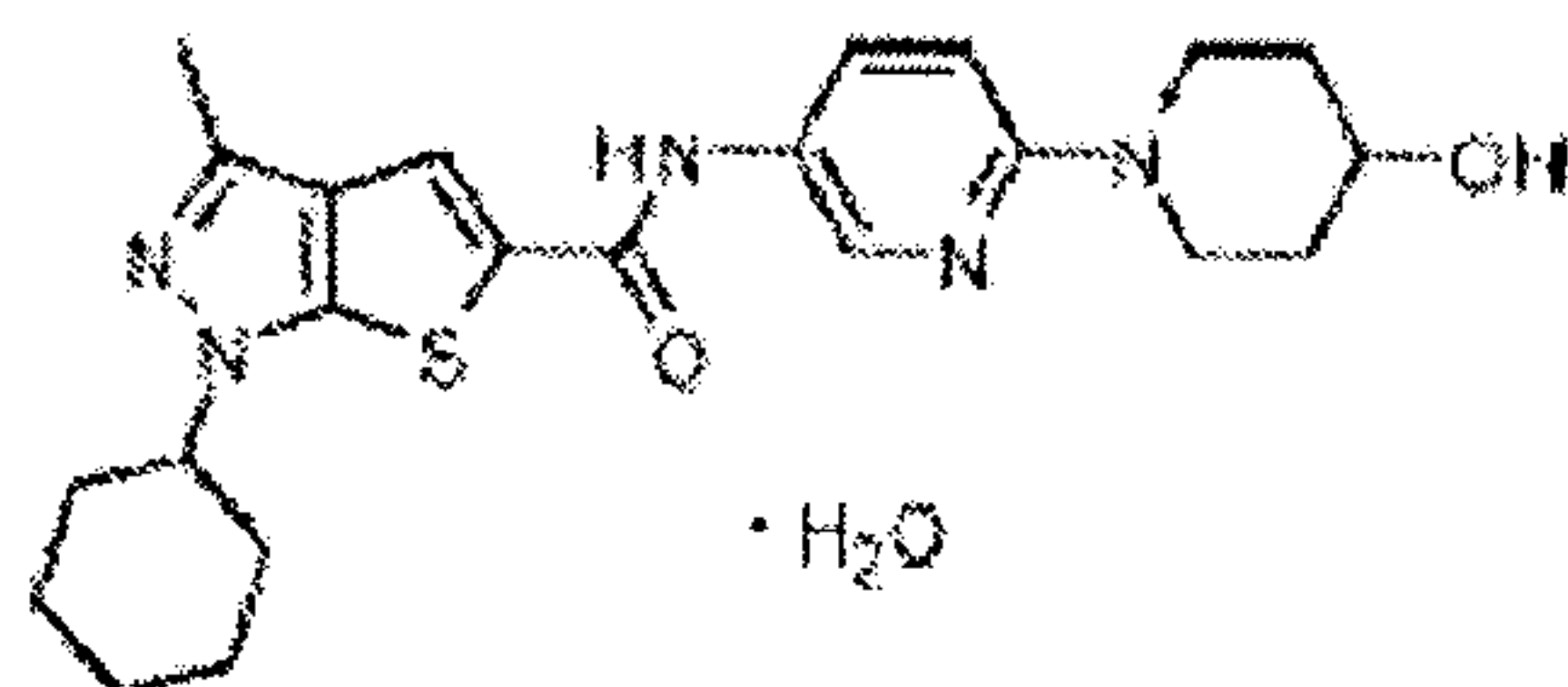
(6H);



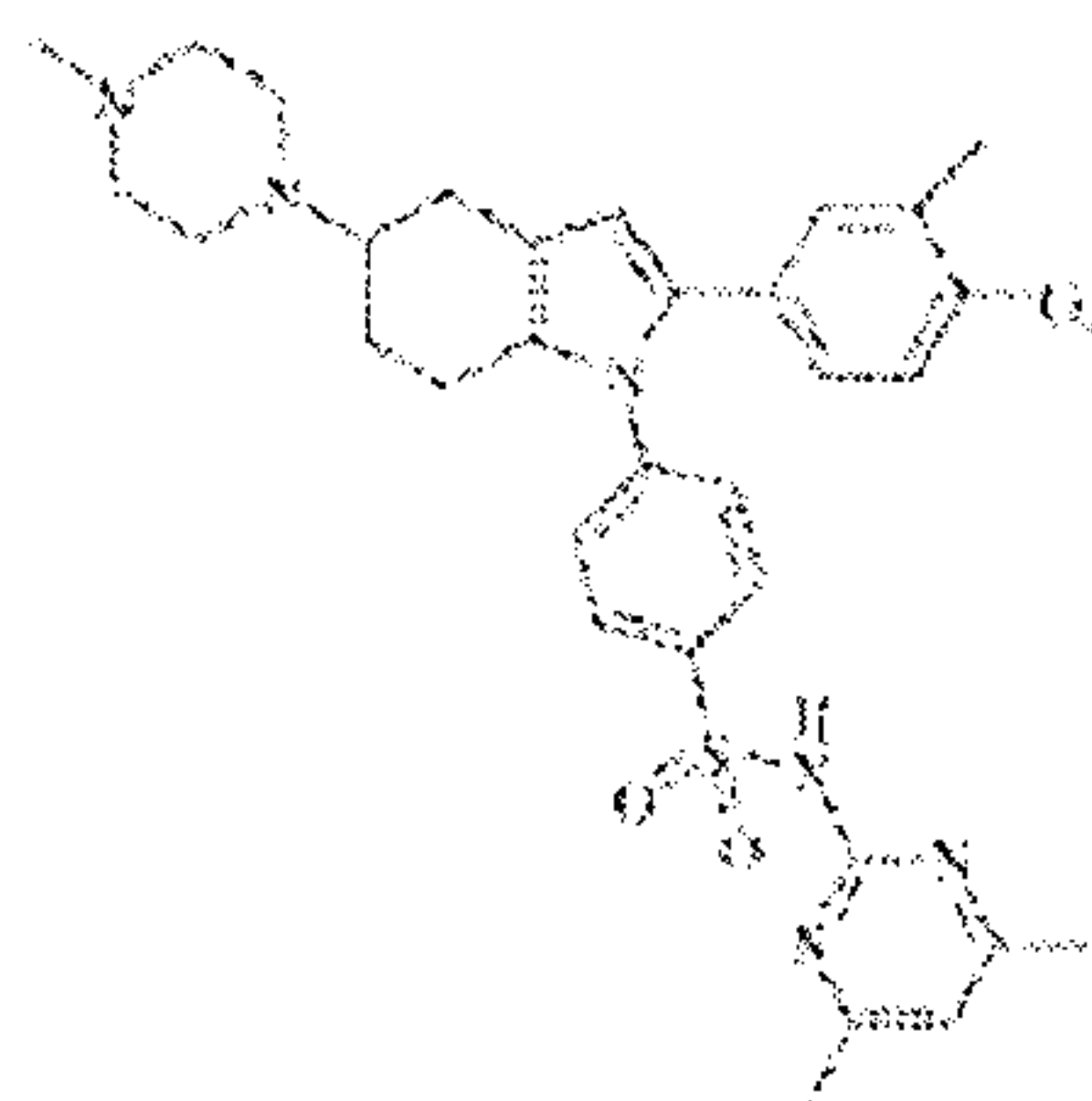
(43A);



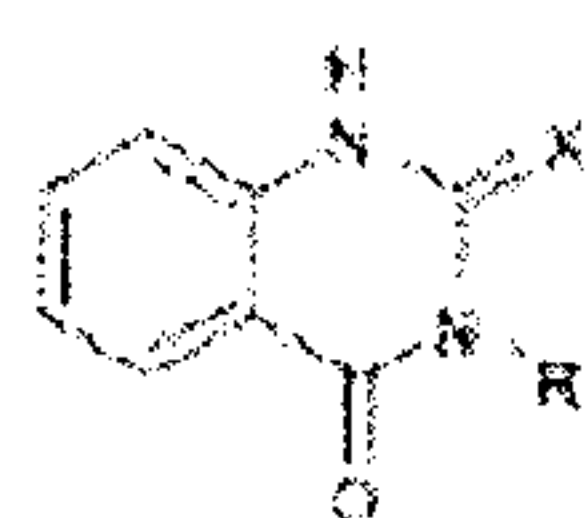
(43B);



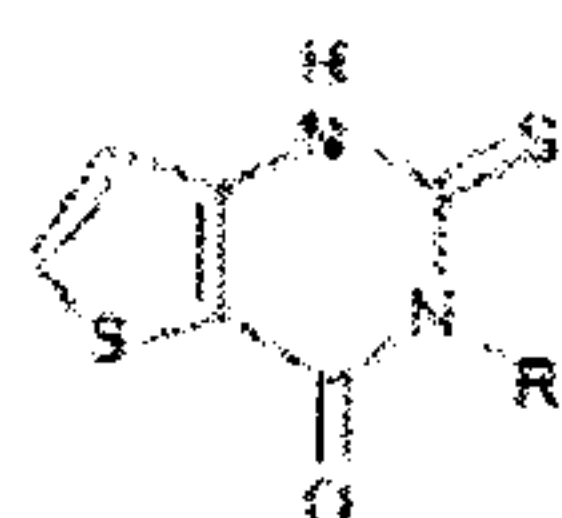
(45);



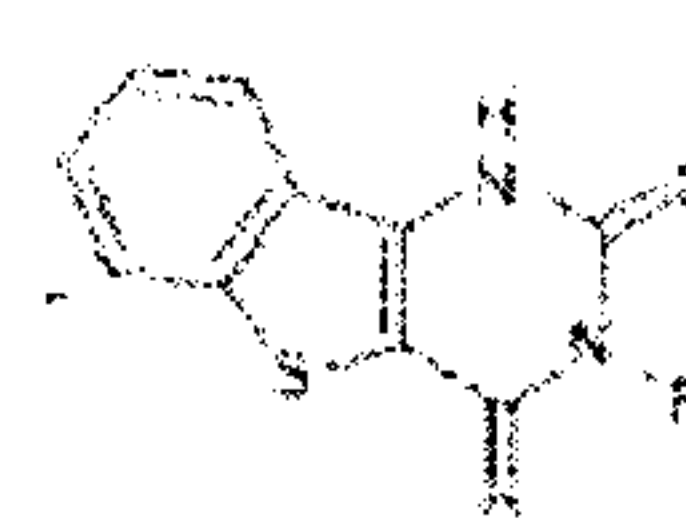
(46);



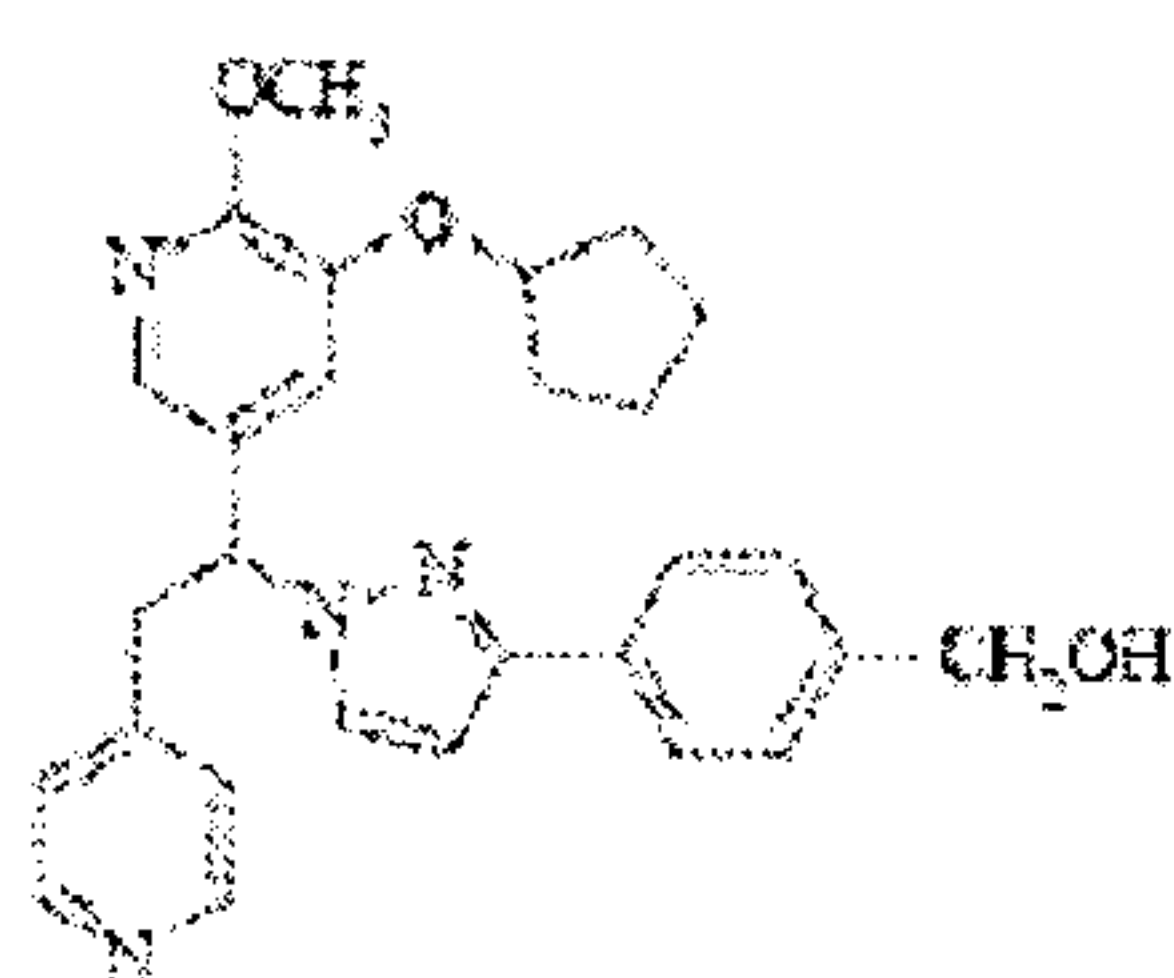
(47);



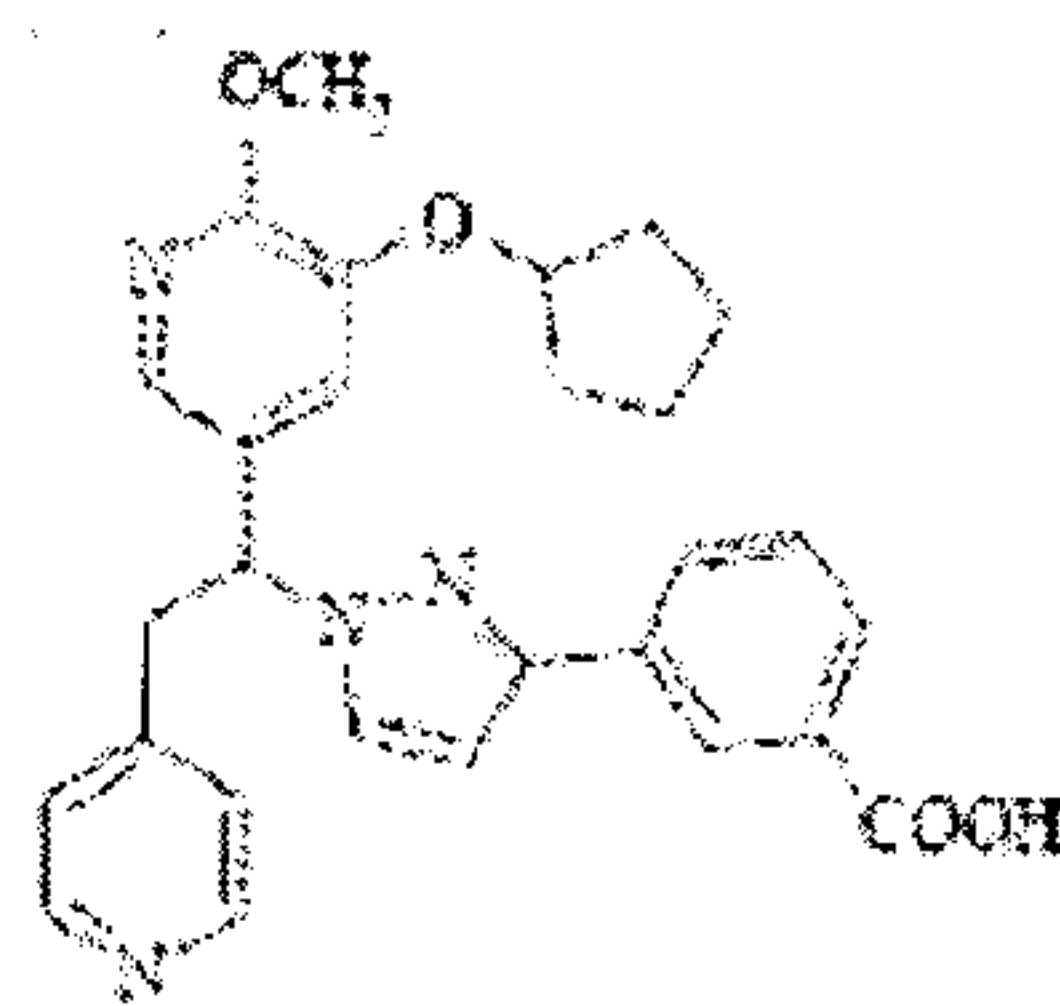
(48);



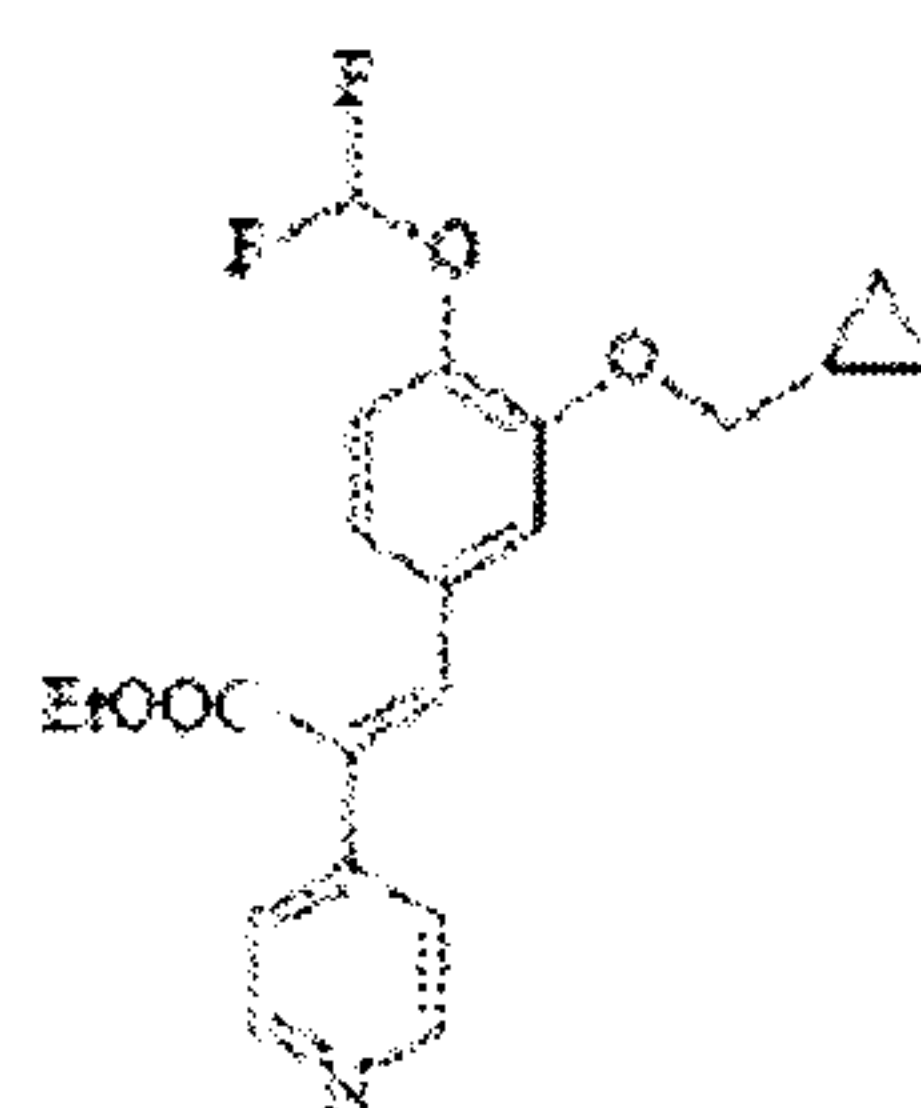
(49);



(51);

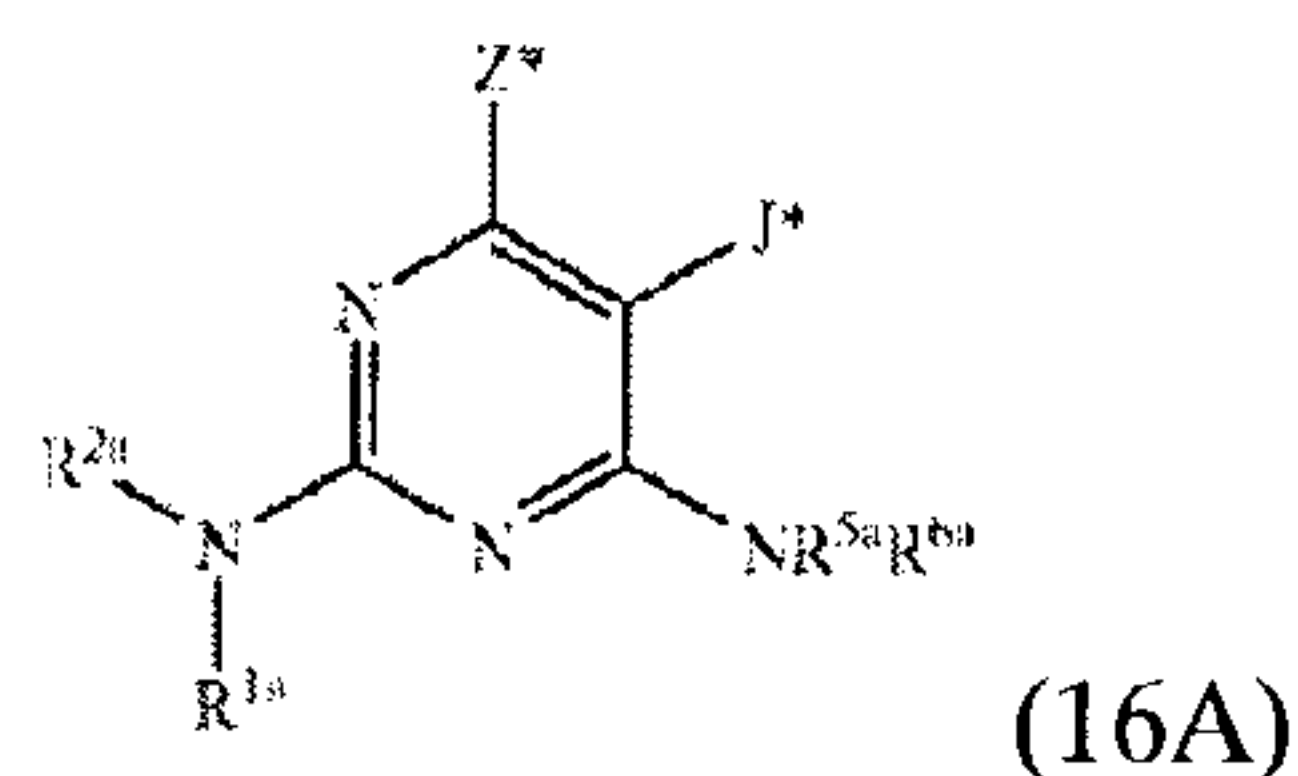


(52); and



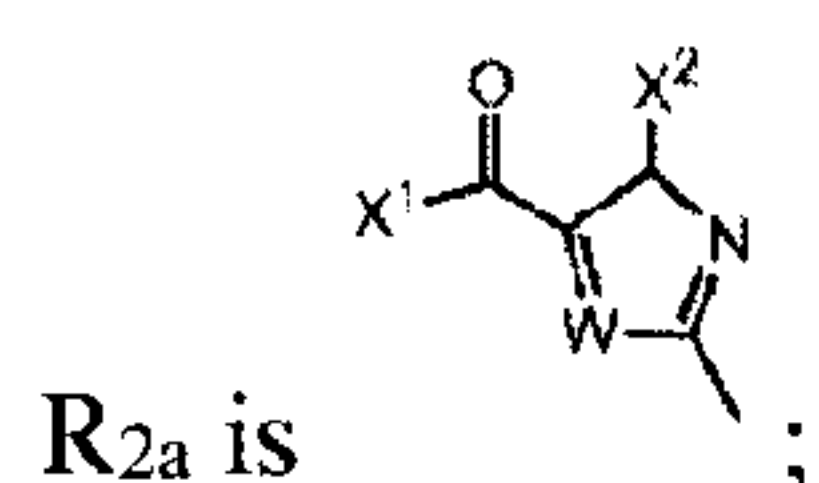
(53).

31. The pharmaceutical composition of Claim 27, wherein the PDE7 inhibitor is:



wherein:

R_{1a} is hydrogen or alkyl;



W is S;

X₁ is alkoxy;

X₂ is alkyl;

Z* is halogen, haloalkyl, oxazolyl, NR_{3a}R_{4a}, C(O)-N(H)-alkylene-COOH, or phenyl which is unsubstituted or substituted with heteroaryl, CO₁H, or CO₁T₆;

R_{3a} is hydrogen or alkyl;

R_{4a} is alkyl, alkoxy, unsubstituted or substituted (heteroaryl) alkyl, unsubstituted or substituted heterocyclo, unsubstituted or substituted (heterocyclo) alkyl, or (aryl) alkyl wherein the aryl group is substituted with one or two groups T₁ and/or T₂ and/or further substituted with a group T₃; or

R_{3a} and R_{4a} together with the nitrogen atom to which they are attached combine to form an unsubstituted or substituted heterocyclo ring;

R_{5a} is an unsubstituted or substituted (heteroaryl) alkyl, or (aryl) alkyl wherein the aryl group is substituted with one or two groups T1 and/or T2 and/or further substituted with a group T3; or

R_{5a} and R_{6a} together with the nitrogen atom to which they are attached combine to form an unsubstituted or substituted heterocyclo ring;

R_{6a} is hydrogen or alkyl;

J* is hydrogen or alkyl;

T1 and T2 are independently alkoxy, alkoxycarbonyl, heteroaryl, SO₃H, or SO₂R_{8a} where R_{8a} is alkyl, amino, alkylamino or dialkylamino; or

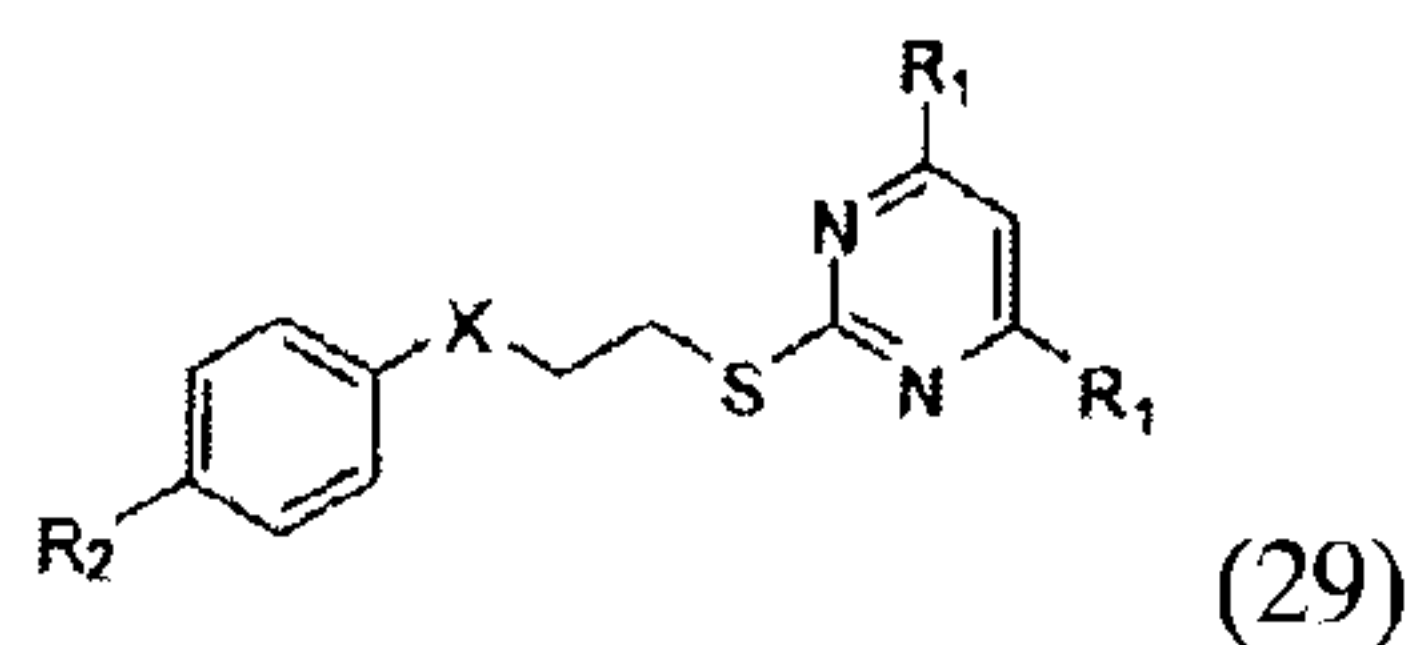
T1 and T2 together with the aryl ring to which they are attached combine to form a bicyclic ring;

T3 is H, alkyl, halo, halo alkyl, or cyano;

t is 1 or 2; and

T6 is alyl, halo alkyl, cycloalkyl, alkoxy, or heteroaryl.

32. The pharmaceutical composition of Claim 27, wherein the PDE7 inhibitor is selected from the following compounds:

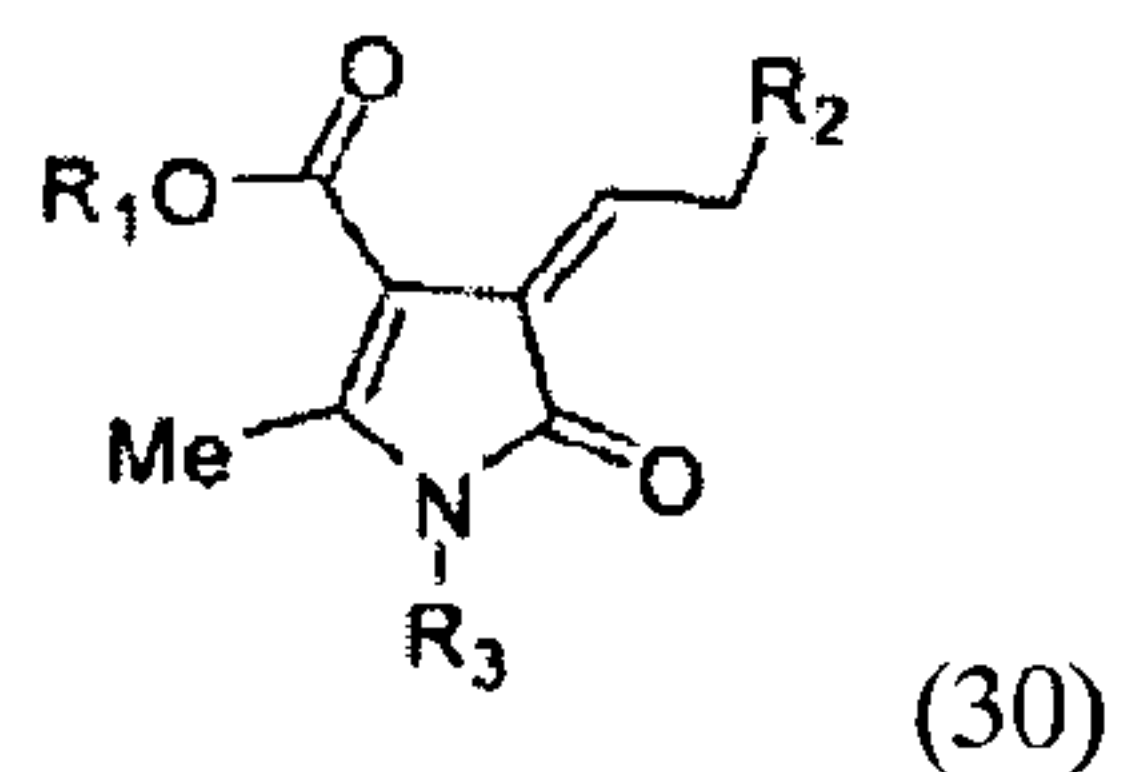


wherein:

X is SO, or SO₂,

R1 is H, or alkyl,

R2 is alkyl, or halogen;

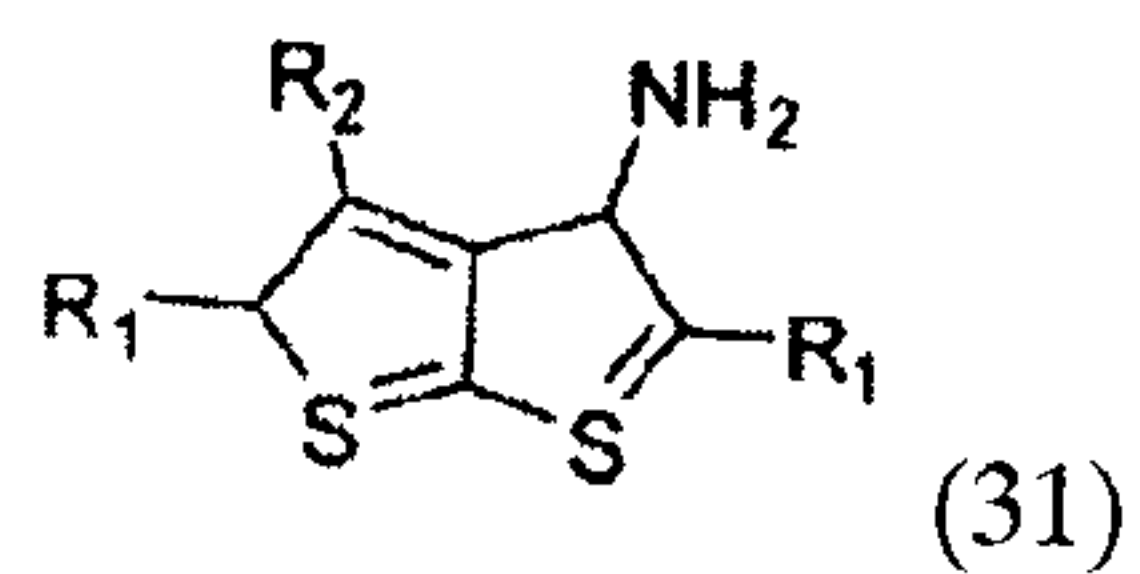


wherein:

R1 is alkyl,

R2 is aryl or heteroaryl,

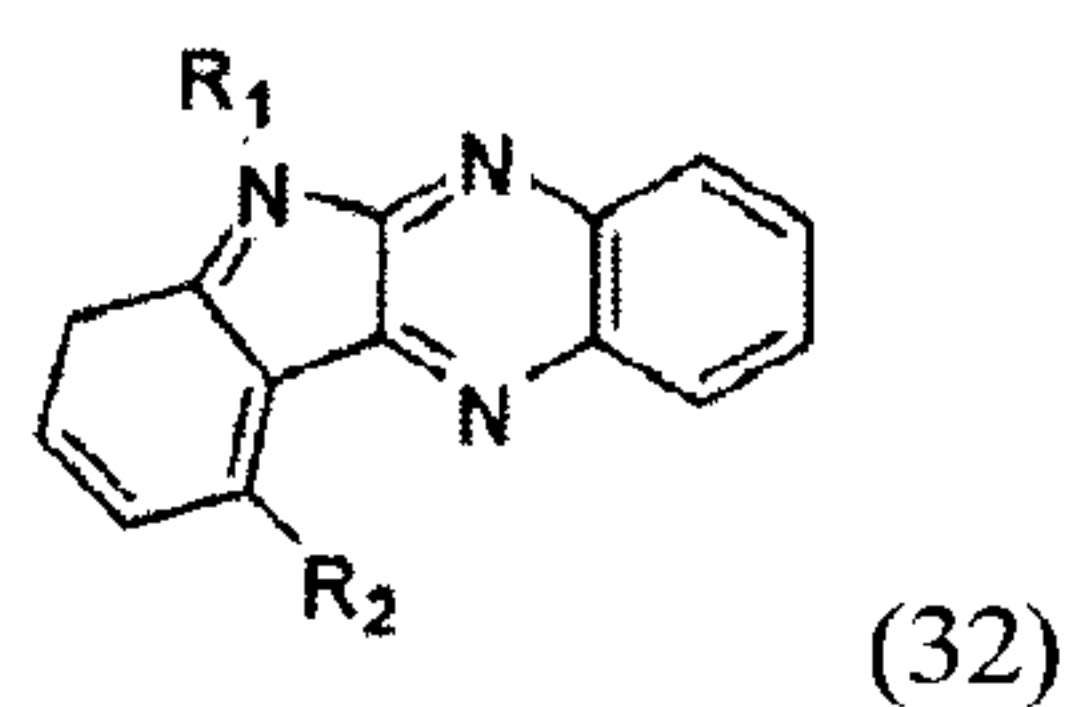
R3 is alkyl, aryl, cycloalkyl, or alkyl aryl;



wherein:

R1 is nitrile, or alkylcarboxylate,

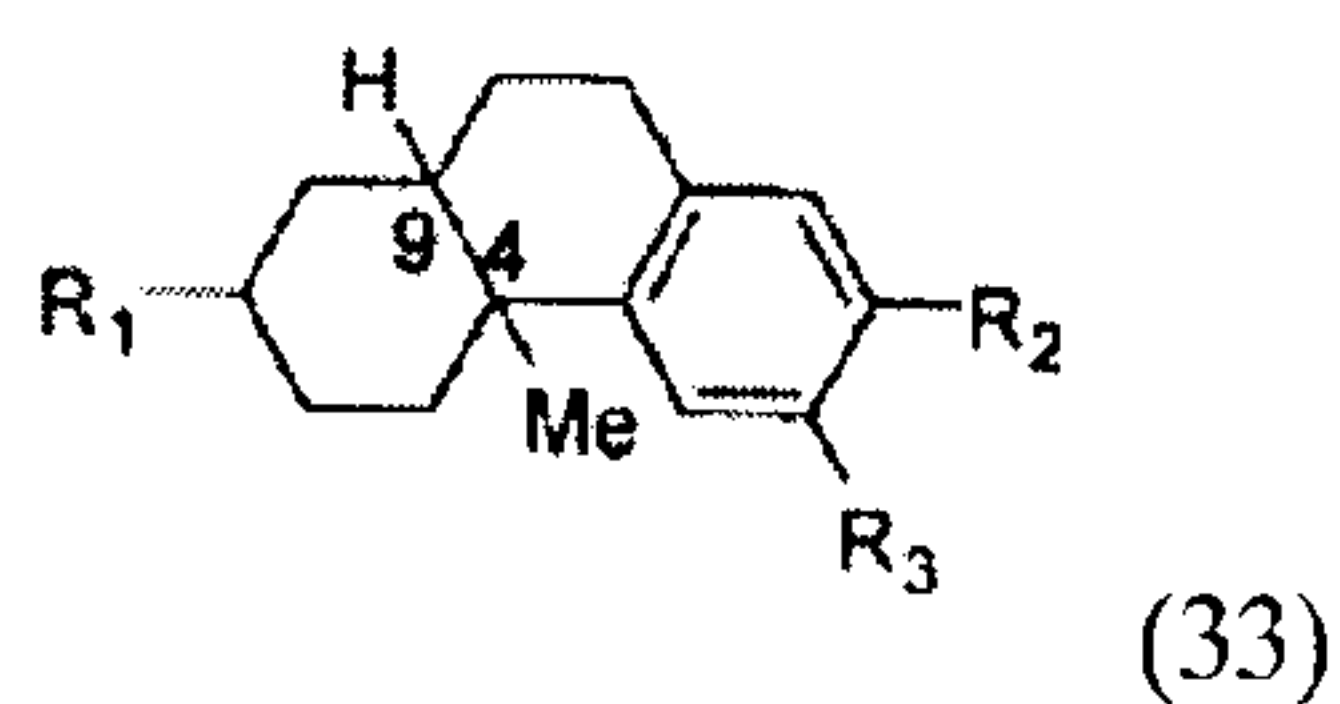
R2 is alkyl, aryl, or heteroaryl;



wherein:

R1 is alkyl, alkenyl, or alkylcarboxylic acid,

R2 is halogen;



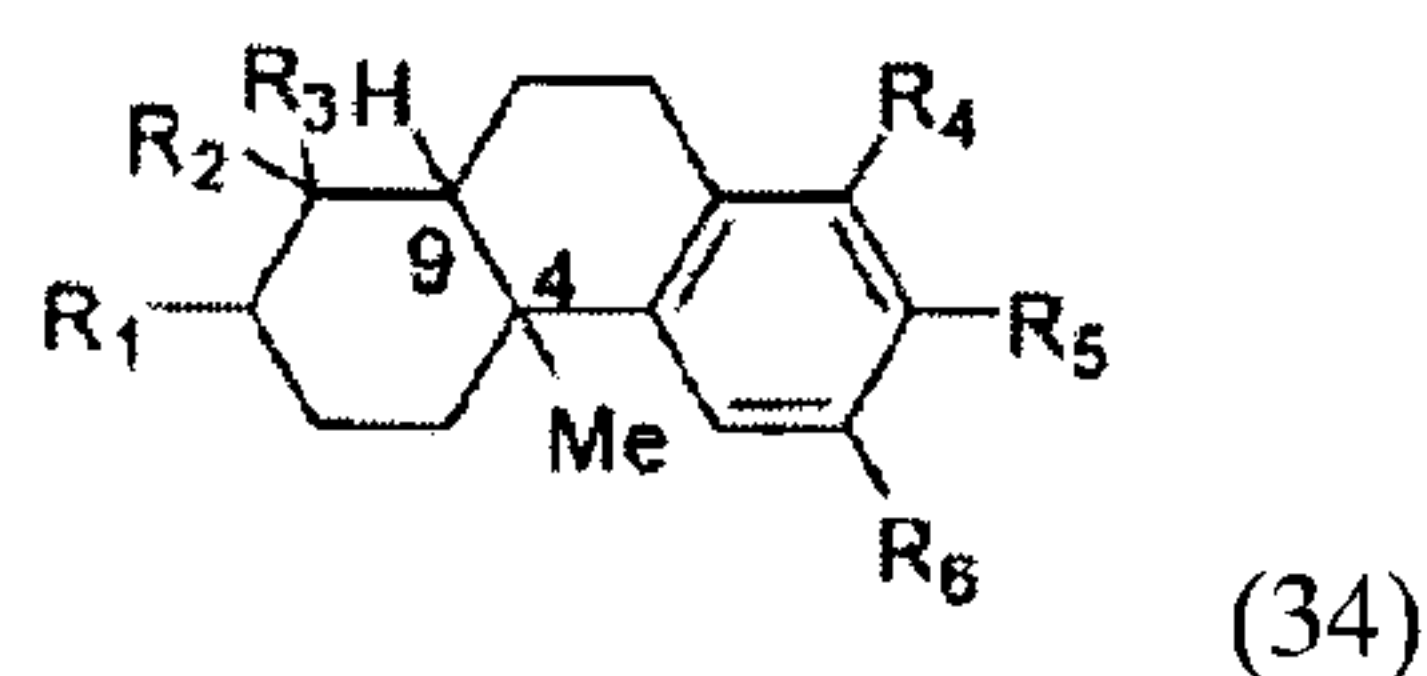
wherein:

R1 is CO, or alkylalcohol,

R2 is alkyl,

R3 is alkoxy, and

the C4 and C9 stereocenters are independently (R) or (S);



wherein:

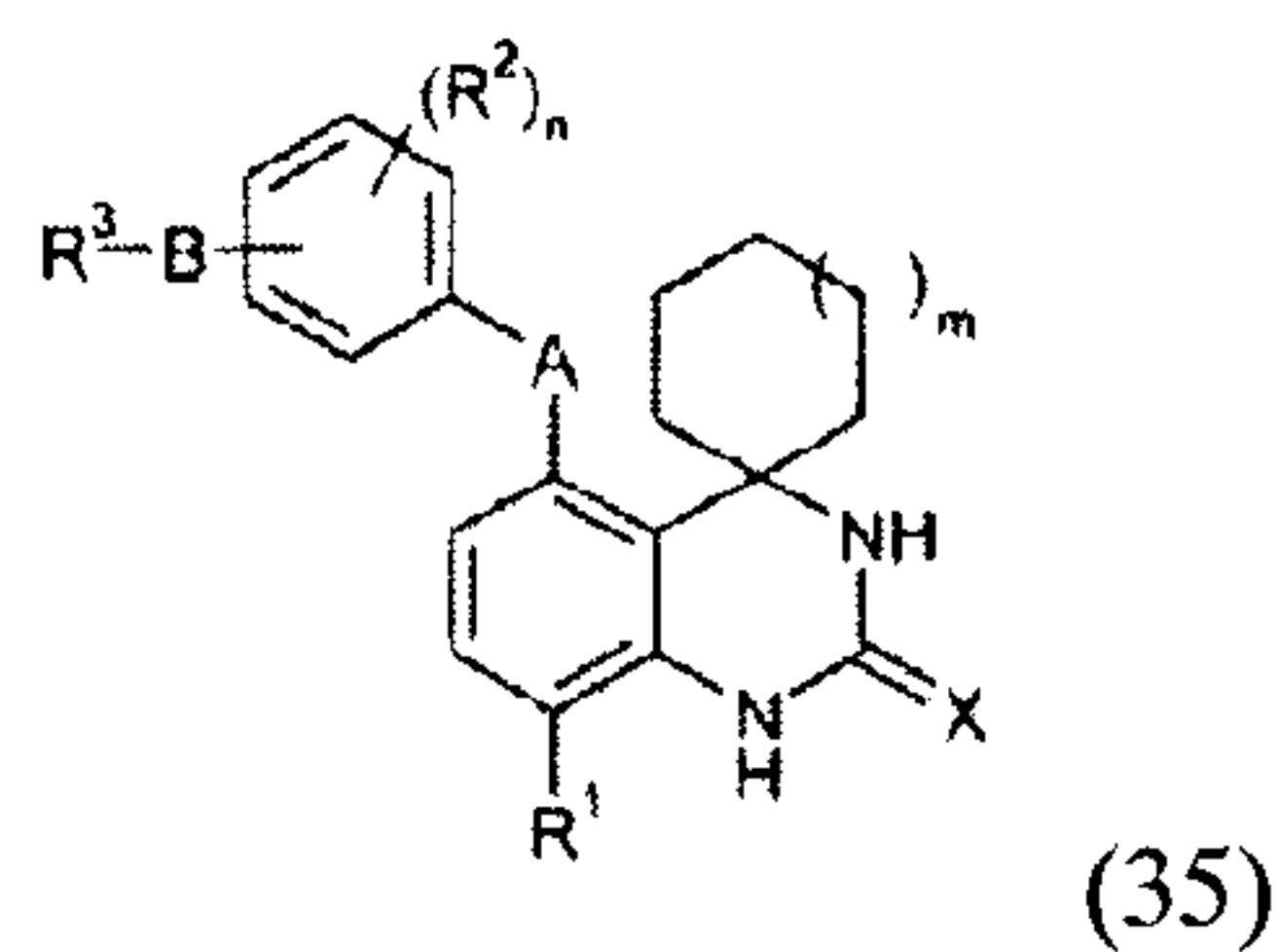
R1 is hydrogen, hydroxyl, carbonyl, or alkylalcohol,

R2 and R3 are independently selected from hydrogen, alkyl, alkylcarboxylate, and carboxylic acid,

R4 is hydrogen, or alkyl,

R5 is hydrogen, alkyl, hydroxyl, or acetate,

R6 is hydrogen, or alkoxy, and the C4 and C9 stereocenters are independently (R) or (S);



wherein:

m is 0, 1 or 2,

n is 0, 1, 2 or 3,

X is O, S or N-CN,

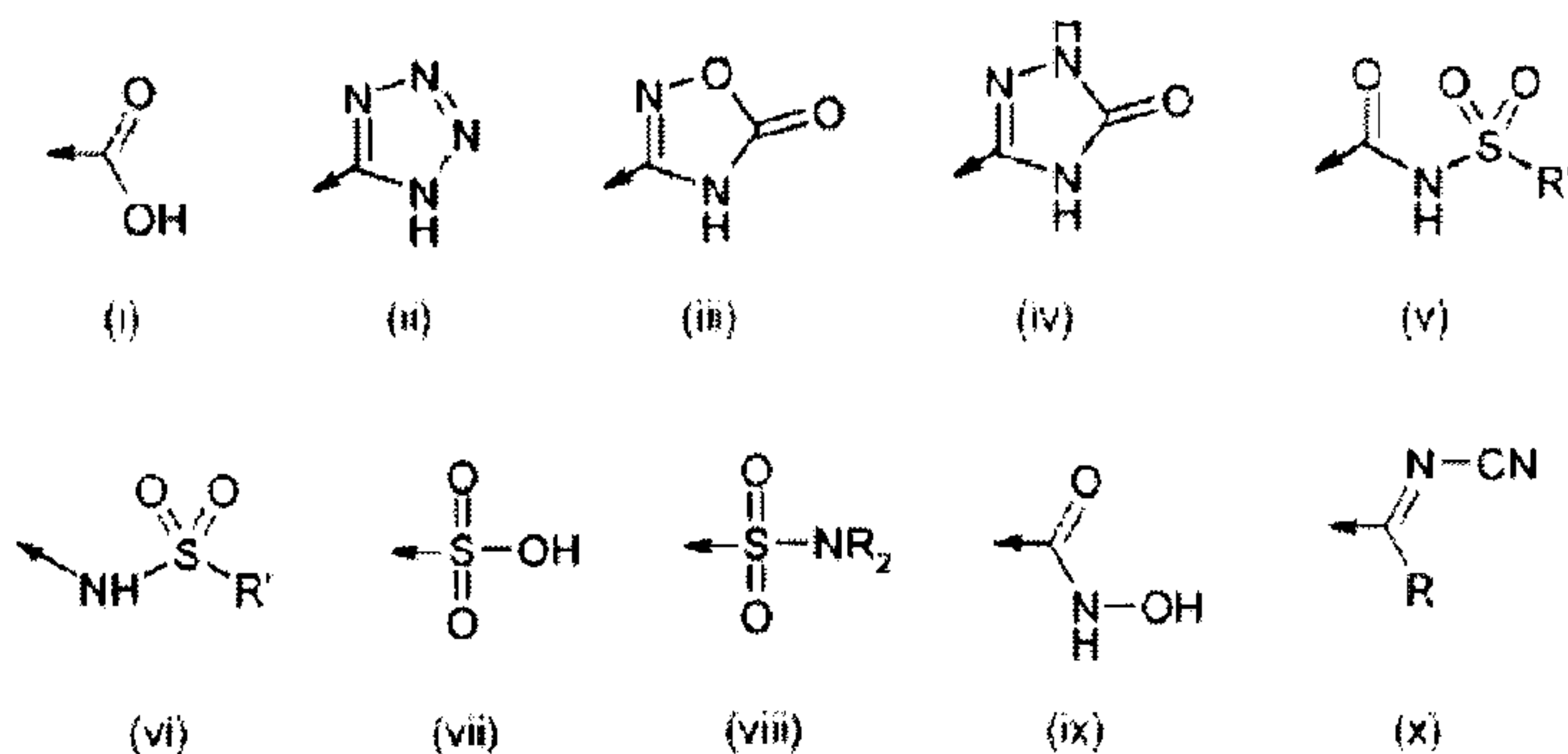
R¹ is halogen or CN,

A is a single bond, CH₂, O or S,

B is a single bond, CH₂ or OCH₂,

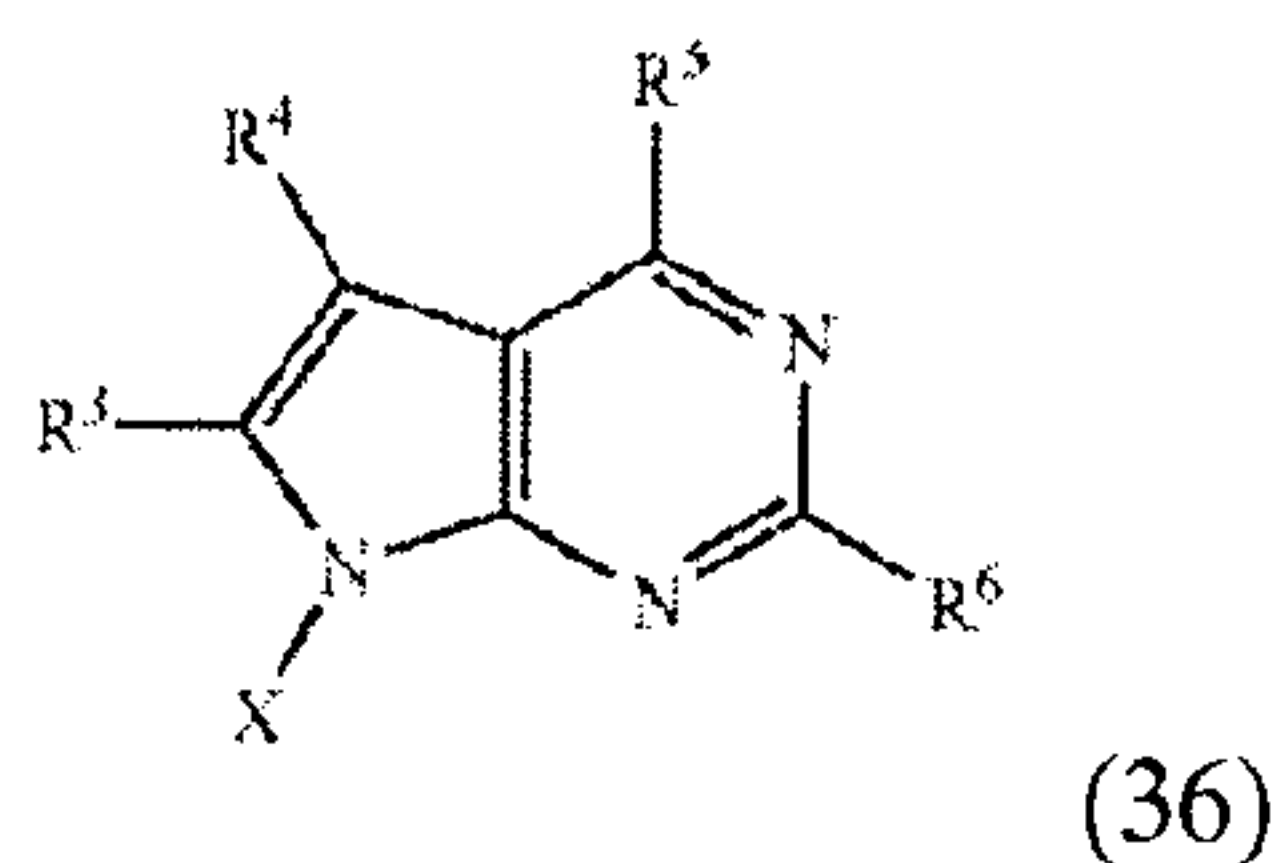
each R² is independently halogen, (C₁₋₆)alkyl optionally substituted by 1 to 3 fluorine atoms, OH, (C₁₋₆)alkylthio or CN,

R³ is selected from the following groups (i) to (x):



R is H or (C₁₋₆)alkyl optionally substituted by 1 to 3 fluorine atoms, R' is (C₁₋₆)alkyl optionally substituted by 1 to 3 fluorine atoms, or

a pharmaceutically acceptable salt, solvate, polymorph or prodrug thereof; and



wherein:

X is phenyl or Het, each of which is unsubstituted or monosubstituted or polysubstituted by R₁ and/or R₂,

R1 and R2 are each, independently of one another, A, OH, OA, SA, SOA, SO₂A, SO₂NH₂, SO₂NHA, SO₂AA', CN, NO₂, NH₂, NHA, NAA', NHCOA, NHCOOA, COOH, COOA, CONH₂, CONHA, CONAA' or Hal,

R1 and R2 together are alternatively -OCH₂O- or -OCH₂CH₂O-,

R3 is A, OH, OA, SA, SOA, SO₂A, SO₂NH₂, SO₂NHA, SO₂AA', CN, NO₂, NH₂, NHA, NHB, NAA', NHCOA, NHCOOA, NHCOB, NHCOOB, COOH, COOA, COOB, CONH₂, CONHA, CONHB, CONAA' or Hal,

R4 is branched or unbranched alkyl or alkenyl having up to 10 carbon atoms, which may be substituted by from 1 to 5 F and/or Cl atoms and/or in which one or more CH₂ groups may be replaced by O, S, SO, SO₂, NH, NA, NHCO, NACO, NHCOO or NACOO, or cycloalkyl or cycloalkenyl having from 3 to 7 carbon atoms, in which one or two CH₂ groups may be replaced by O, S, SO, SO₂, SO₂NH, SO₂NA, NH, NHA, NHCONH, NACONH, NACONA, NHCO, NACO, NHCOO or NACOO,

R5 is OH, OA, SA, SOA, SO₂A, SO₂NH₂, SO₂NHA, SO₂AA', CN, NO₂, NH₂, NHA, NAA', NHCOA, NHCOOA, COOH, COOA, CONH₂, CONHA, CONAA' or Hal,

R6 is H, OH, OA, SA, SOA, SO₂A, SO₂NH₂, SO₂NHA, SO₂AA', CN, NO₂, NH₂, NHA, NAA', NHCOA, NHCOOA, COOH, COOA, CONH₂, CONHA, CONAA' or Hal, A and A' are each, independently of one another, branched or unbranched alkyl or alkenyl having up to 10 carbon atoms, which may be substituted by from 1 to 5 F and/or Cl atoms and/or in which one or more CH₂ groups may be replaced by O, S, SO, SO₂, NH, NR₇, NHCO, NR₇CO, NHCOO or NR₇COO,

A and A' together are alternatively alkylene having from 3 to 7 carbon atoms, in which one or two CH₂ groups may be replaced by CHR₇, CHR₇R₈, O, S, SO, SO₂, NH, NR₇, NHCO, NR₇CO, NHCOO or NR₇COO,

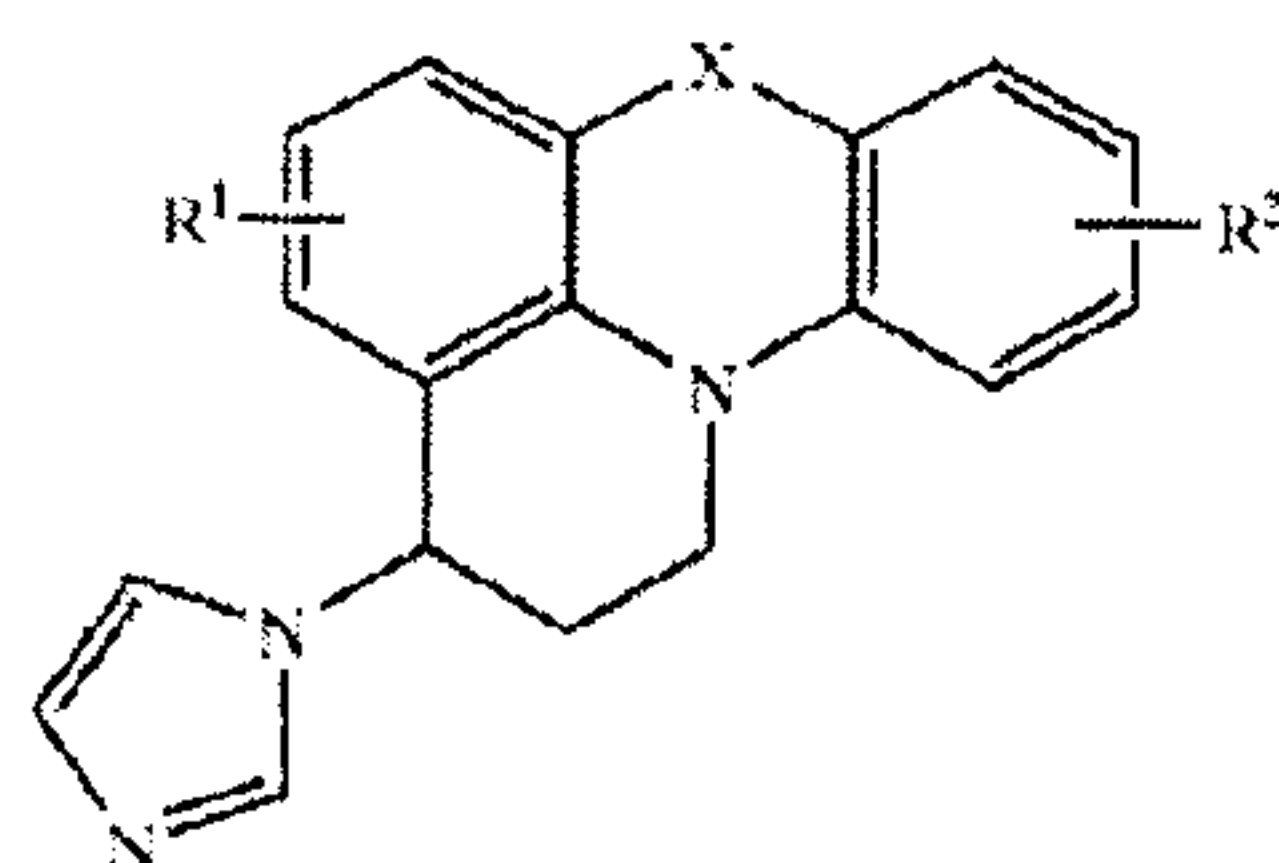
B is phenyl or Het, each of which is unsubstituted or monosubstituted or polysubstituted by R₁ and/or R₂, Het is an aromatic 5- or 6-membered heterocyclic ring having 1-3 N, O and/or S atoms which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A'', Hal or CF₃,

R₇ and R₈ are each, independently of one another, branched or unbranched alkyl or alkenyl having up to 5 carbon atoms, which may be substituted by from 1 to 5 F and/or Cl atoms and/or in which one or more CH₂ groups may be replaced by O, S, SO, SO₂ or NH,

A'' is alkyl having from 1 to 6 carbon atoms, and

Hal is F, Cl, Br or I, and pharmaceutically acceptable salts, prodrugs, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

33. The pharmaceutical composition of Claim 27, wherein the PDE7 inhibitor is selected from the following compounds:



(37)

wherein:

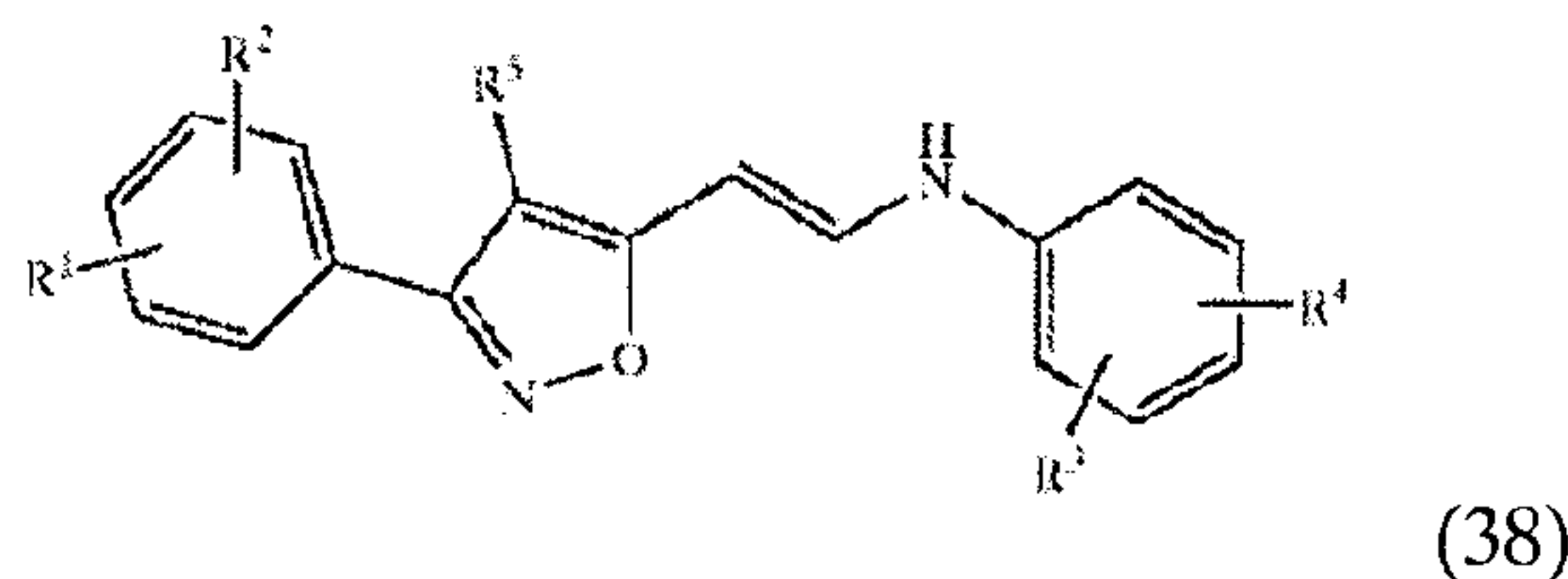
R₁ and R₂ are each, independently of one another, A₁, OA₁, SA₁ or Hal,

A₁ is H, A, alkenyl, cycloalkyl or alkylenecycloalkyl,

A is alkyl having 1-10 carbon atoms,

Hal is F, Cl, Br or I, and

x is O, S, SO or SO₂;



wherein:

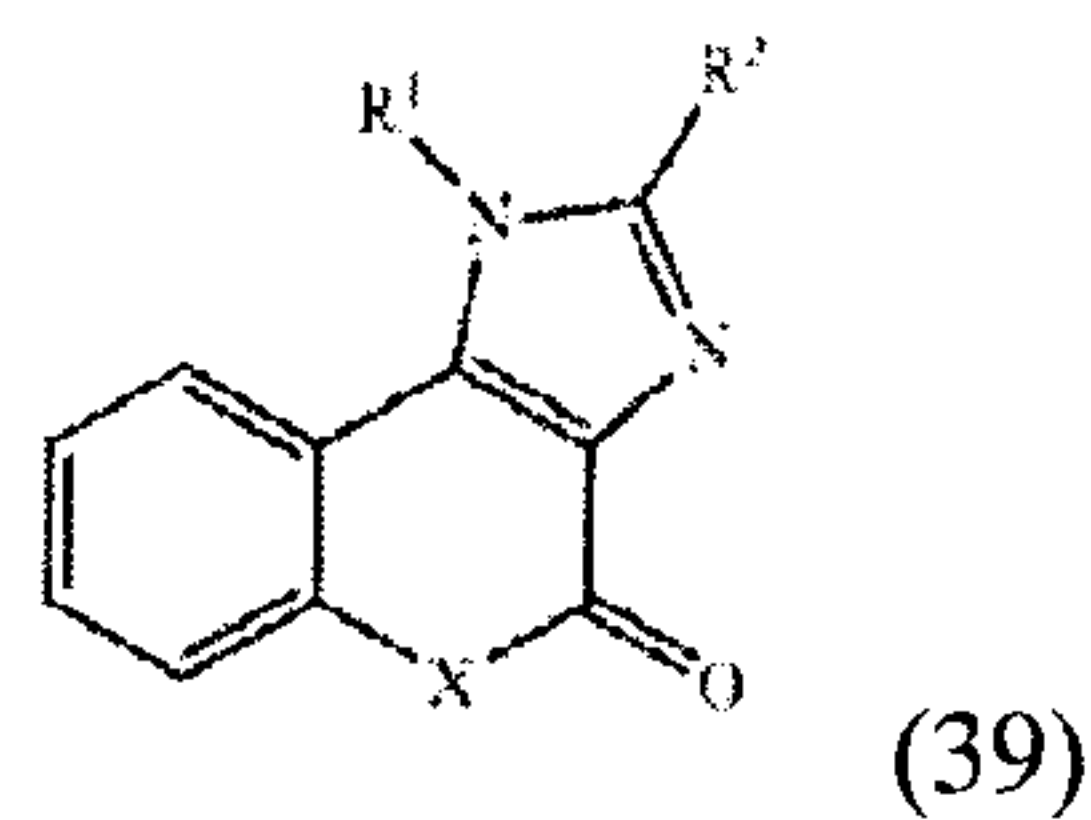
R1, R2, R3, R4 are each, independently of one another, Hal, OA1, SA1, A, H, COOA1, CN or CONA1A2,

R5 is COOA1, CN or CONA1A2,

A1, A2 are each, independently of one another, H, A, alkenyl, cycloalkyl or alkylencycloalkyl,

A is alkyl having 1 to 10 C atoms,

Hal is F, Cl, Br or I;



wherein:

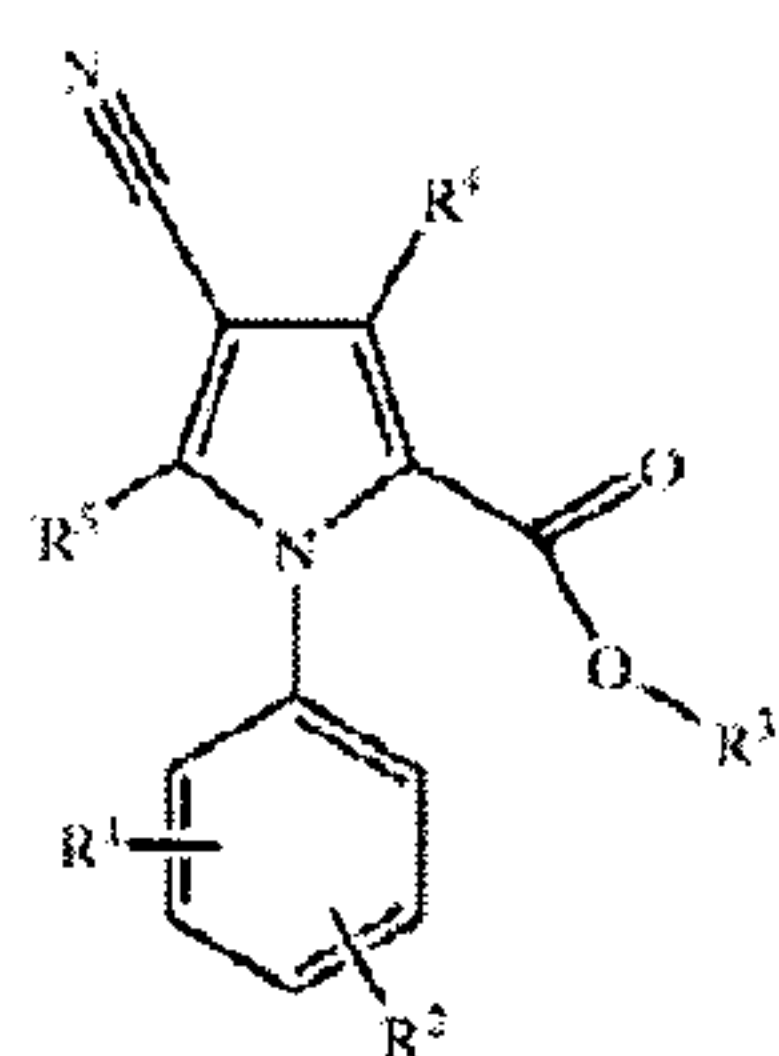
R1 is H, A, benzyl, indan-5-yl, 1,2,3,4-tetrahydronaphthalen-5-yl, dibenzothien-2-yl, or phenyl which is unsubstituted or mono-, di- or trisubstituted by Hal, A, A- CONH, benzyloxy, alkoxy, COOH or COOA,

R₂ is H or A,

X is O or S,

Hal is F, Cl, Br or I,

A is alkyl with 1 to 6 C atoms;



(40)

wherein:

R₁ and R₂ are each, independently of one another H, A, OA, SA or Hal,

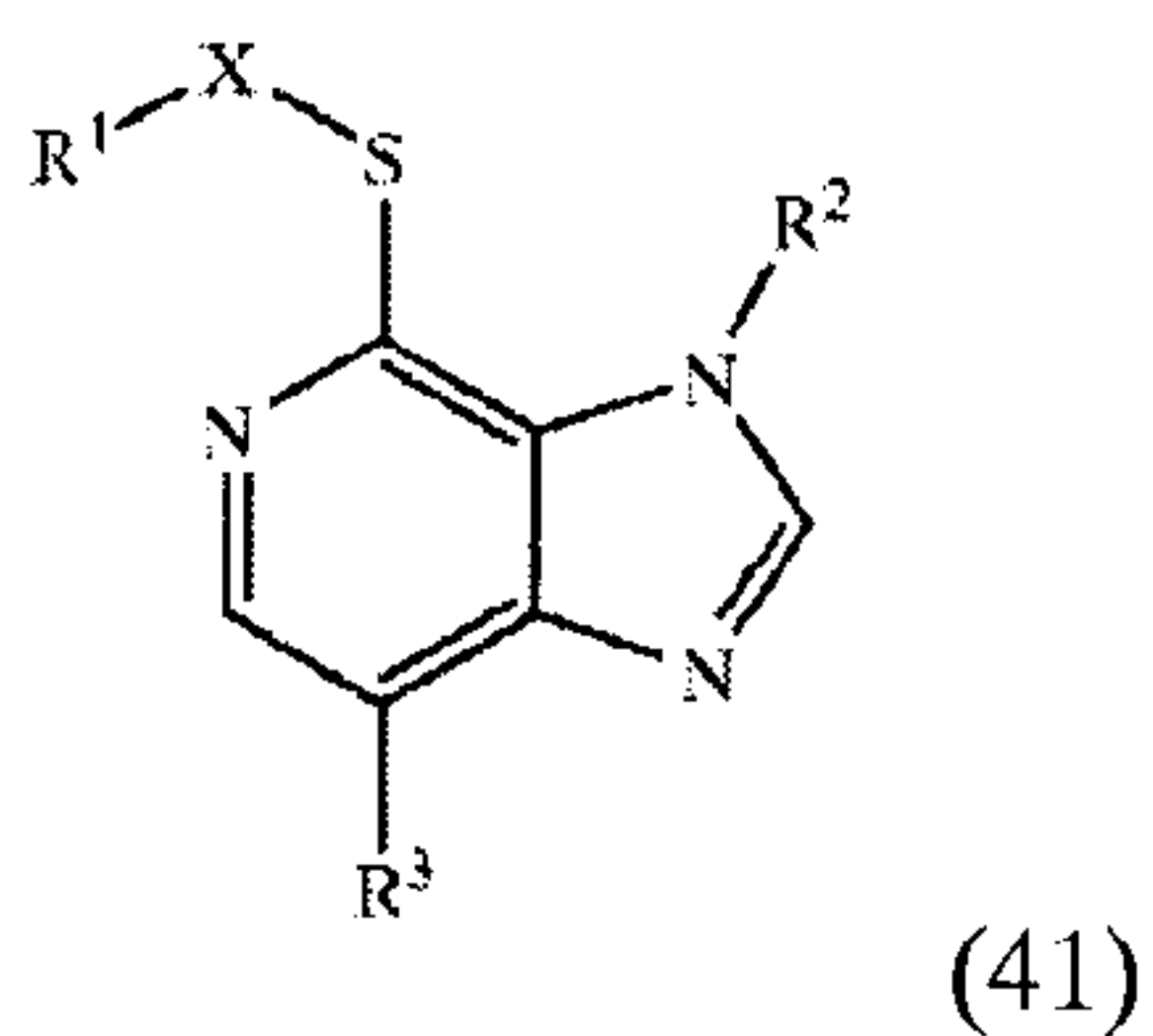
R₃ is H or A,

R₄ is A or NH₂,

R₅ is H, NH₂, NHA or NA₂,

A is alkyl having 1 to 10 carbon atoms, alkenyl, cycloalkyl or alkylencycloalkyl,

Hal is F, Cl, Br or I; and



wherein:

R1 is CONR4R5,

R2 is H or A,

R4 and R5 are each, independently of one another, H or A1,

R3 is Hal,

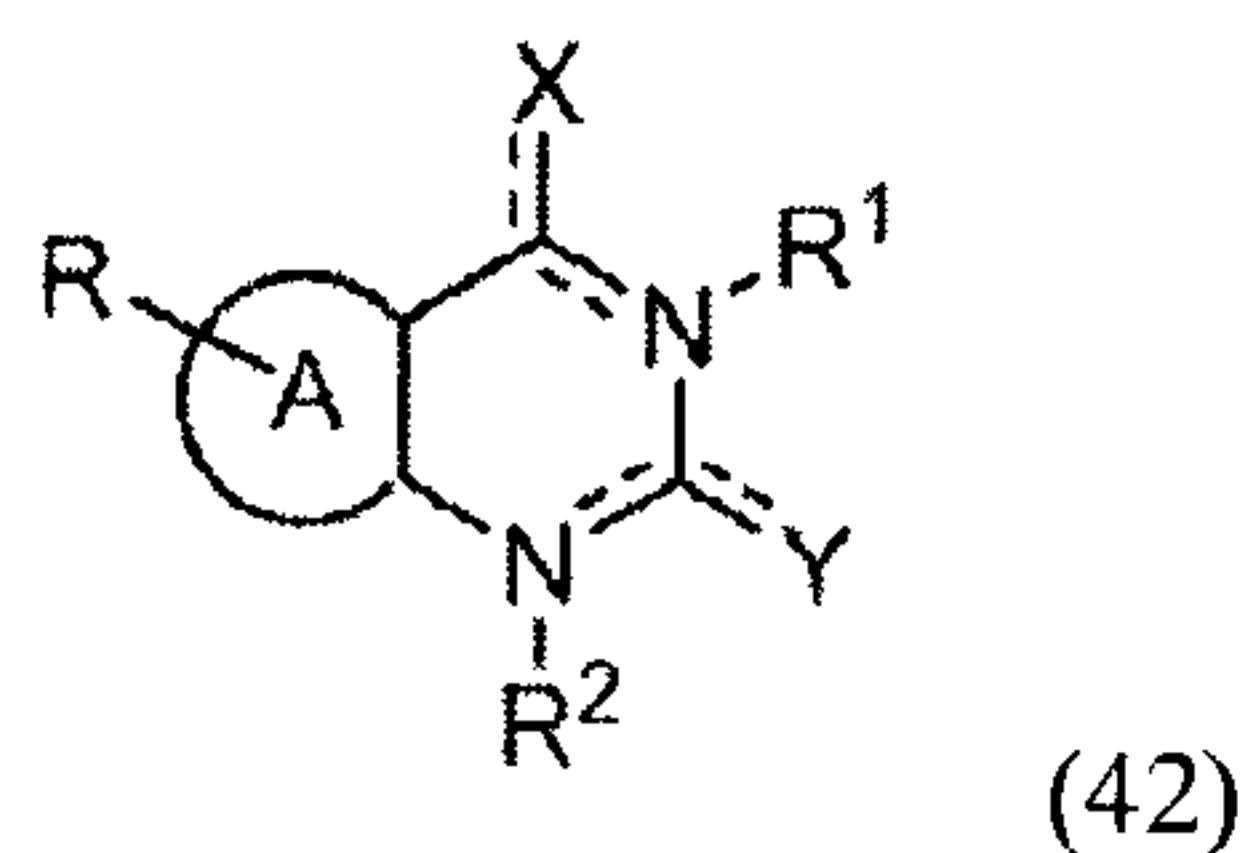
Hal is F, Cl, Br or I,

A is alkyl having 1-4 carbon atoms,

A1 is alkyl having 1-10 carbon atoms,

X is alkylene having 1-4 carbon atoms, in which an ethylene group may also be replaced by a double or triple bond, and their physiologically acceptable salts and/or solvates.

34. The pharmaceutical composition of Claim 27, wherein the PDE7 inhibitor is:



wherein:

A is fused carbocyclo or heterocyclo of 5, 6 or 7 members and may be saturated or unsaturated;

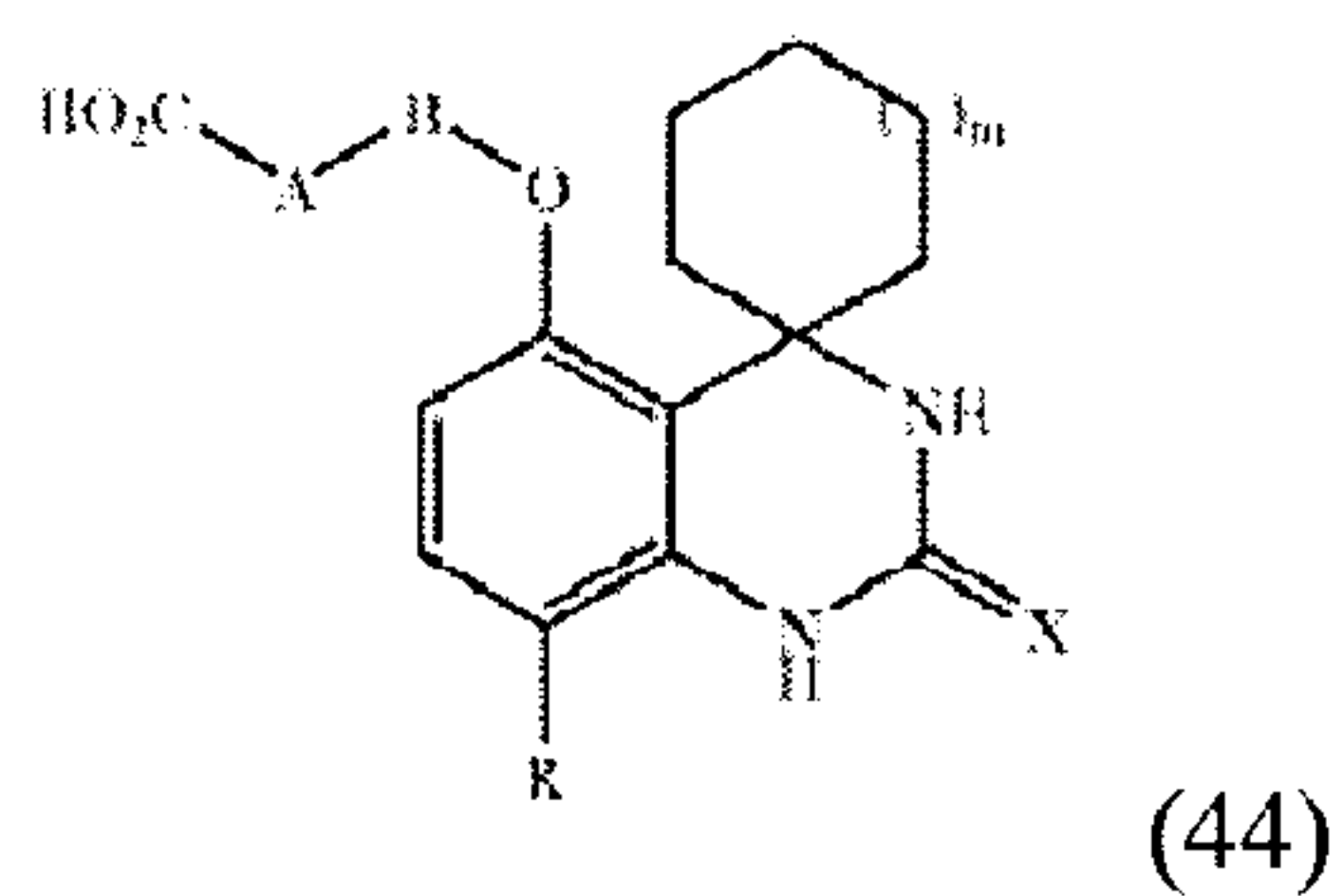
the dashed lines represent, independently, a single or double bond;

X and Y are chosen independently from the group consisting of alkyl, hydrogen, =O, =S, -N (alkyl), -N(aryl), aryl, O-alkyl, O-aryl, alkyl-S and -S-aryl; and

R1 and R2 are chosen independently from the group consisting of hydrogen, halogen, alkyl, halo alkyl, aryl, cycloalkyl, (Z)n-aryl, hetero aryl, -OR3; -C(O)OR3, -(Z)n-C(O)OR3 and -S(O), or a pharmaceutically acceptable salt, prodrug, solvate or stereoisomer of the same;

wherein, when A is unsubstituted benzene, X=O, Y=S, when A is unsubstituted benzene, X=O, Y=O, when A is unsubstituted benzene, X=O, Y=S-Me, when A is unsubstituted thiophene, X=O, Y=S, and when A is unsubstituted benzothiophene, X=O, Y=S.

35. The pharmaceutical composition of Claim 27, wherein the PDE7 inhibitor is selected from the following compounds:



wherein:

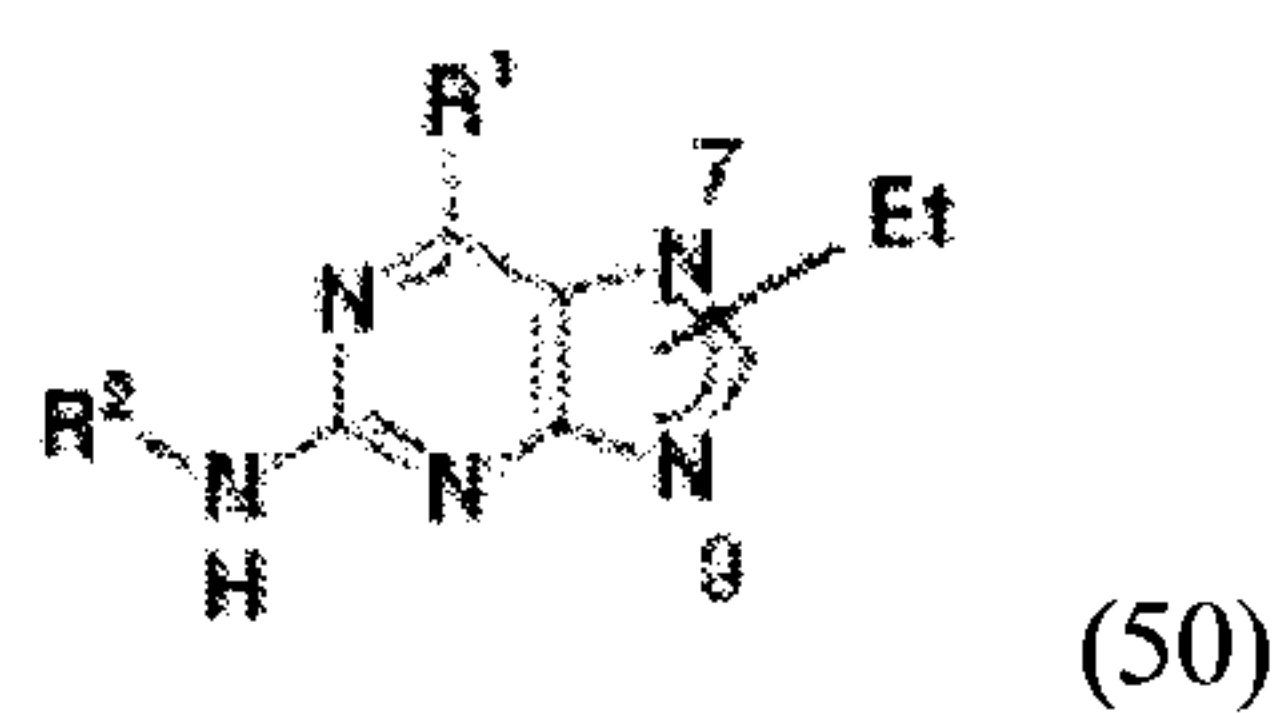
m is 0, 1 or 2;

X is O, S or N--CN;

R is F, Cl or CN;

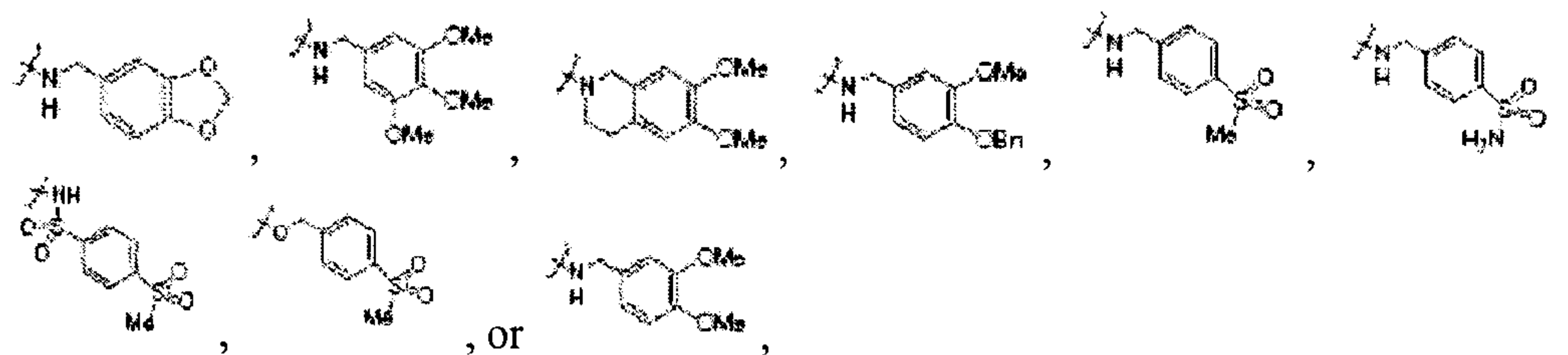
A is a C₃₋₆ cycloalkylene group optionally substituted with a C₁₋₄ alkyl group;
and

B is a single bond or a C₁₋₂ alkylene group;

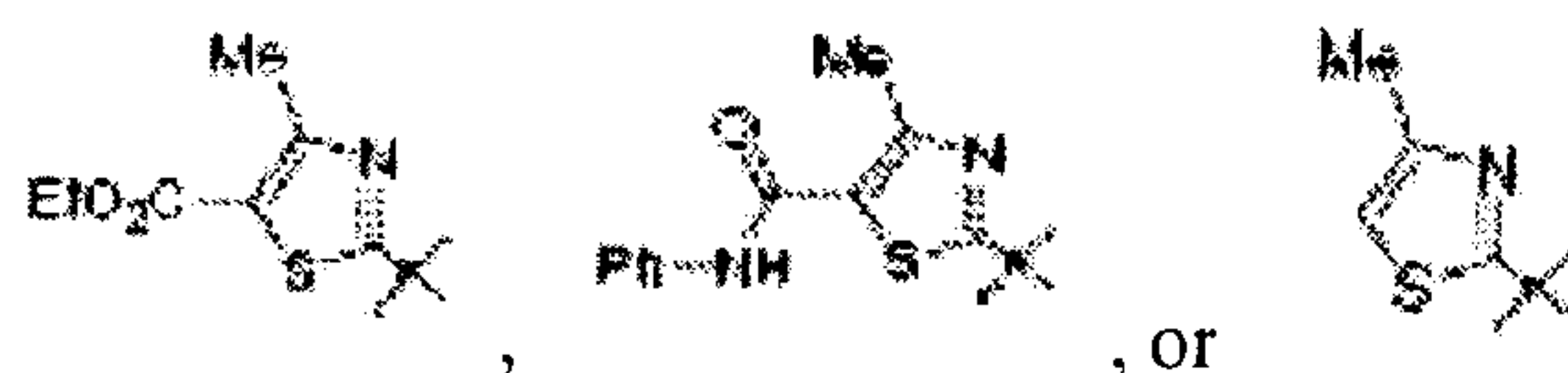


wherein:

R1 is:

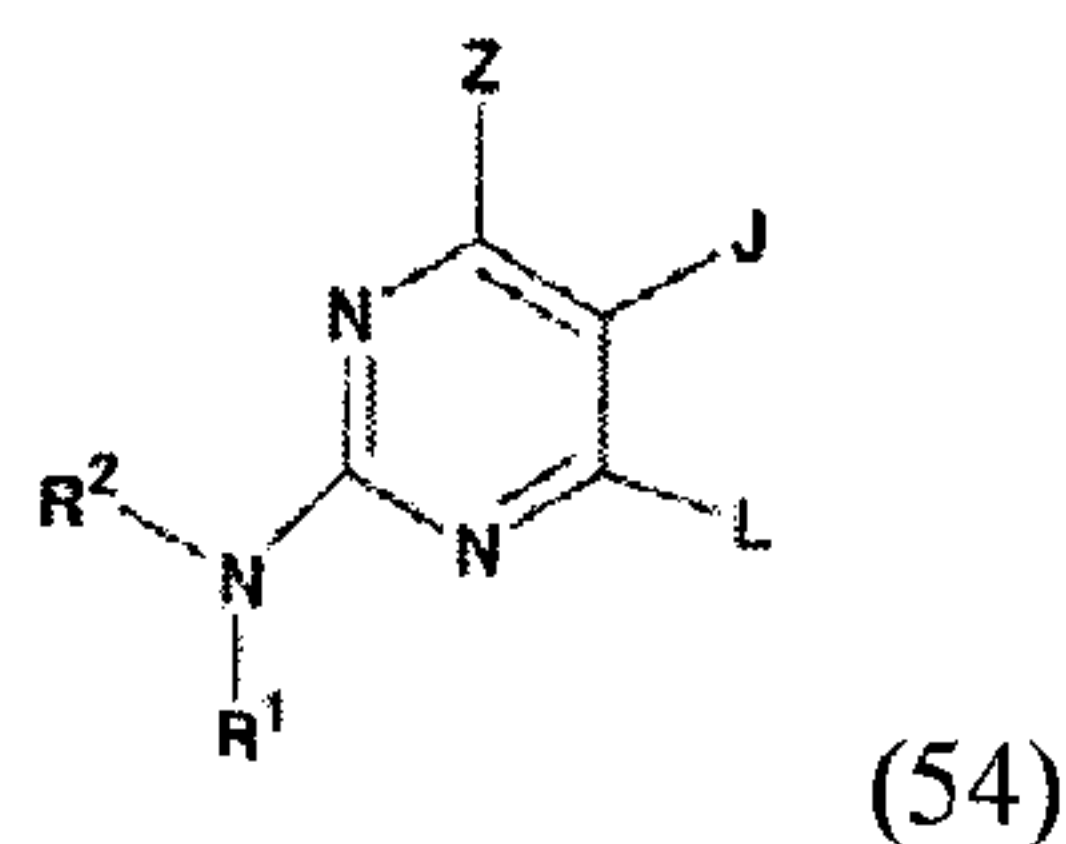


R2 is:



wherein the ethyl group may be attached to the 7 or 9 position.

36. The pharmaceutical composition of Claim 27, wherein the PDE7 inhibitor is:



wherein:

R1 is H or alkyl;

R2 is (a) heteroaryl, or heterocyclo, either of which may be optionally substituted with one to three groups T1, T2, T3; (b) aryl substituted with one to three groups T1, T2, T3 provided that at least one of T1, T2, T3 is other than H; or (c) aryl fused to a heteroaryl or heterocyclo ring wherein the combined ring system may be optionally substituted with one to three groups T1, T2, T3;

Z is (a) -OR4, -C(O)R4, -C(O)OR4, -SR4, -NR3R4, -C(O)NR3R4, -NR3S02R4c, halogen, nitro, halo alkyl; or (b) alkyl, aryl, hetero aryl, heterocyclo, or cycloalkyl any of which may be optionally substituted with one to three groups T1a, T2a T3a;

J is (a) hydrogen, halo, -OR4a, or (b) alkyl, alkenyl, or alkynyl any of which may be optionally substituted with one to three groups T1b, T2b or T3b;

L is (a) hydrogen, -OR4b, -C(O)R4b, -C(O)OR4b, -SR4b, -NRSR6, -C(O)NRSR6, -NRSS02R4d, halogen, haloalkyl, nitro, or (b) alkyl, aryl,

heteroaryl, heterocyclo, or cycloalkyl any of which may be optionally substituted with one to three groups T1c, T2c or T3c;

R3 and R4 are independently H, alkyl, alkenyl, aryl, (aryl)alkyl, hetero aryl, (heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocylo or (heterocyclo)alkyl any of which may be optionally substituted with one to three groups T1a, T2a or T3a; or

R3 and R4 together with the nitrogen atom to which they are attached may combine to form a 4 to 8 membered heterocyclo ring optionally substituted with one to three groups T1a, T2a or T3a;

R4a is hydrogen, alkyl, alkenyl, aryl, heteroaryl, (aryl)alkyl, (heteroaryl)alkyl, heterocylo, (heterocyclo)alkyl, cycloalkyl or (cycloalkyl)alkyl any of which may be optionally substituted with one to three groups T1 b, T2b or T3b;

R4b is hydrogen, alkyl, alkenyl, aryl, heteroaryl, (aryl)alkyl, (heteroaryl)alkyl, heterocylo, (heterocyclo)alkyl, cycloalkyl or (cycloalkyl)alkyl any of which may be optionally substituted with one to three groups T1c, T2c or T3c;

R4c and R4d are independently alkyl, alkenyl, aryl, (aryl)alkyl, heteroaryl, (heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocylo or (heterocyclo)alkyl any of which may be optionally substituted with one to three groups T1a, T2a or T3a;

R5 and R6 are independently H, alkyl, alkenyl, aryl, (aryl)alkyl, heteroaryl, (heteroaryl)alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocylo or (heterocyclo)alkyl any of which may be optionally independently substituted where valance allows with one to three groups T1c, T2c or T3c; or

R5 and R6 together with the nitrogen atom to which they are attached may combine to form a 4 to 8-membered heterocyclo ring optionally substituted with one to three groups T1c, T2c or T3c;

T1-1c, T2-2c, and T3-3c are each independently (1) hydrogen or T6, where T6 is (i) alkyl, (hydroxy)alkyl, (alkoxy)alkyl, alkenyl, alkynyl, cyclo alkyl, (cycloalkyl)alkyl, cycloalkenyl, (cycloalkenyl)alkyl, aryl, (aryl)alkyl, heterocyclo, (heterocyclo)alkyl, heteroaryl, or (heteroaryl)alkyl; (ii) a group (i) which is itself substituted by one or more of the same or different groups (i); or (iii) a group (i) or (ii) which is independently substituted by one or more of the following groups (2) to (13) of the definition of T1-1c, T2-2c and T3-3c (2) -OH or -OT6, (3) -SH or -ST6, (4) -C(O)tH, -C(O)tT6, or -O-C(O)T6, where t is 1 or 2; (5)-SO₃H, -S(O)T6, or S(O)tN(T9)T6, (6) halo, (7) cyano, (8) nitro, (9) -T4-NT7T8, (10) -T4-N(T9)-T5-NT7T8, (11) -T4-N(T10)T5-T6, (12) -T4-N(T10)-T5-H, (13) oxo, T4 and T5 are each independently (1) a single bond, (2) -T11-S(O)t-T12-, (3) T11-C(O)-T12-, (4) -T11-C(S)-T12-, (5) -T11-O-T12-, (6) -T11-S-T12-, (7) -T11-O-C(O)-T12-, (8) -T11-C(O)-O-T12-, (9) -T11-C(=NT9a)-T12-, or (10) -T11-C(O)-C(O)T12,

T7, T8, T9, T9a and T10 (1) are each independently hydrogen or a group provided in the definition of T6, or (2) T7 and T8 may together be alkylene or alkenylene, completing a 3-to 8- membered saturated or unsaturated ring together with the atoms to which they are attached, which ring is unsubstituted or substituted with one or more groups listed in the description of T1-1c, T2-2c and T3-3c, or (3) T7 or T8, together with T9, may be alkylene or alkenylene completing a 3-to 8-membered saturated or unsaturated ring together with the nitrogen atoms to which they are attached, which ring is unsubstituted or substituted with one or more groups listed in the description of T1-1 c, T2-2c and T3-3c, or (4) T7 and T8 or T9 and T10 together with the nitrogen atom to which they are attached may combine to form a group-N=CT13T14 where T13

and T14 are each independently H or a group provided in the definition of T6;
and

T11 and T12 are each independently (1) a single bond, (2) alkylene, (3) alkenylene, or (4) alkynylene.

37. A kit for the treatment of an addiction, comprising: a first container comprising a phosphodiesterase 7 (PDE7) inhibitor that is selective for PDE7 relative to any other PDE enzyme from the PDE1-6 and PDE8-11 enzyme families; and a second container comprising a dopamine receptor agonist, wherein each of the PDE7 inhibitor and the dopamine receptor agonist contribute to the effective treatment or reduction of use of an addictive agent or practice of a compulsive behavior.

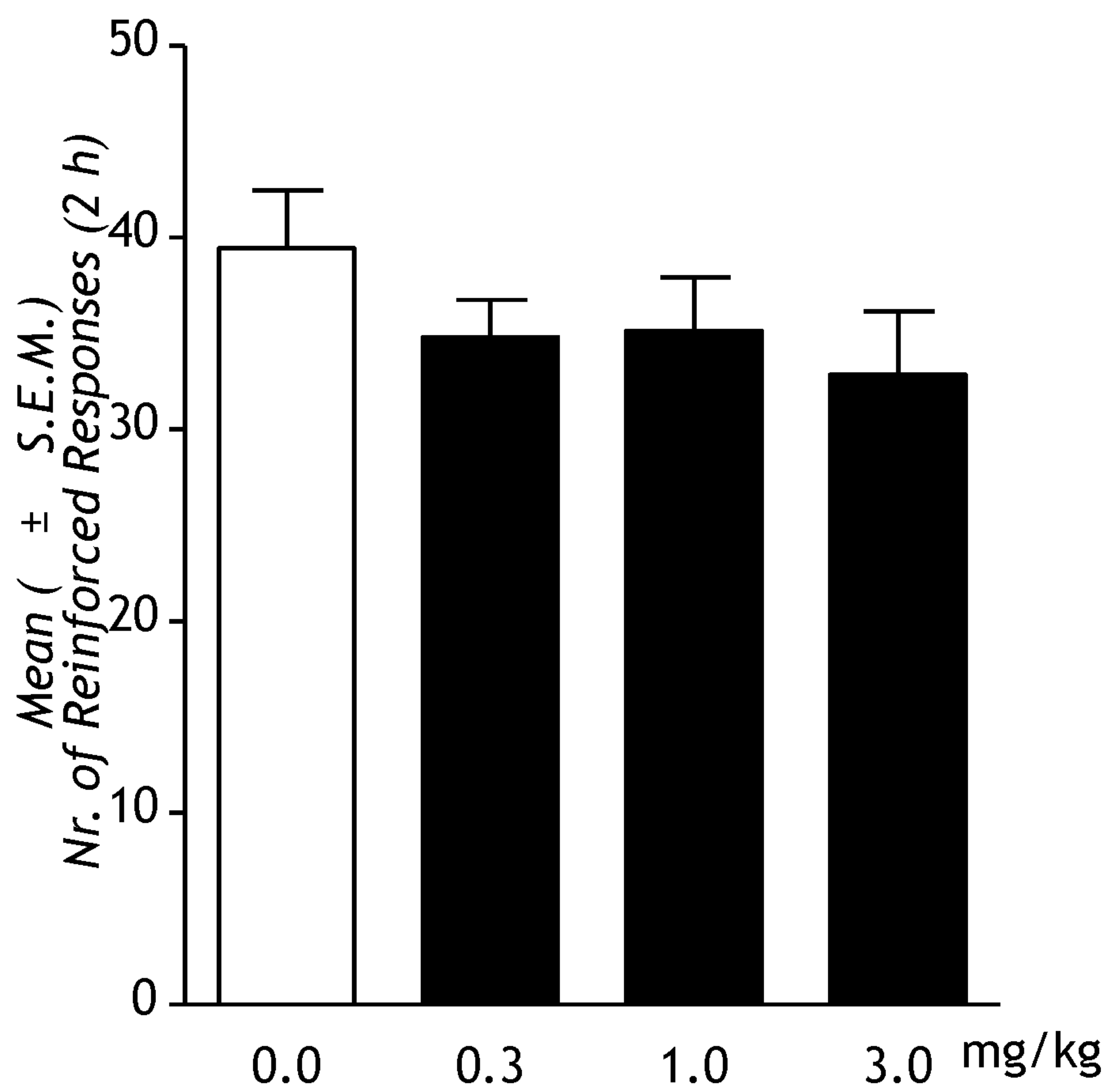
38. Use of a phosphodiesterase 7 (PDE7) inhibitor that is selective for PDE7 relative to any other PDE enzyme from the PDE1-6 and PDE8-11 enzyme families and a dopamine receptor agonist for treating a food addiction in a subject determined to have or to be at risk of developing a food addiction, wherein each of the PDE7 inhibitor and the dopamine receptor agonist contribute to the effective treatment or reduction of practice of the food addiction behavior.

39. A combination comprising a phosphodiesterase 7 (PDE7) inhibitor that is selective for PDE7 relative to any other PDE enzyme from the PDE1-6 and PDE8-11 enzyme families and a dopamine receptor agonist for use to treat a food addiction in a subject determined to have or to be at risk of developing a food addiction, wherein each of the PDE7 inhibitor and the dopamine receptor agonist contribute to the effective treatment or reduction of practice of the food addiction behavior.

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FIGURE 1

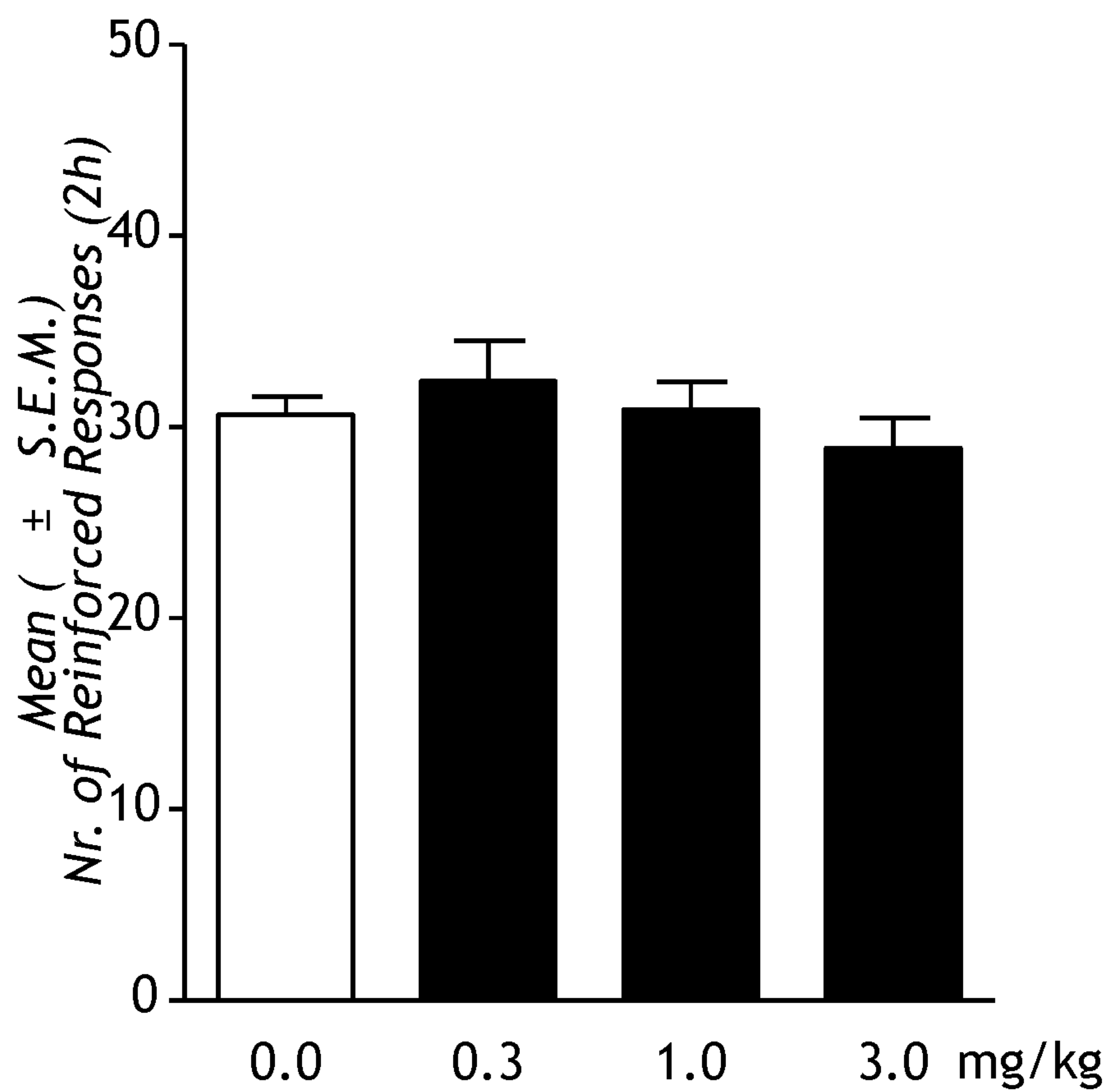
Effect of OMS182056 on Cocaine Self-Administration



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FIGURE 2

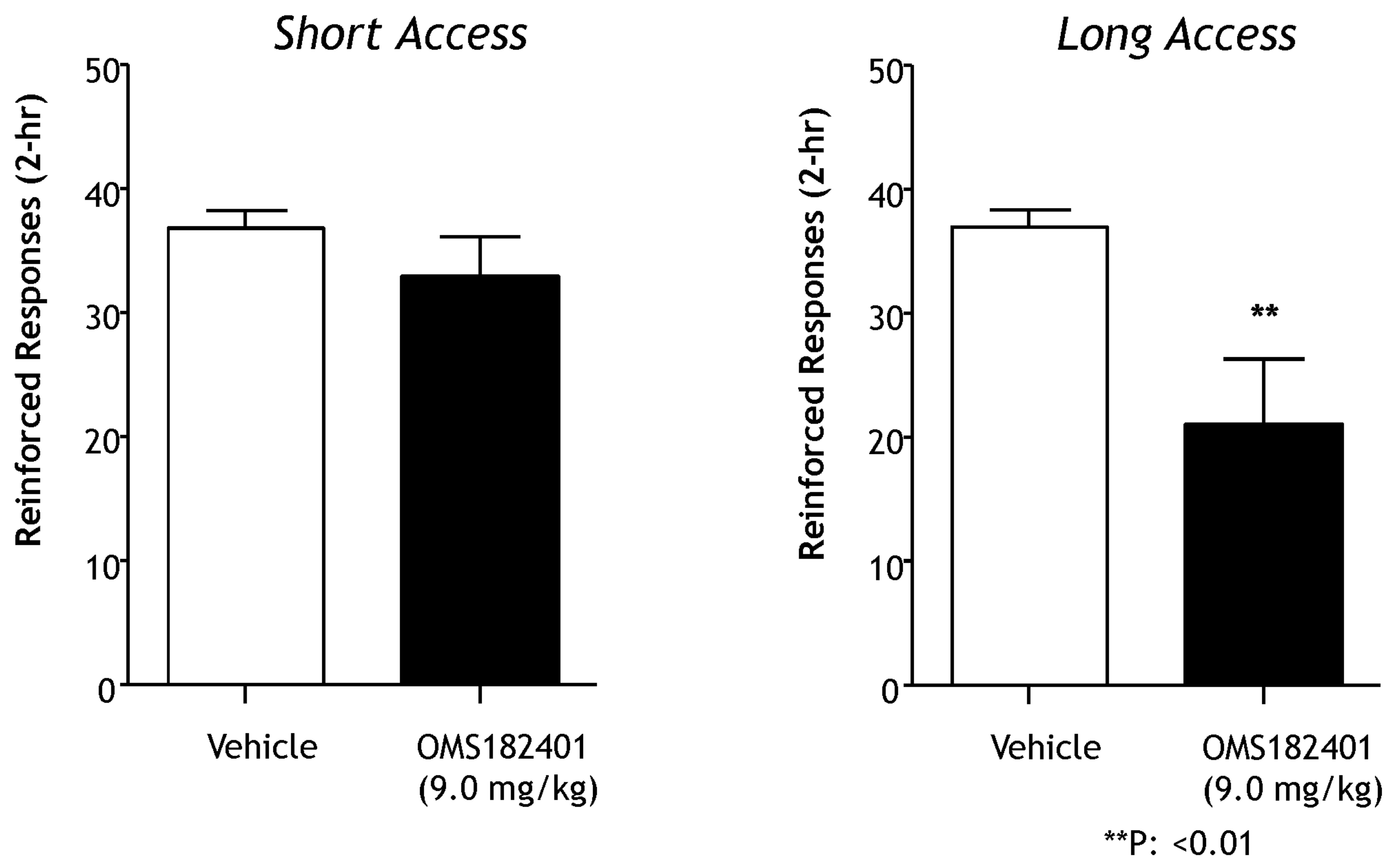
Effect of OMS181869 on Cocaine Self-Administration



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FIGURE 3

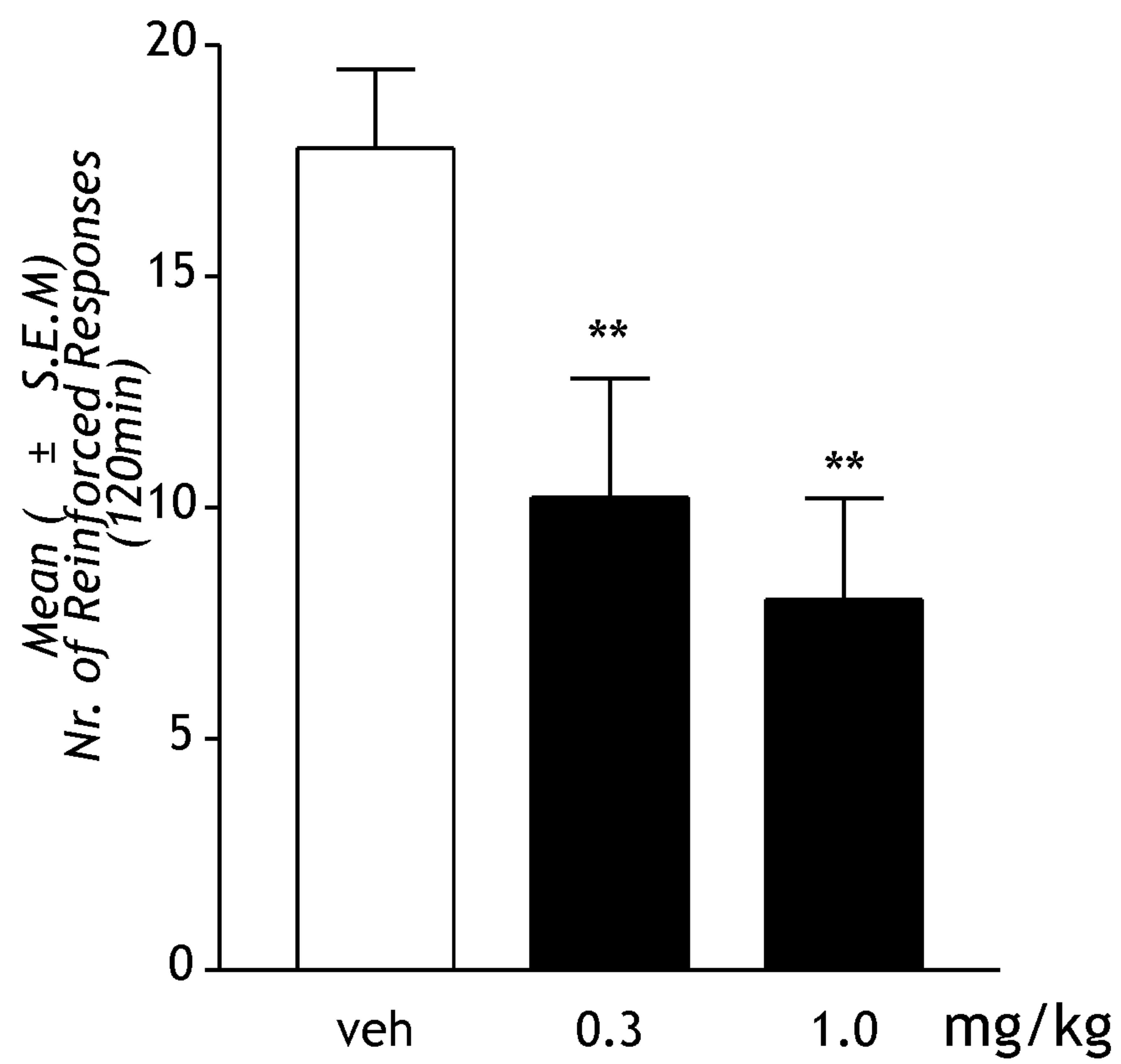
Effect of OMS182401 on Cocaine Self-Administration



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FIGURE 4

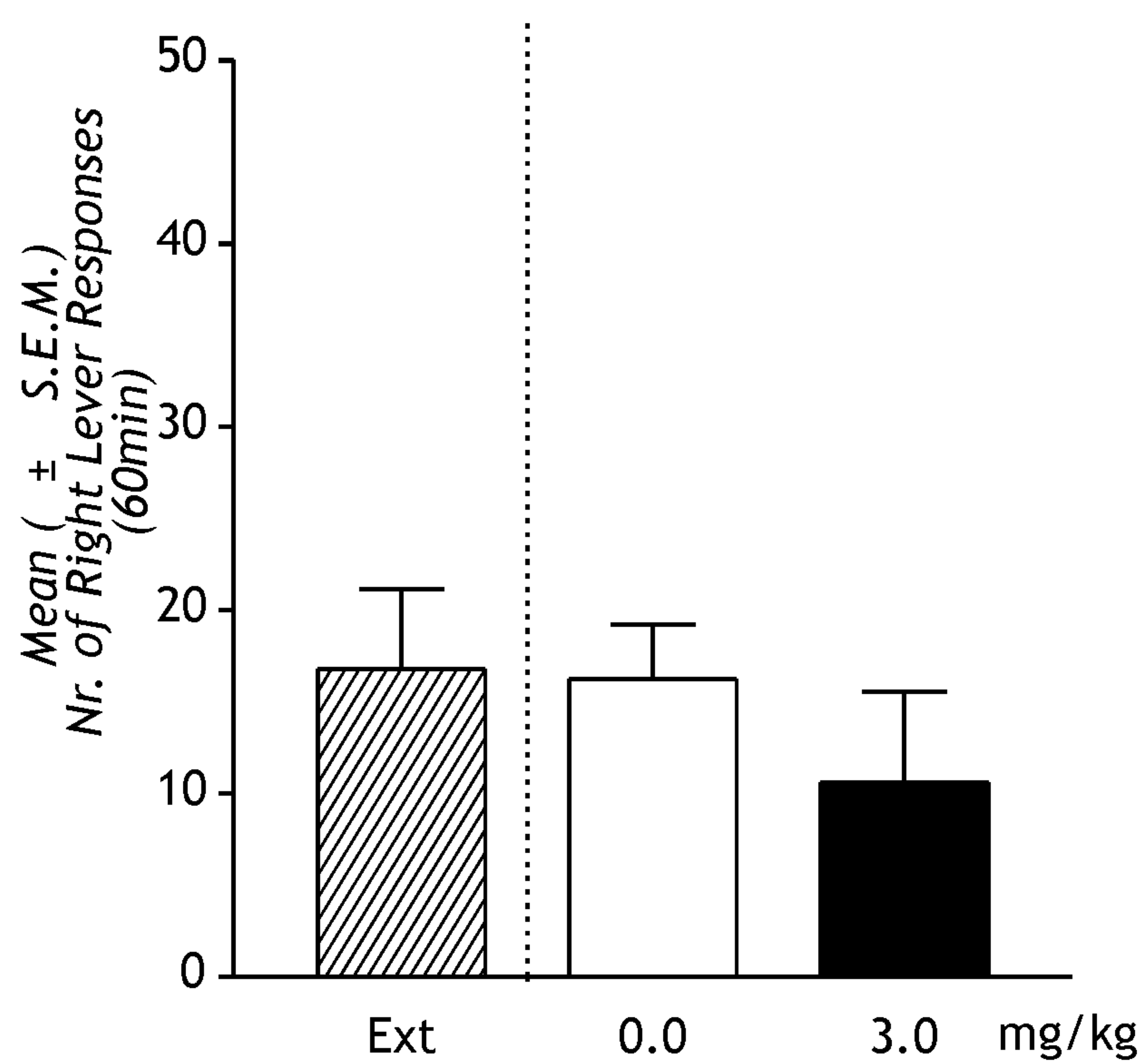
Effect of SKF82958 on Cocaine Self-Administration



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FIGURE 5

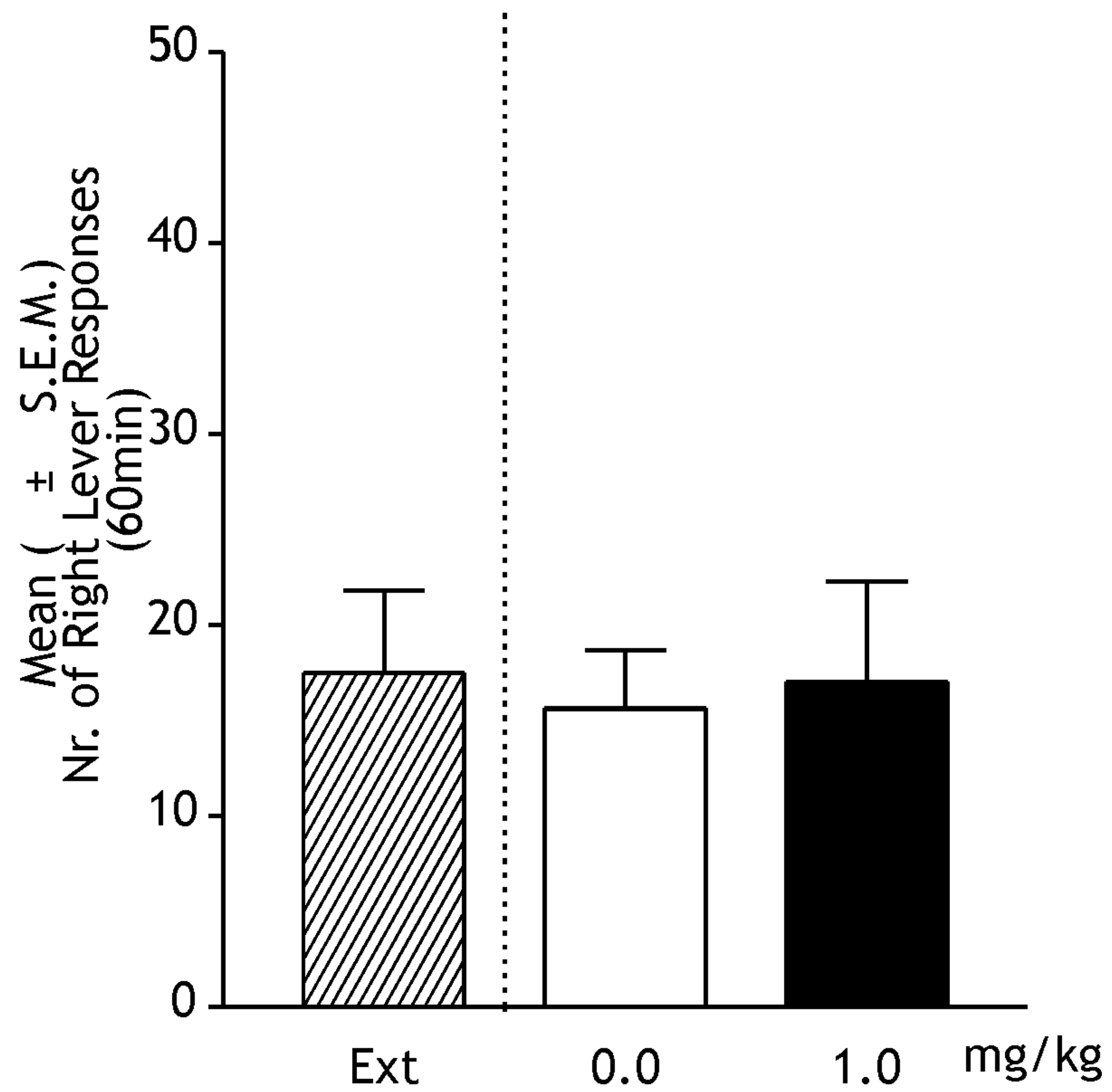
Effect of OMS182056 on Non-Reinforced Lever Press Response



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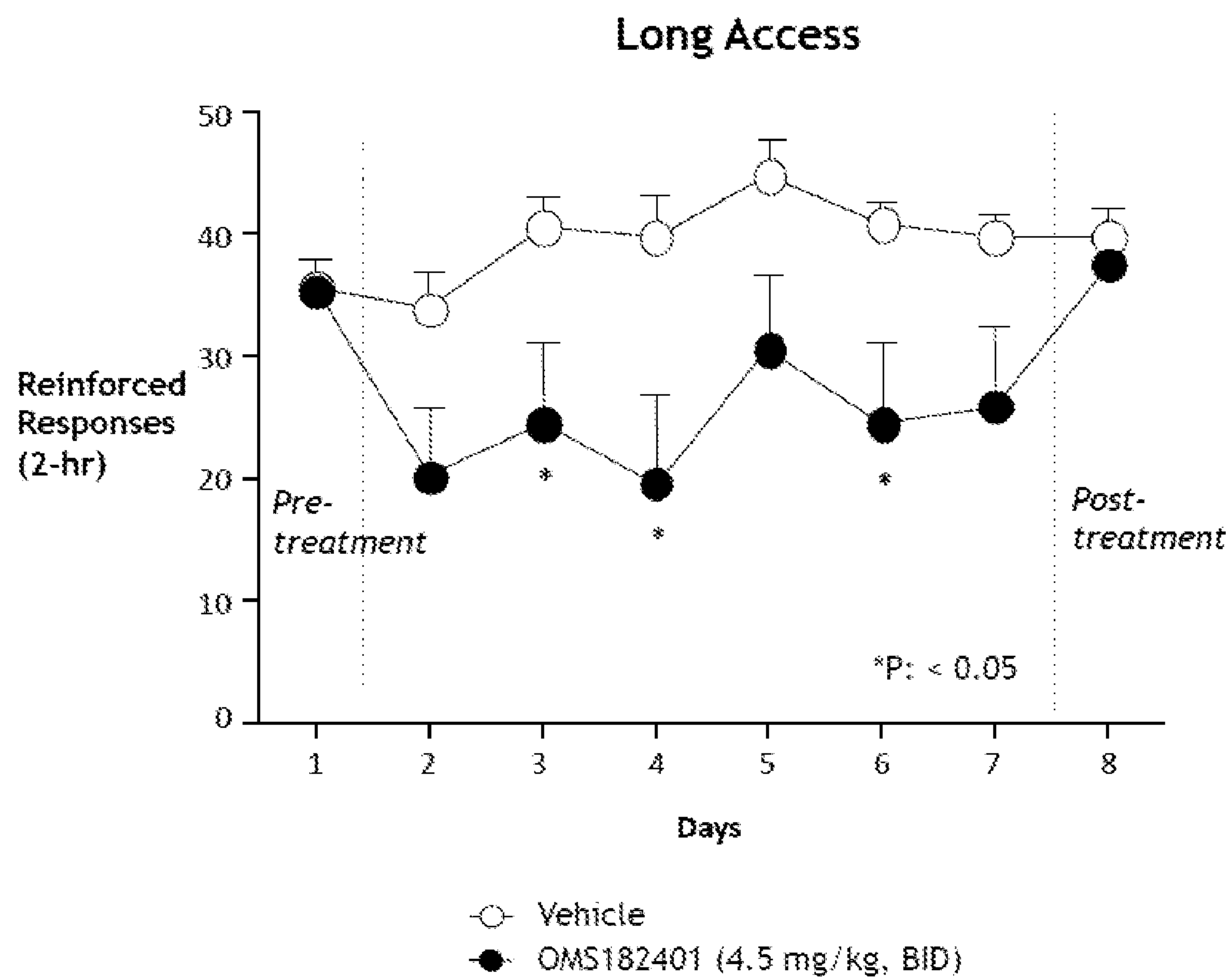
FIGURE 6

Effect of SKF82958 on Non-Reinforced Lever Press Response



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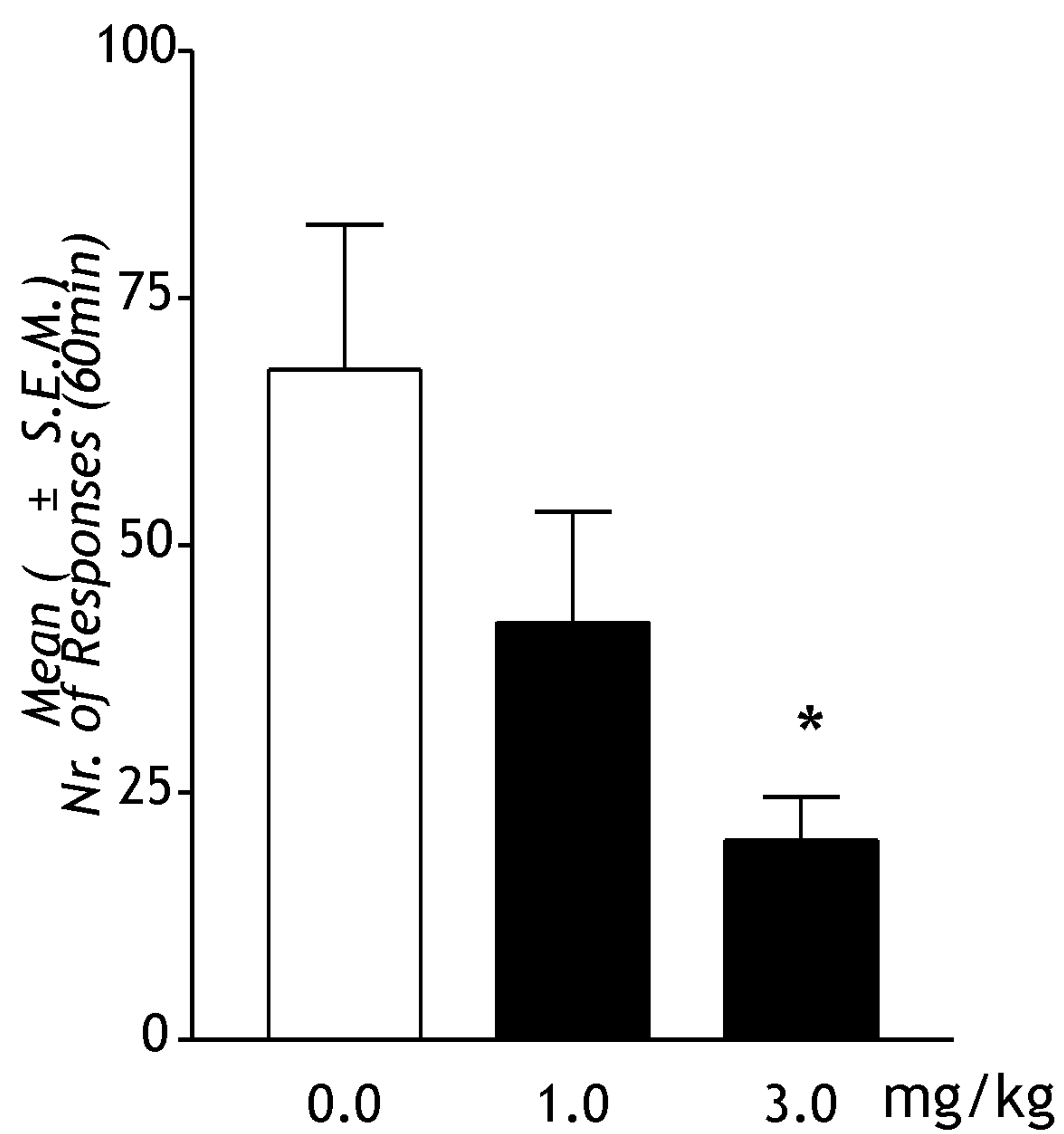
FIGURE 7

Chronic Effect of OMS182401
on Cocaine Self-Administration

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FIGURE 8

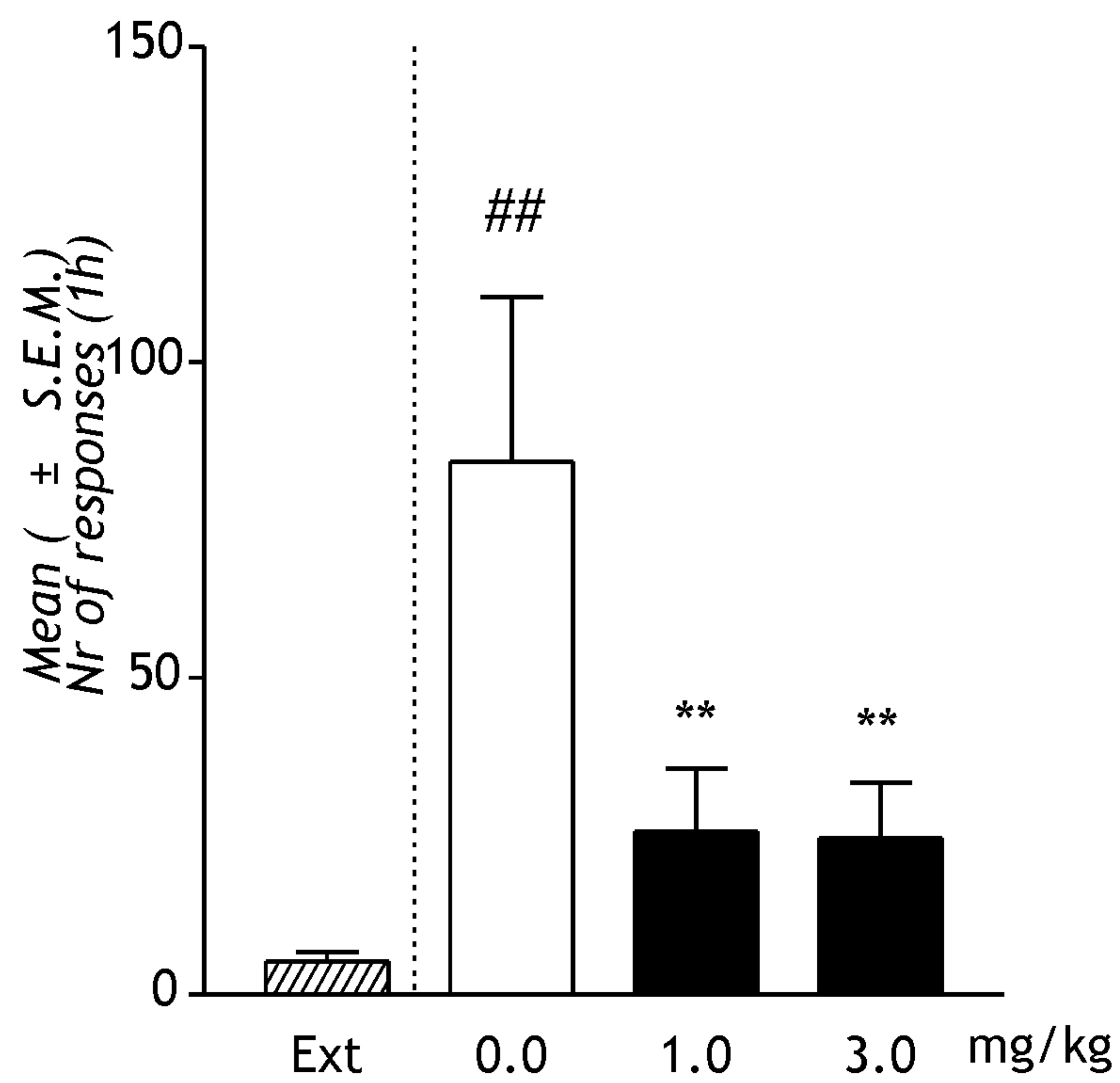
Effect of OMS182056 on First Day of Extinction



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FIGURE 9

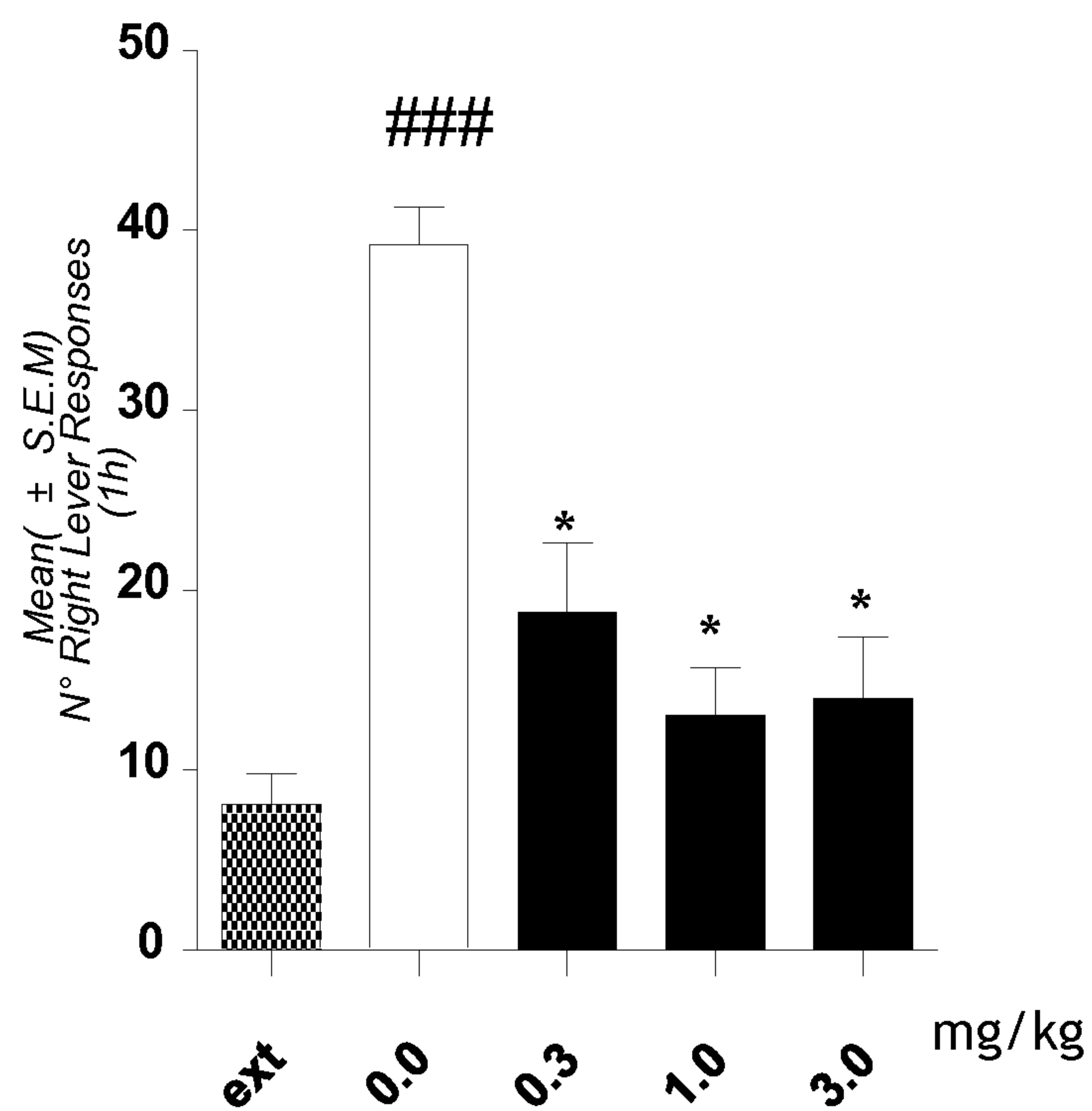
Effect of OMS182056 on Yohimbine-Induced
Relapse to Cocaine Seeking



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FIGURE 10

Effect of OMS182401 on Yohimbine-Induced
Relapse to Cocaine Seeking



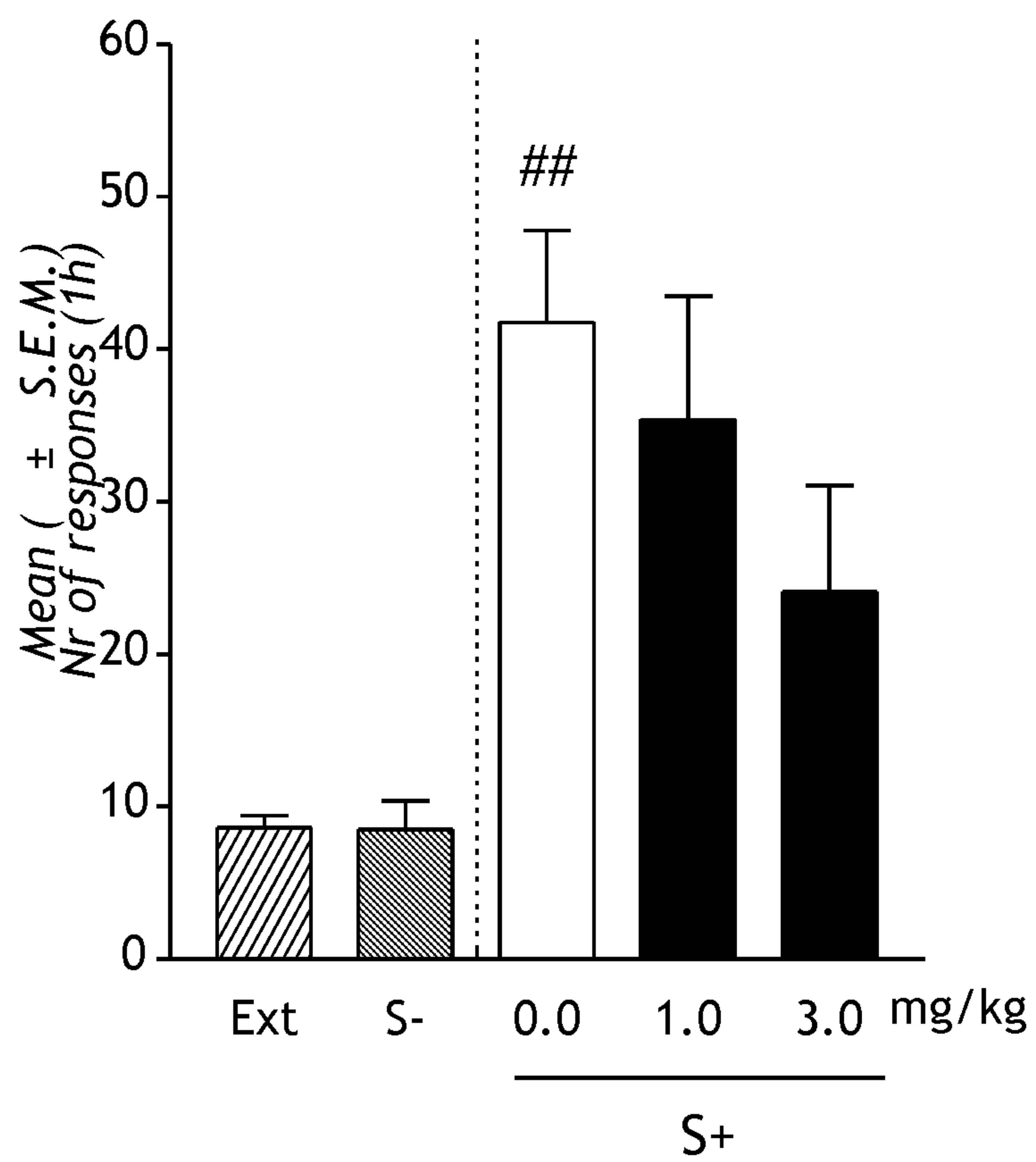
*P: < 0.05 (vs Vehicle)

**P: < 0.001 (vs Extinction)

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FIGURE 11

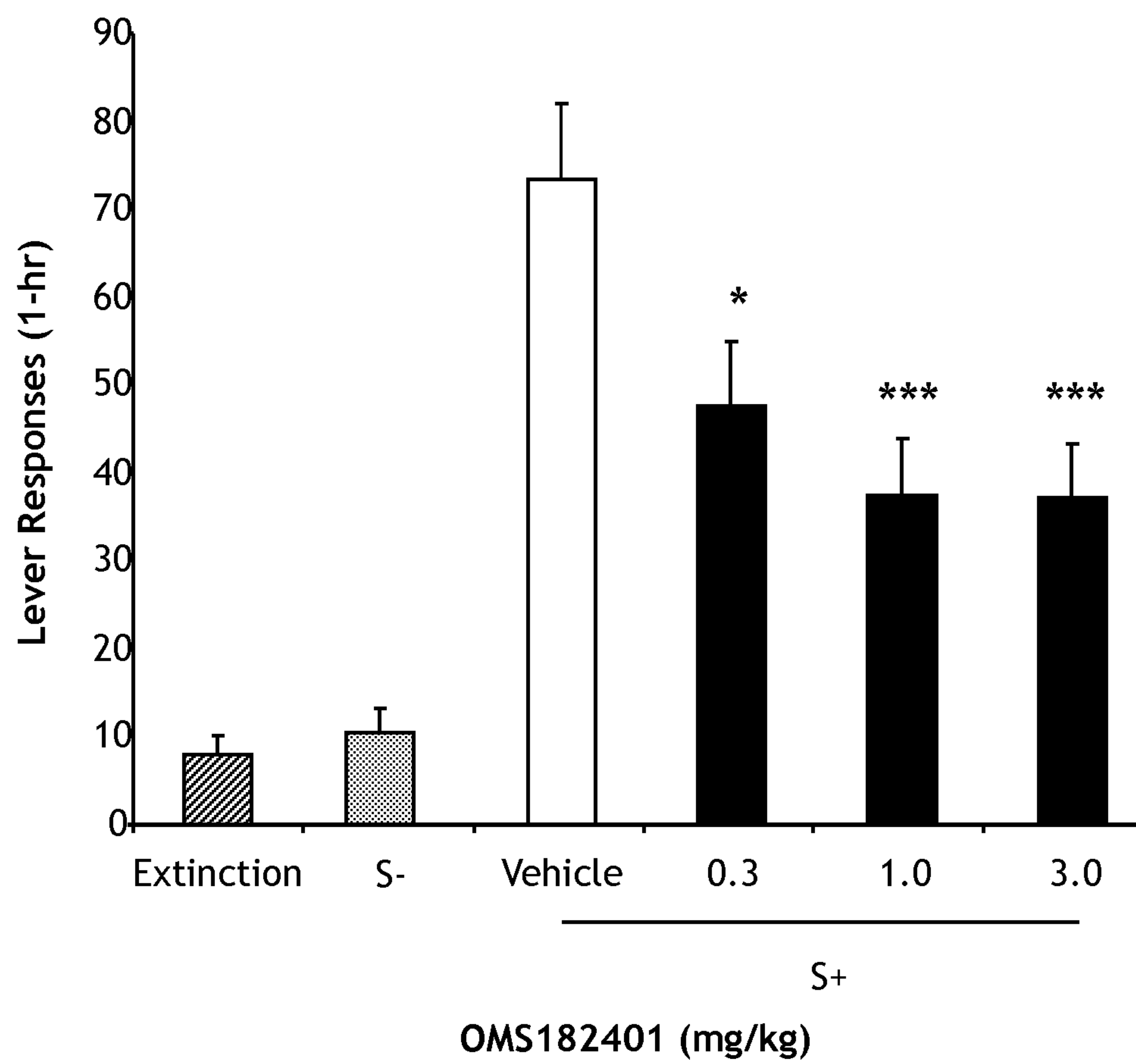
Effect of OMS182056 on Cue-Induced
Relapse to Cocaine Seeking



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FIGURE 12

Effect of OMS182401 on Cue-Induced Relapse to Cocaine Seeking



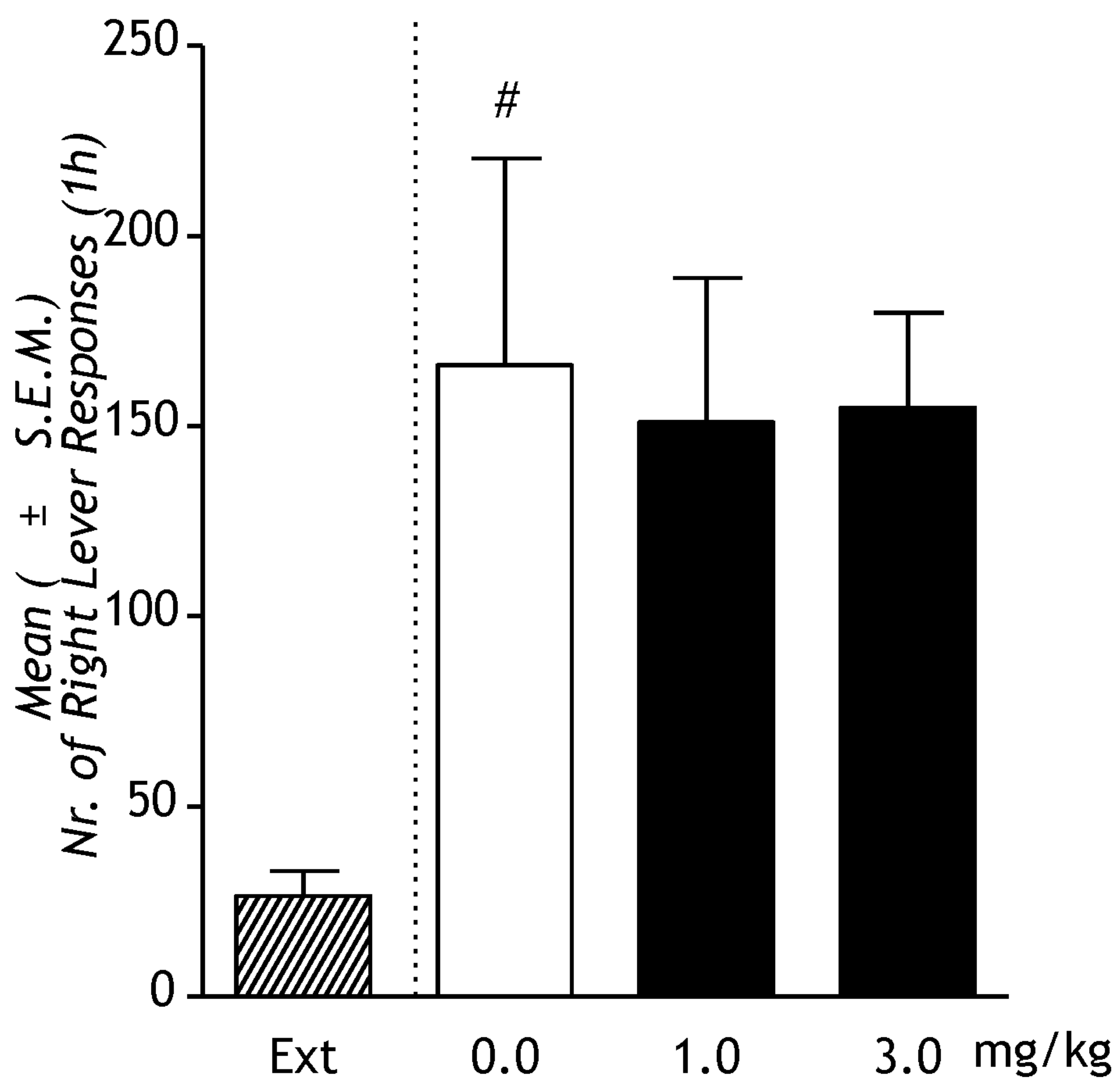
*P: < 0.05 (vs Vehicle)

***P: < 0.001 (vs Vehicle)

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FIGURE 13

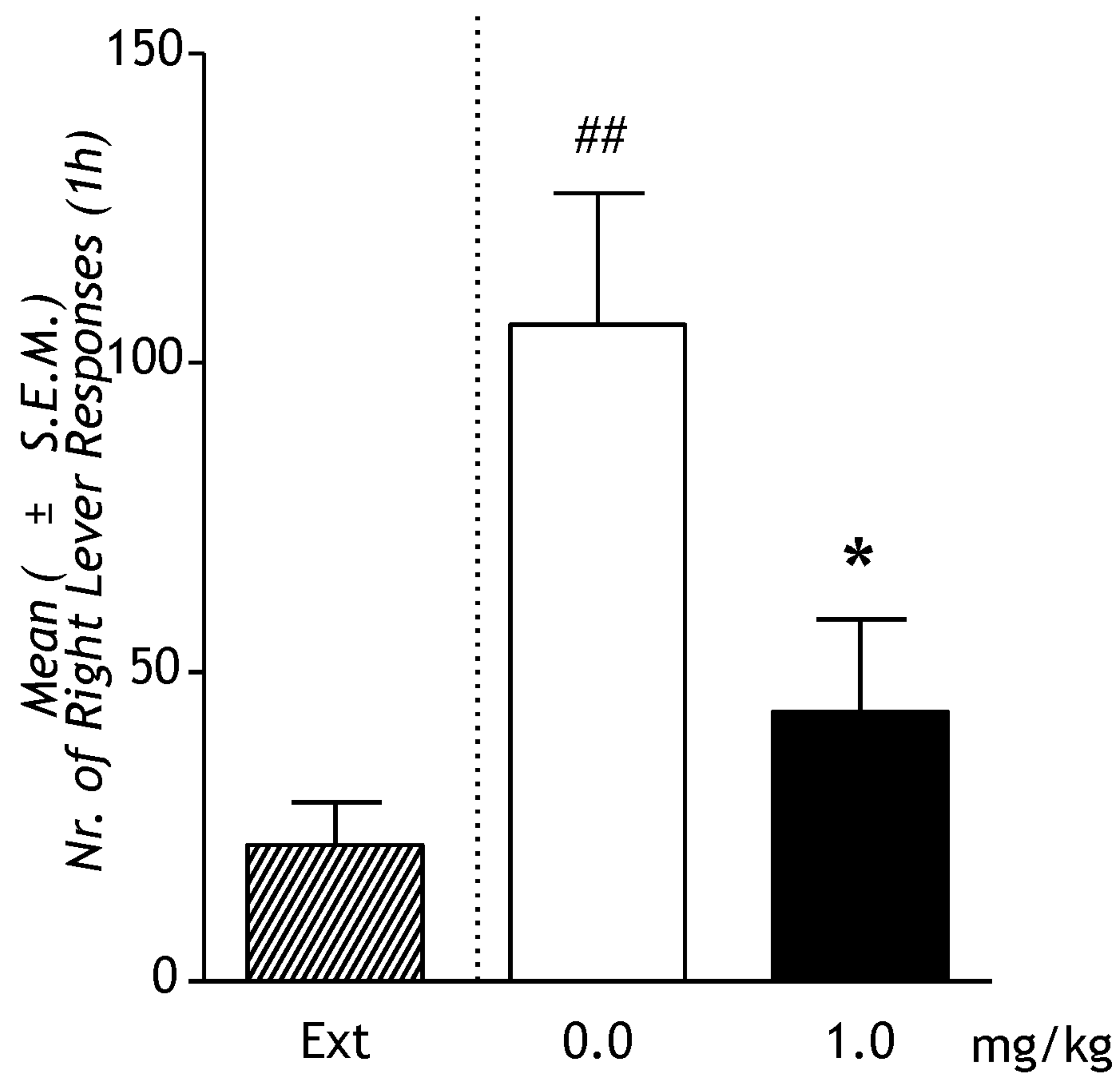
Effect of OMS182056 on Cocaine Priming-Induced Relapse



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FIGURE 14

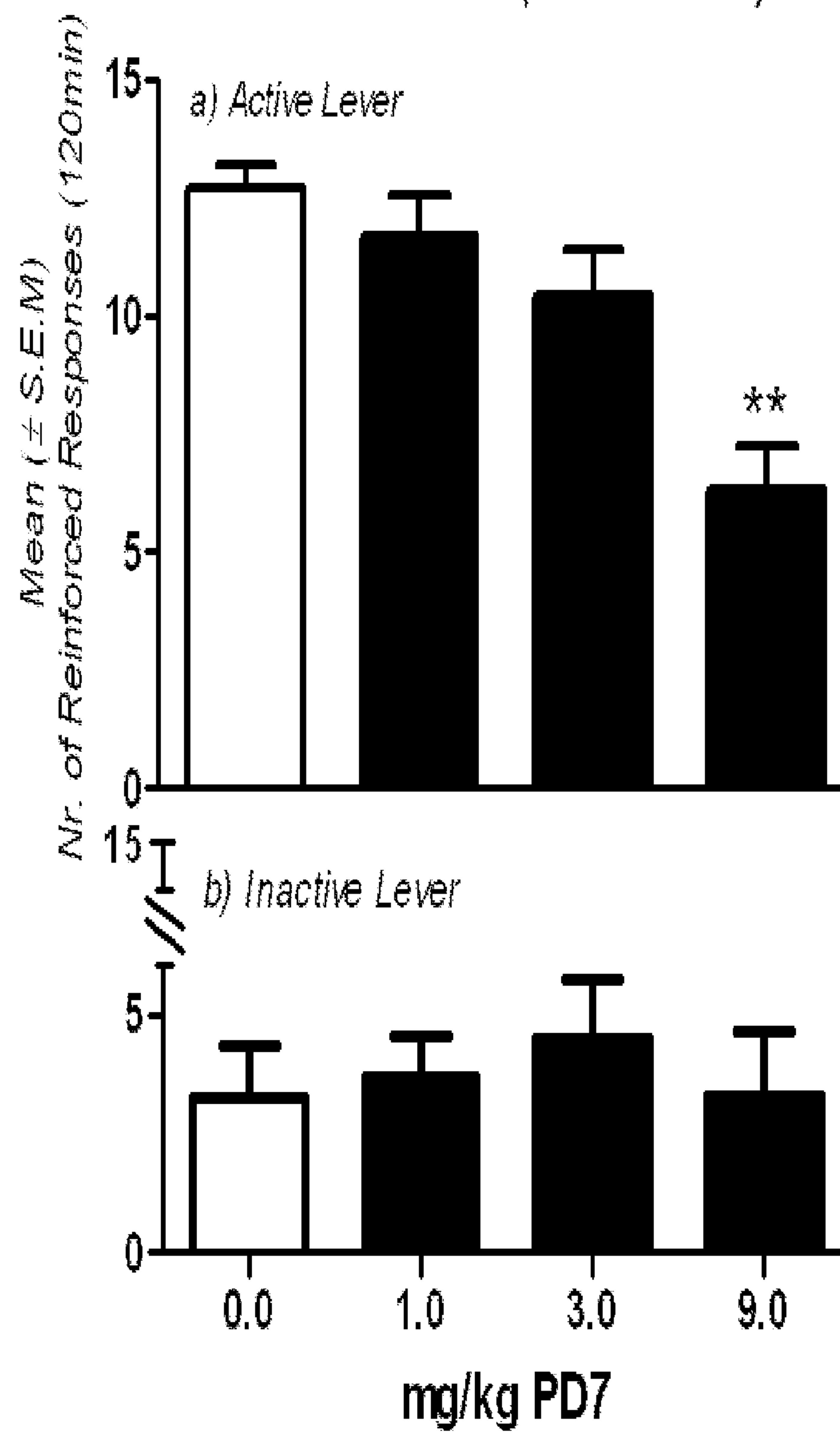
Effect of SKF82959 on Cocaine Priming-Induced Relapse



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FIGURE 15

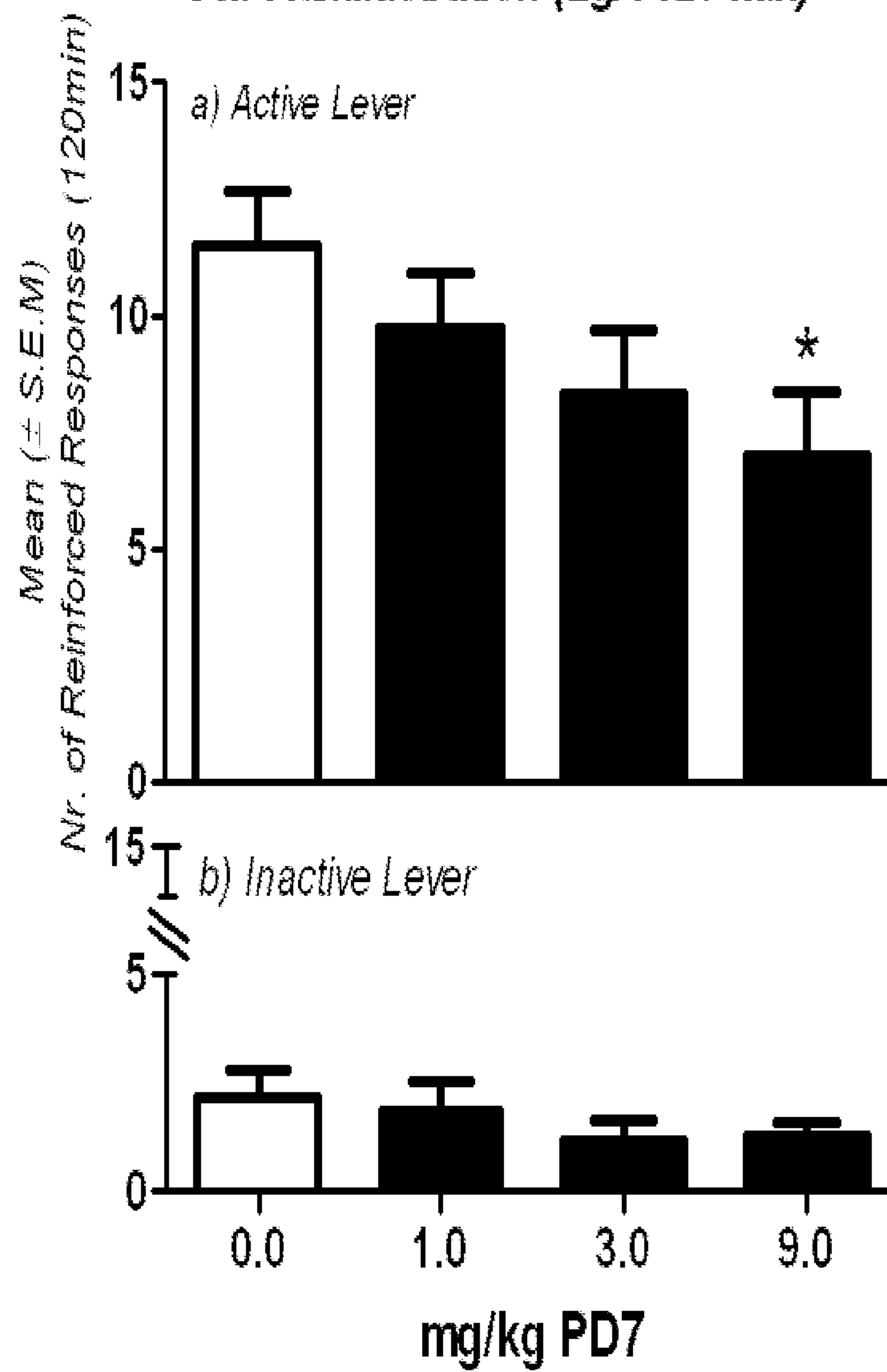
*Effect of OMS 182401 on Nicotine
Self-Administration (ShA 120 min)*



**p<0.01

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FIGURE 16

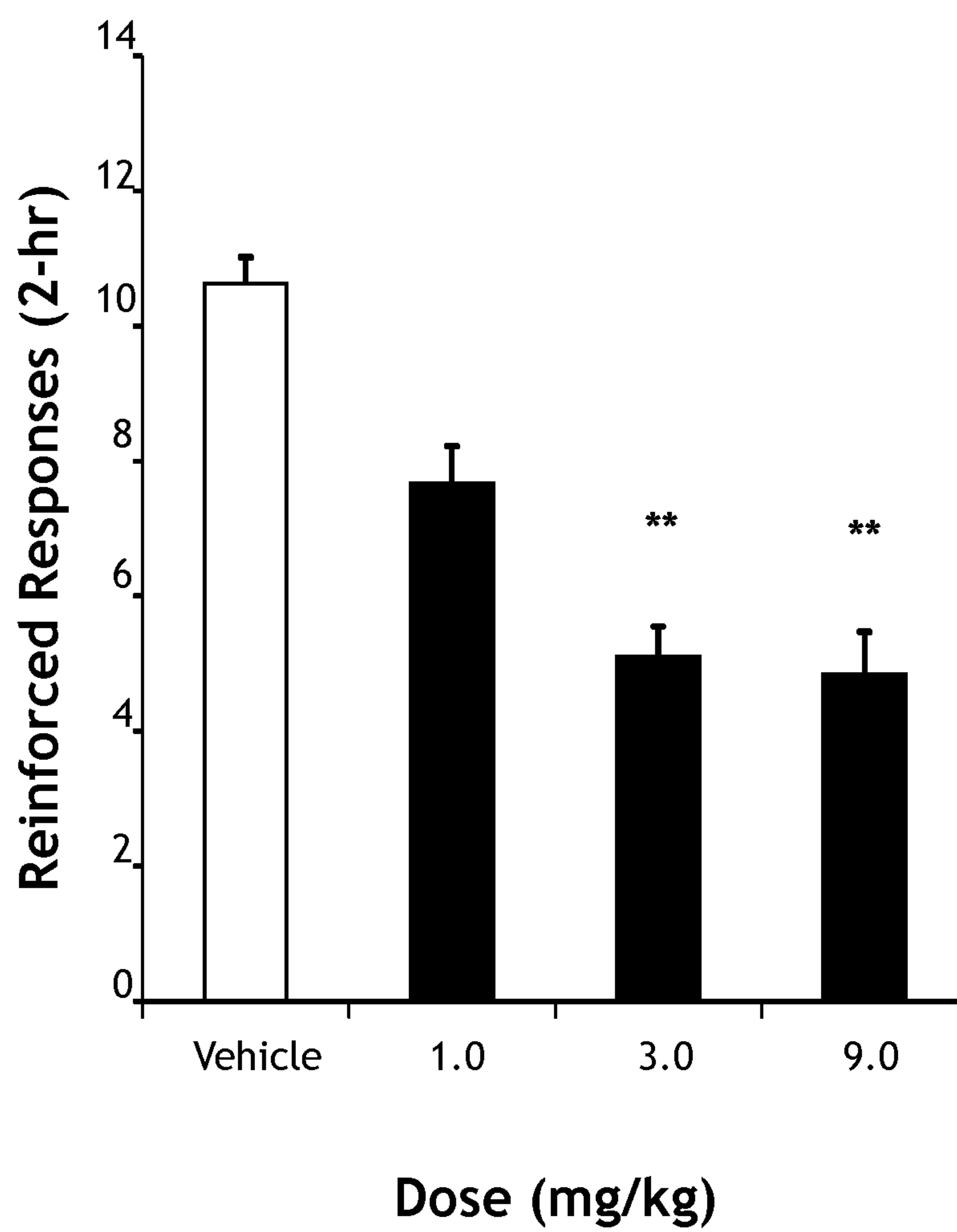
***Effect of OMS 182401 on Nicotine
Self-Administration (LgA 120 min)***

*p<0.05

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FIGURE 17

Effect of OMS182399 on
Nicotine Self-Administration (ShA 120 min)

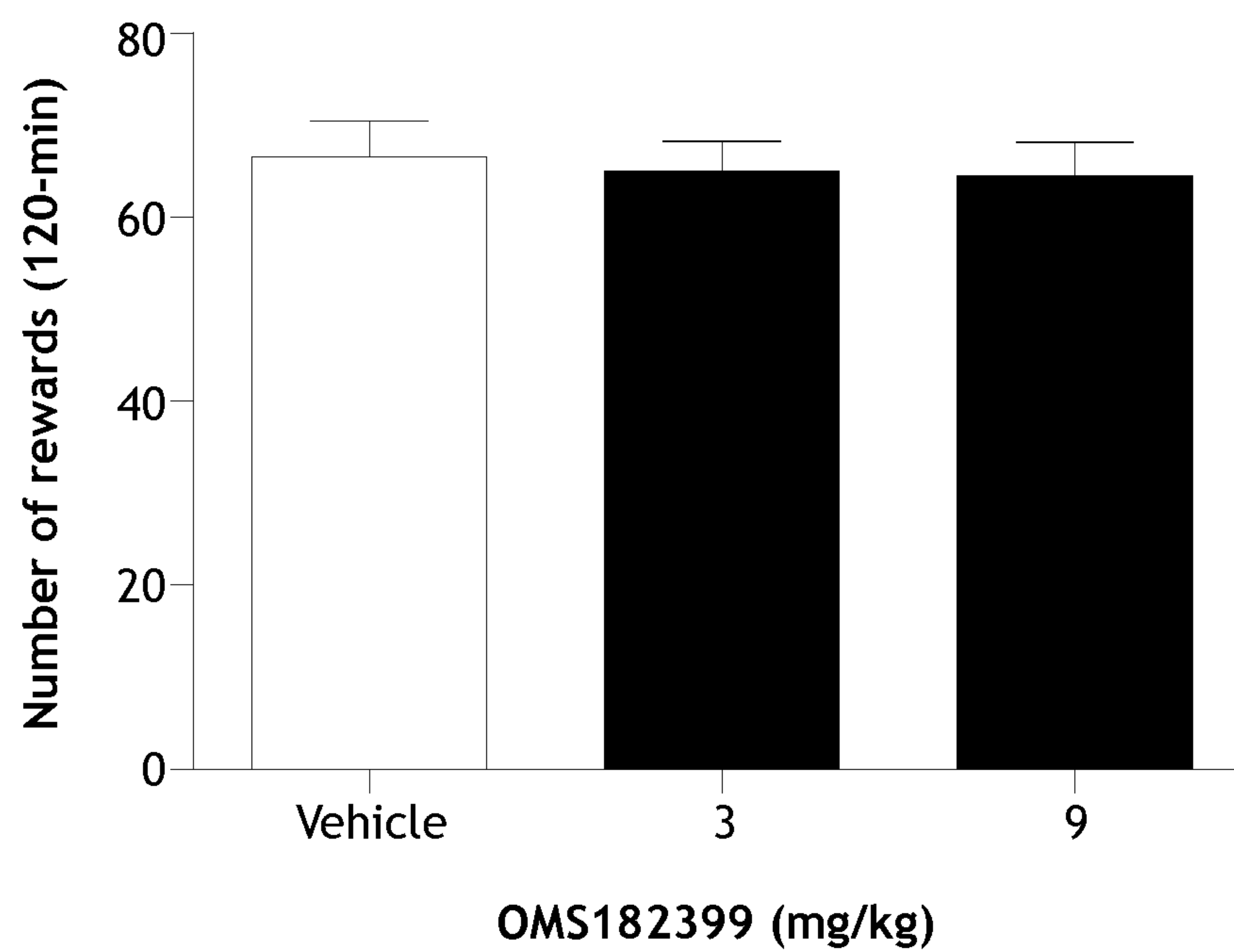


**P<0.01

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FIGURE 18A

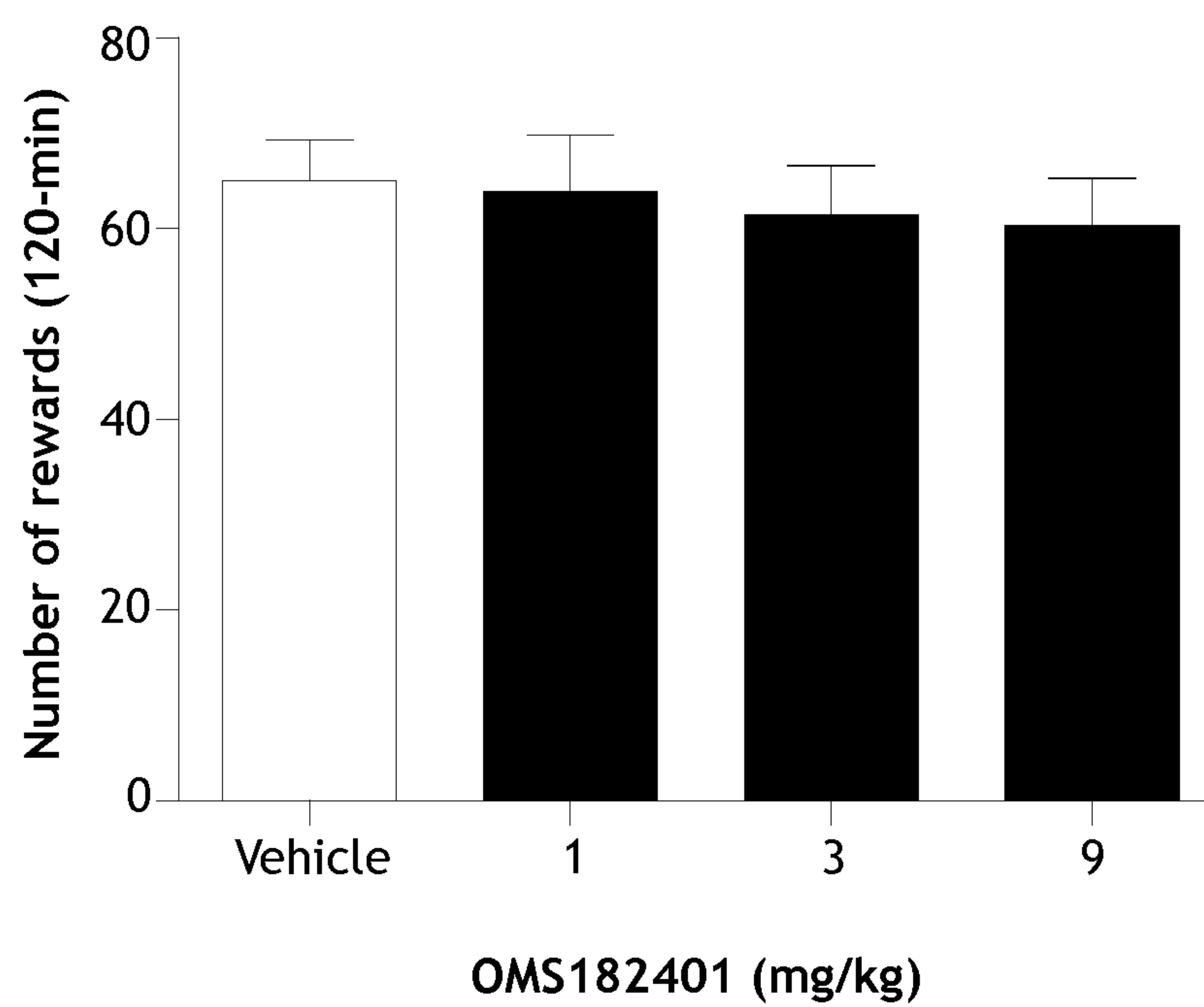
Effects of OMS182399 on food self-administration



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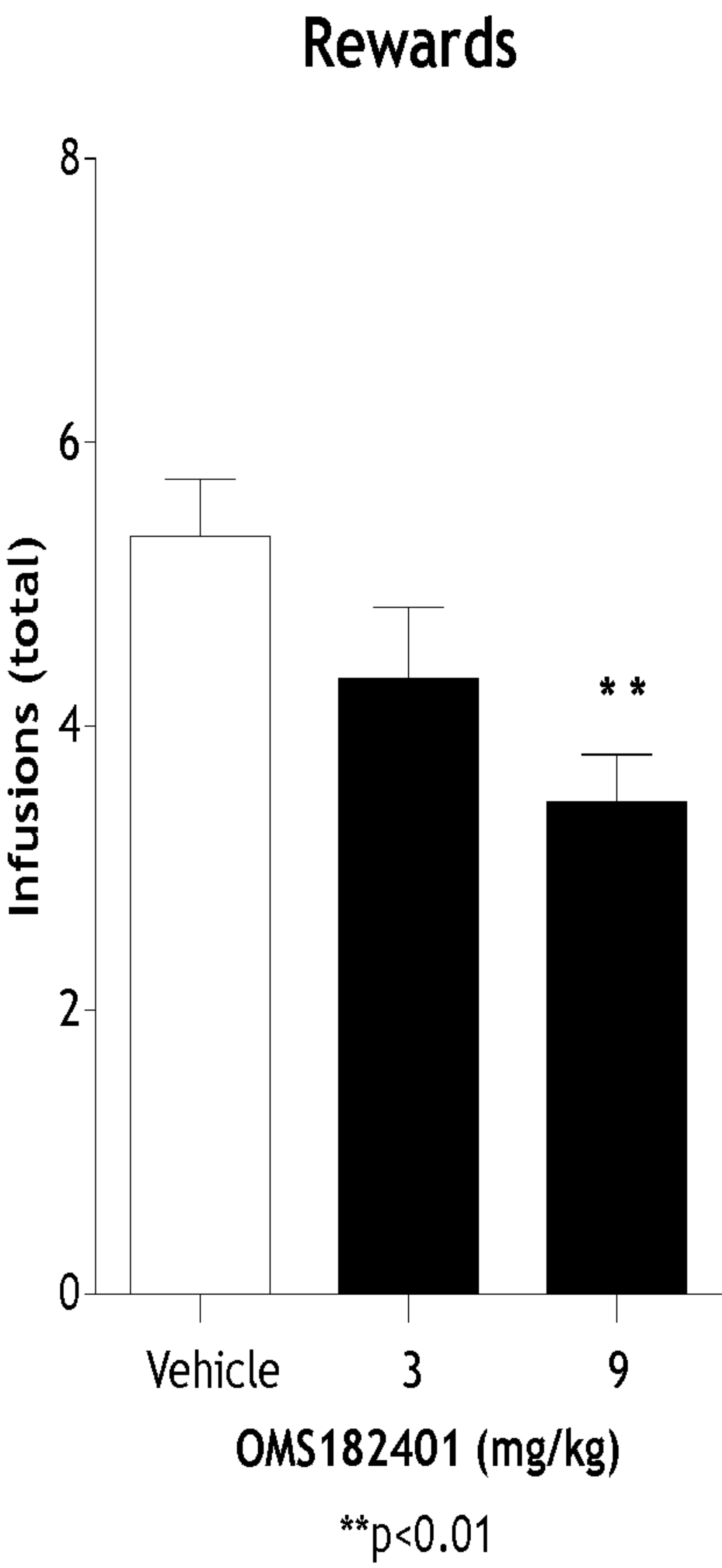
FIGURE 18B

Effects of OMS182401 on food self-administration

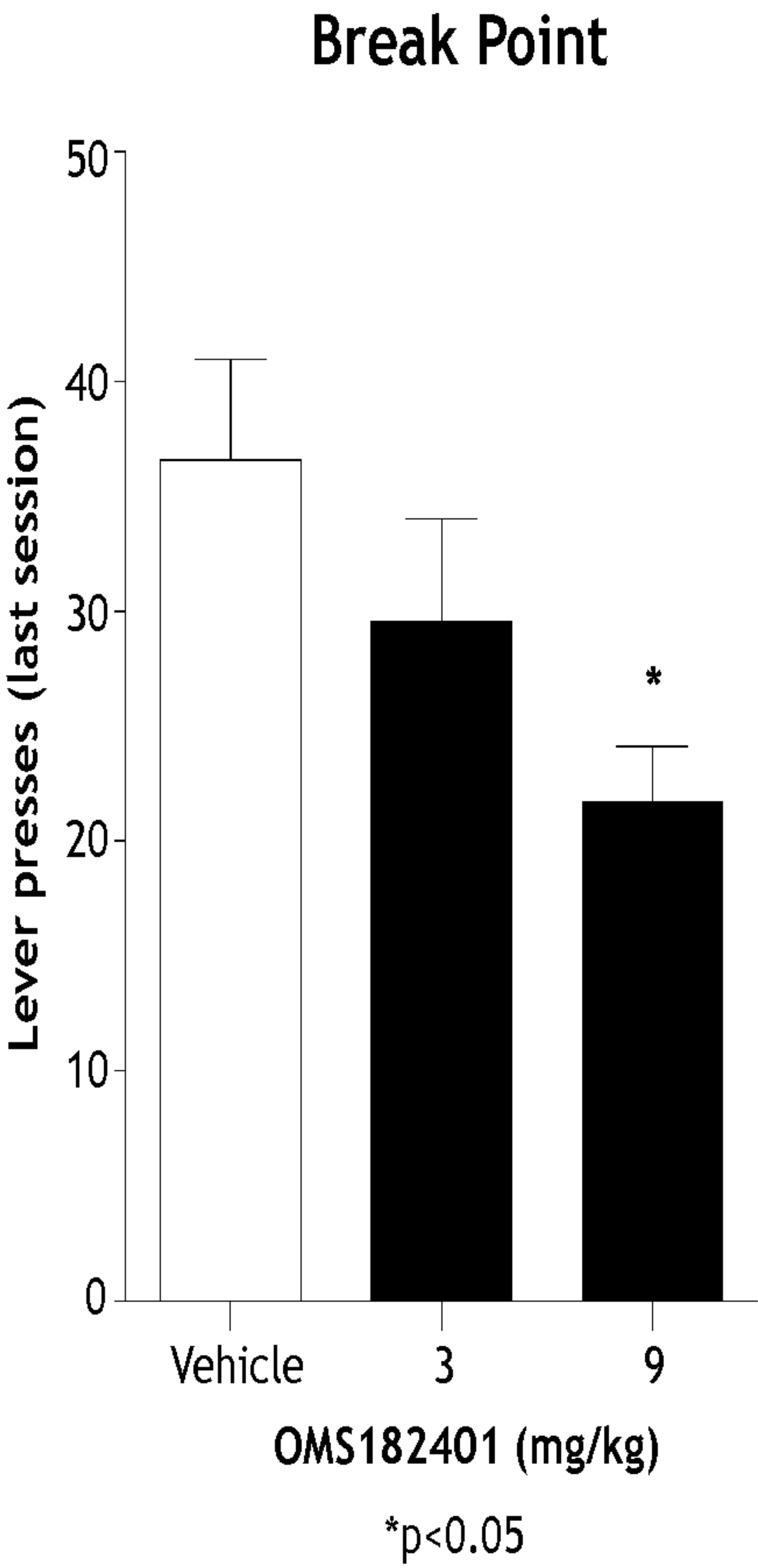


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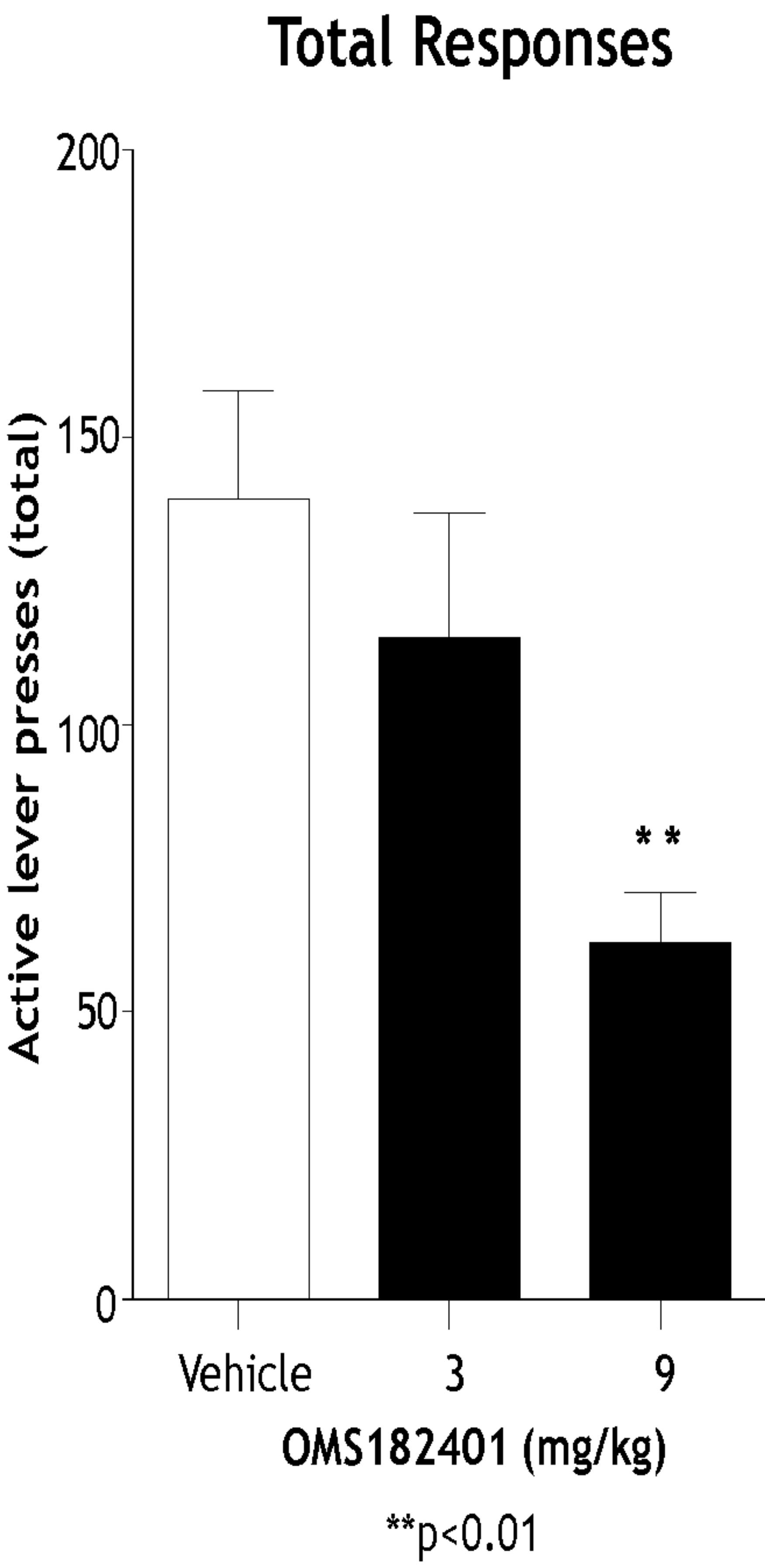
FIGURE 19A-19C



19A



19B

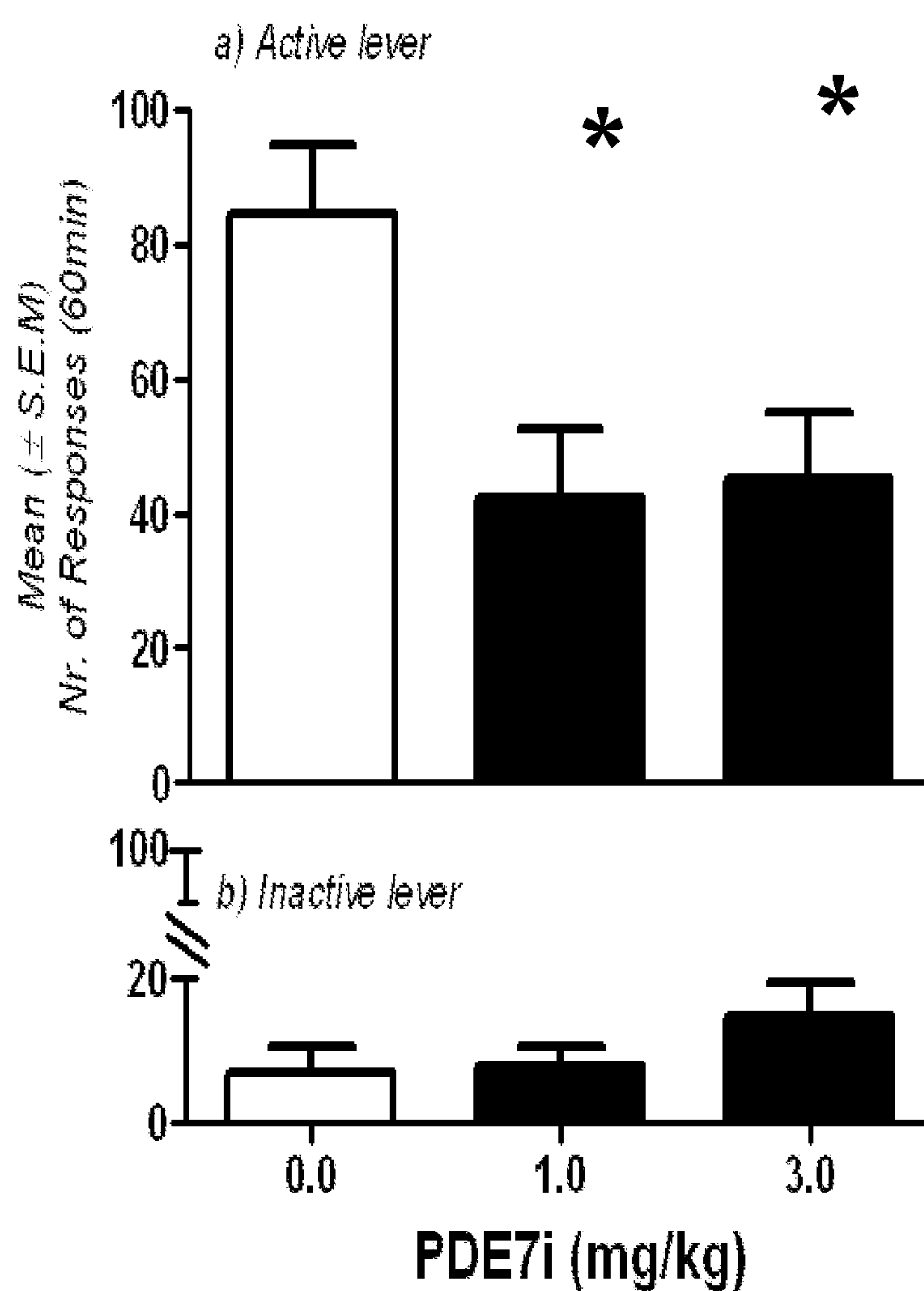


19C

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FIGURE 20

*Effect of OMS 182401 on 1st day of extinction
of Nicotine Self-Administration*

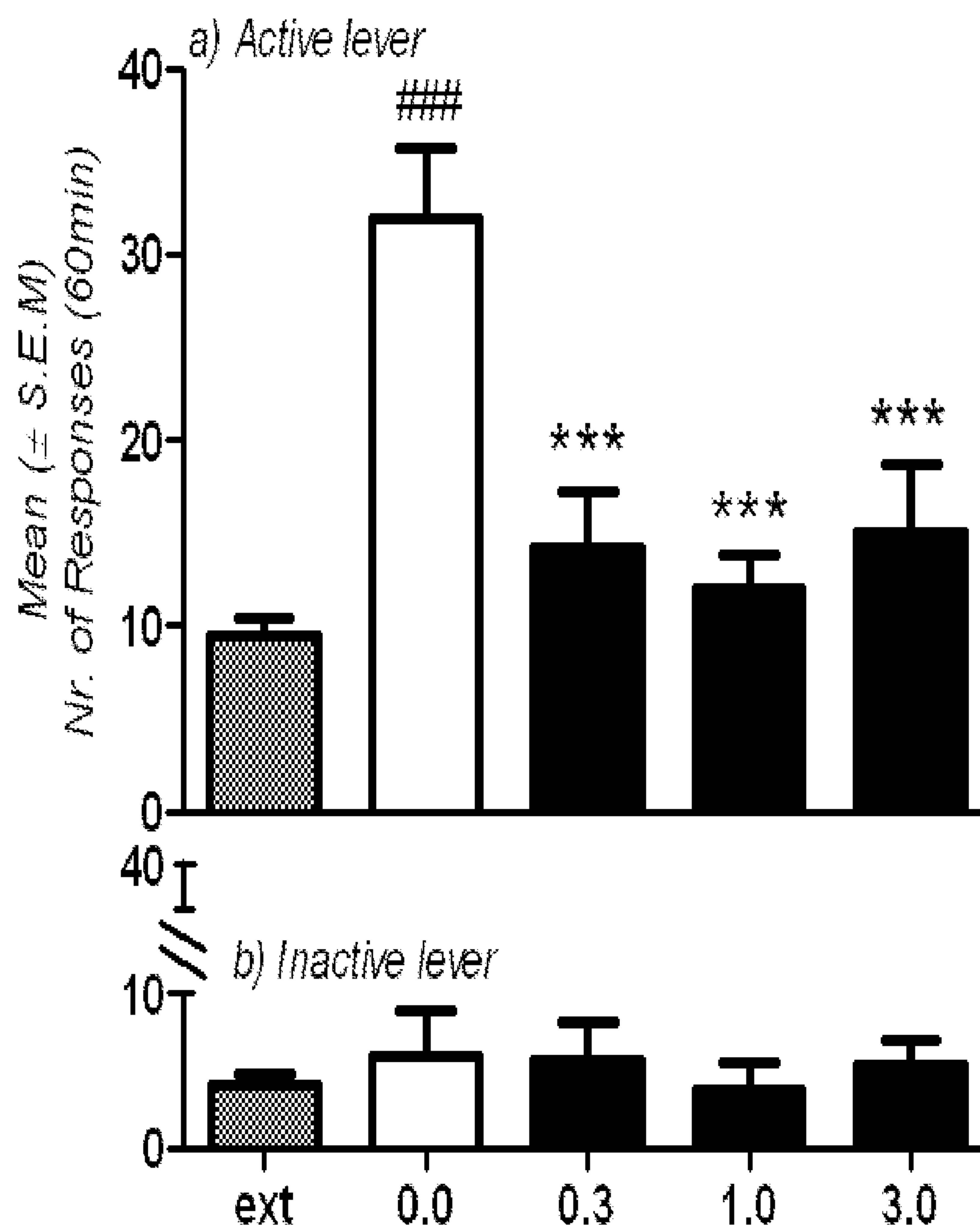


**p < 0.05*

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FIGURE 21

***Effect of OMS 182401 on yohimbine
induced reinstatement of Nicotine seeking***



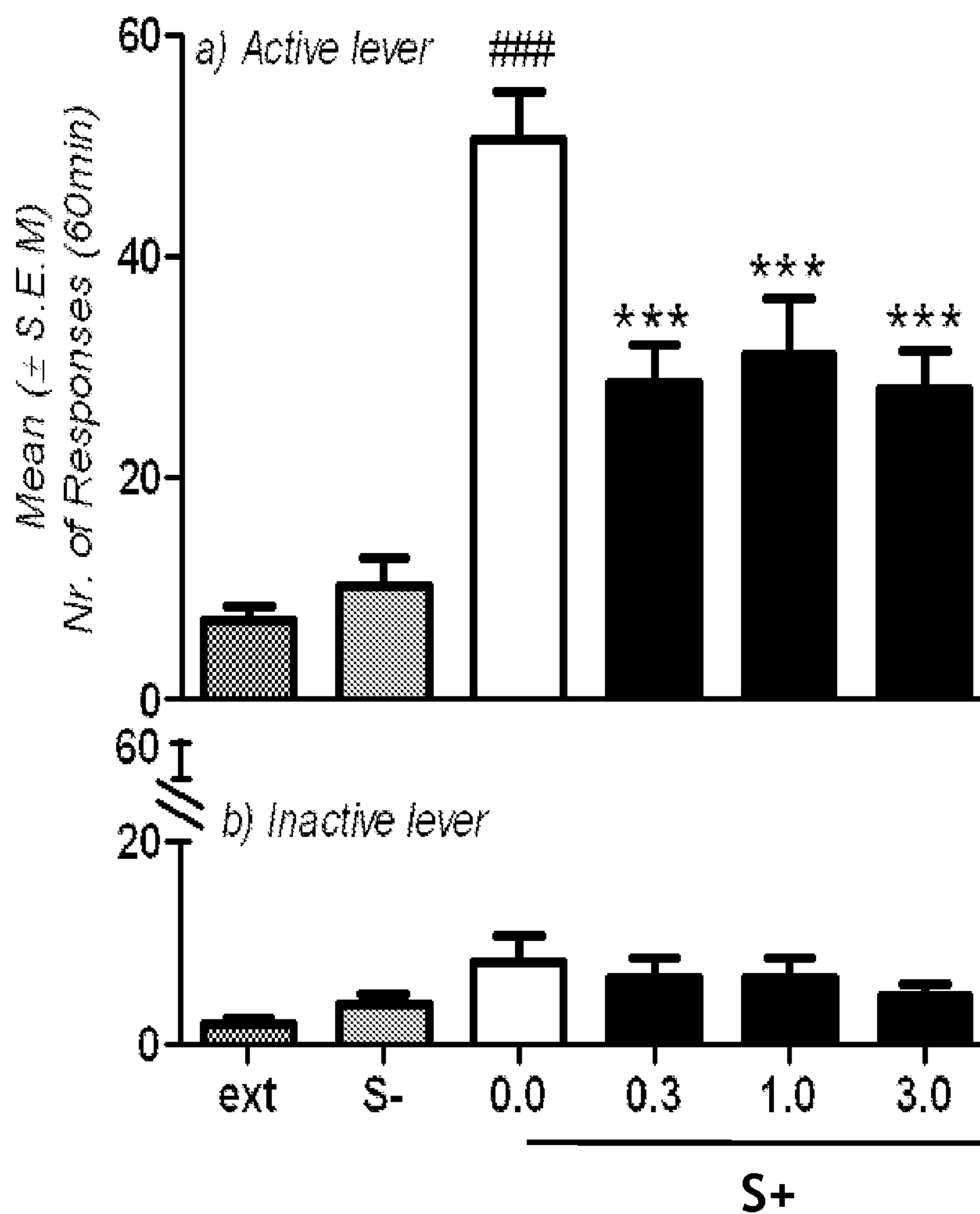
***p: <0.001 (vs vehicle);

###p: <0.001 (vs extinction)

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FIGURE 22

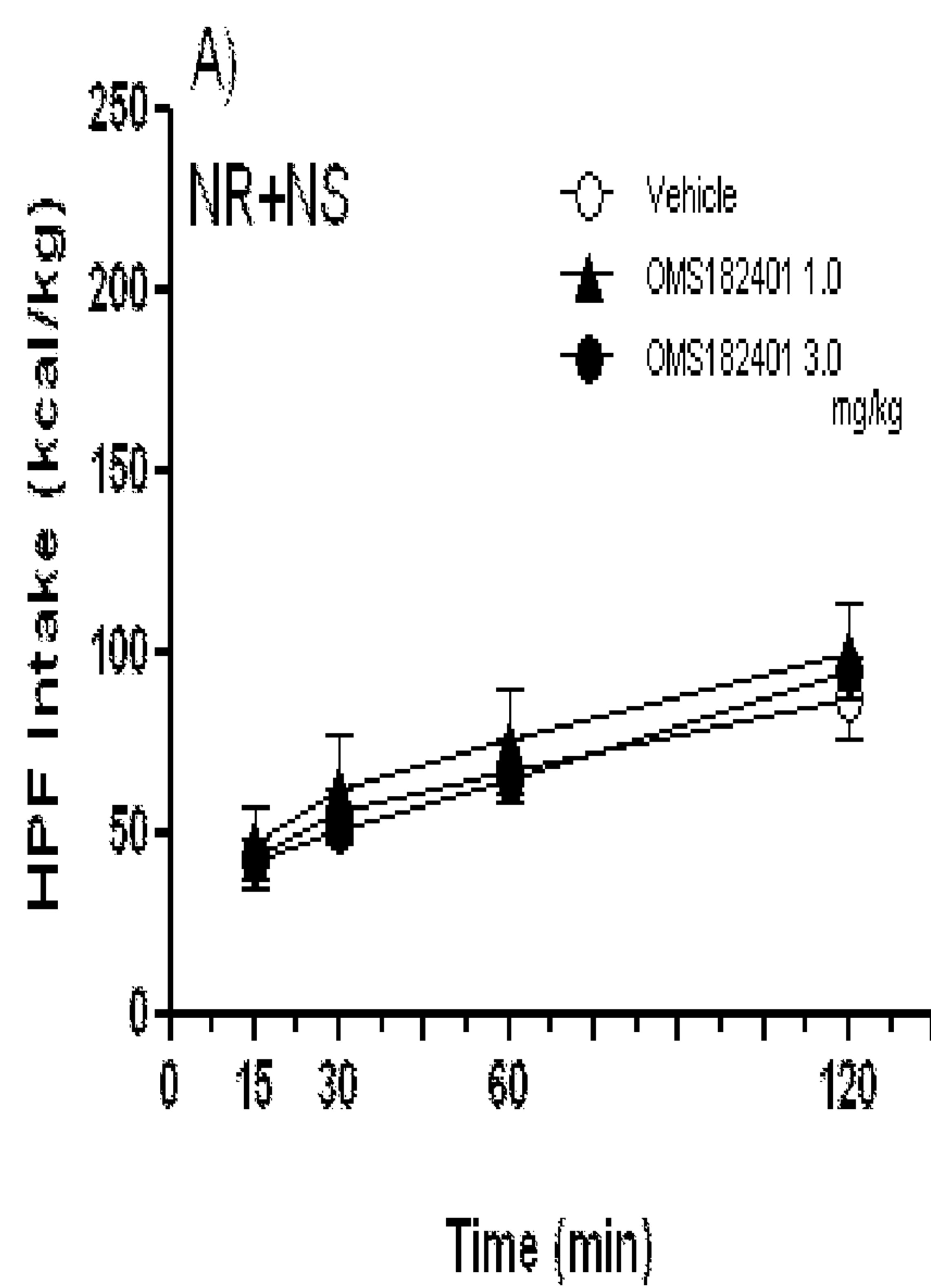
***Effect of OMS 182401 on Nicotine cue
induced reinstatement***



***p: <0.001 (vs vehicle);
###p: <0.001 (vs extinction)

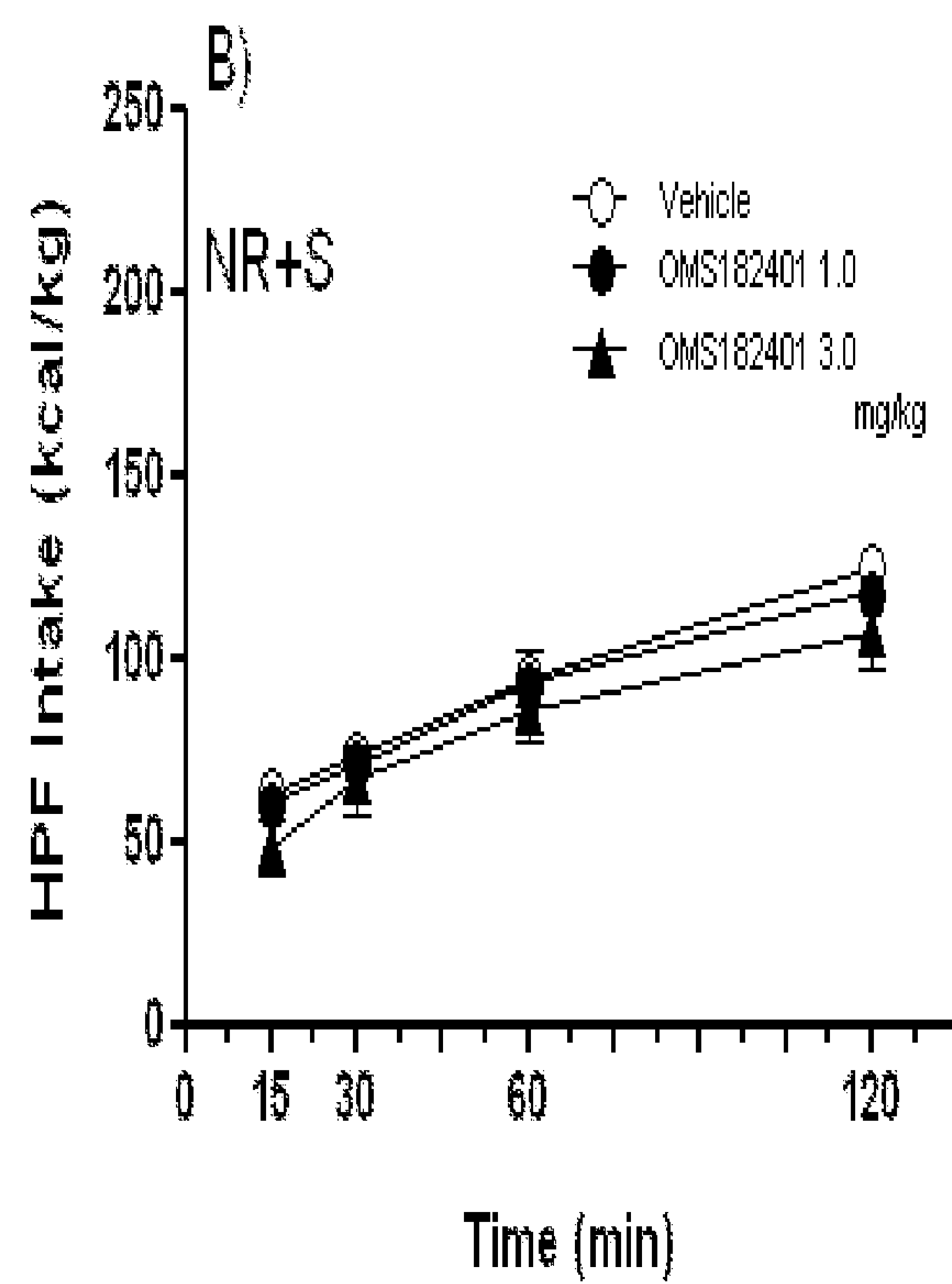
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FIGURE 23A



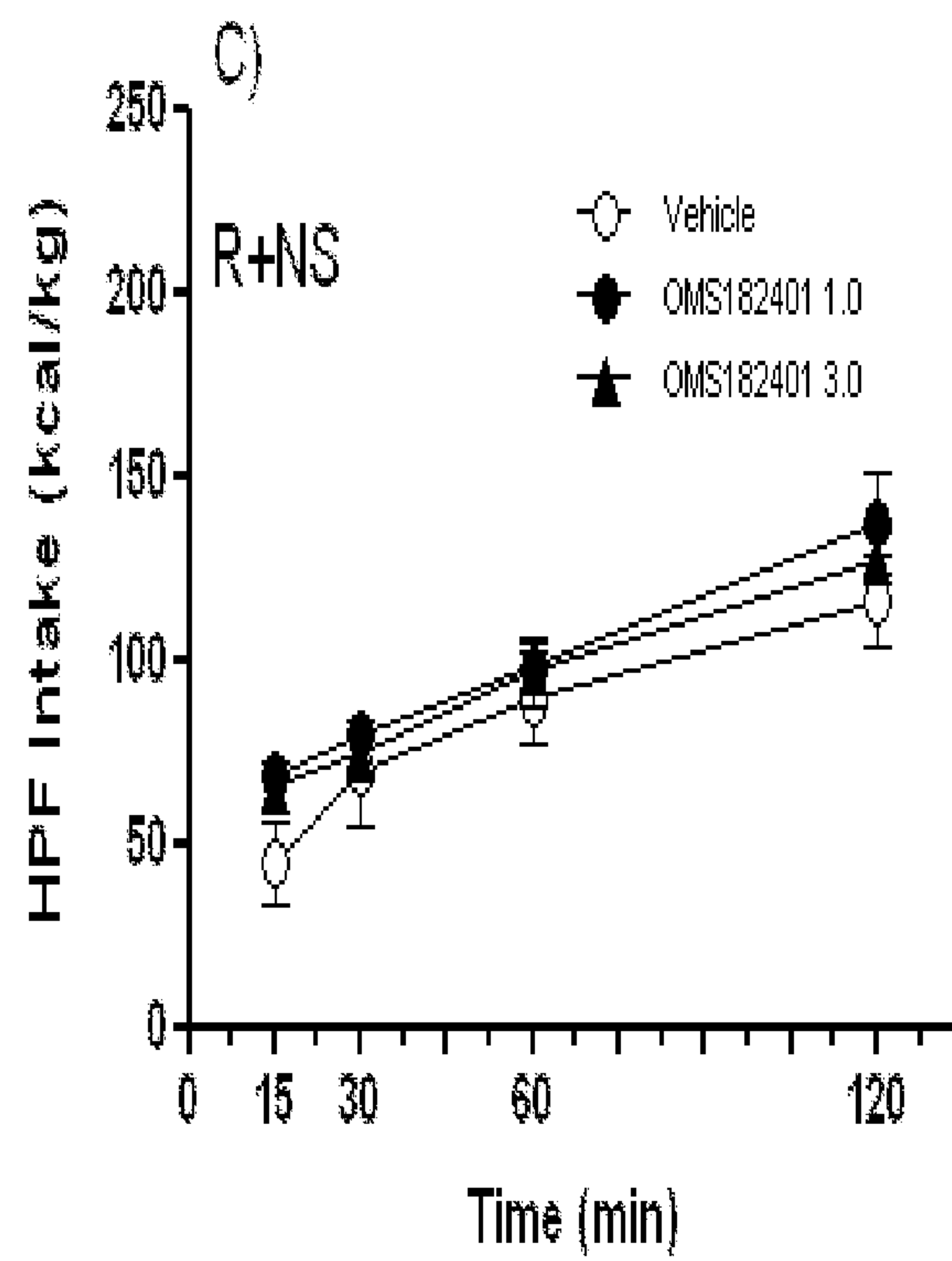
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FIGURE 23B



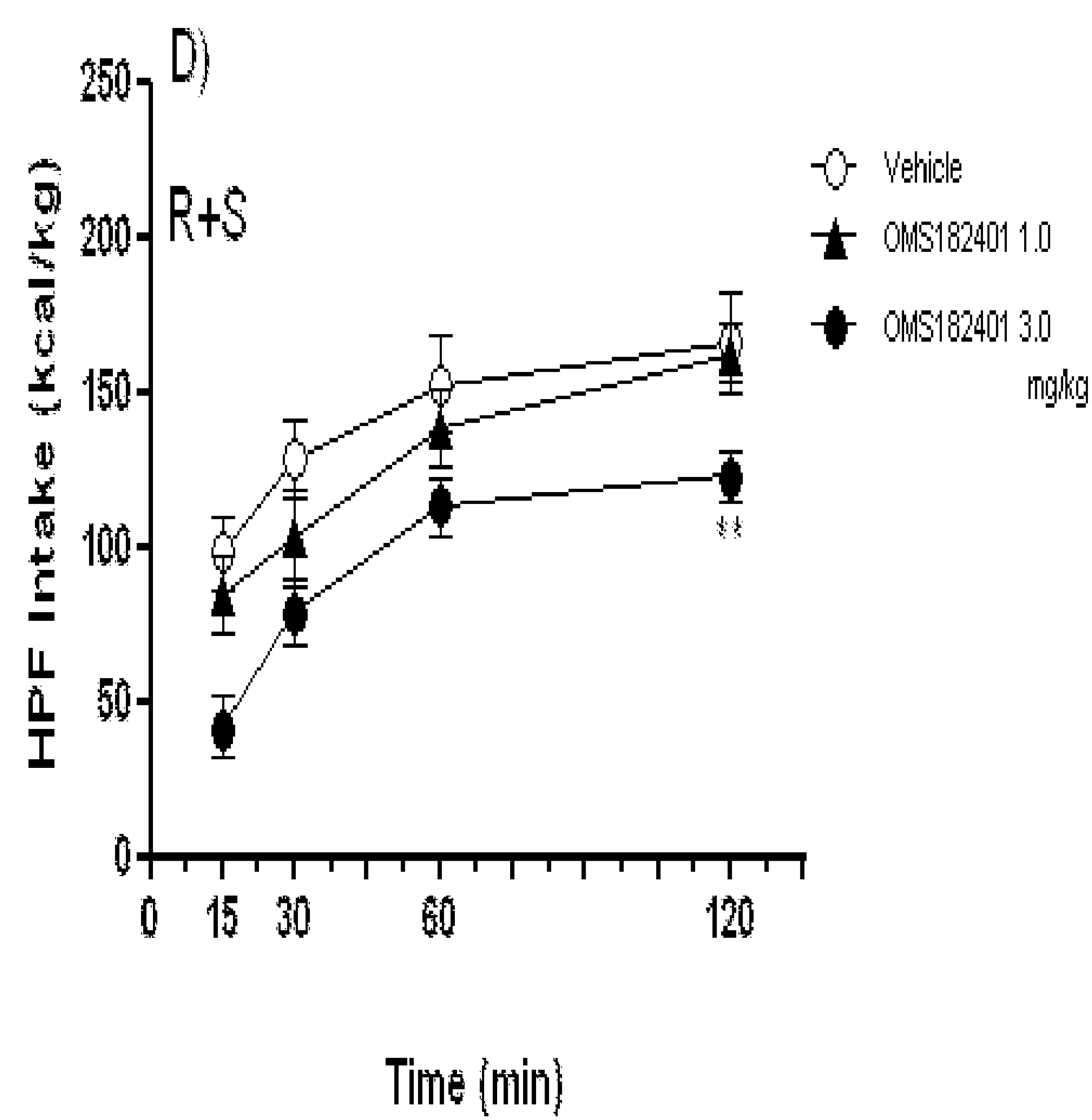
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FIGURE 23C



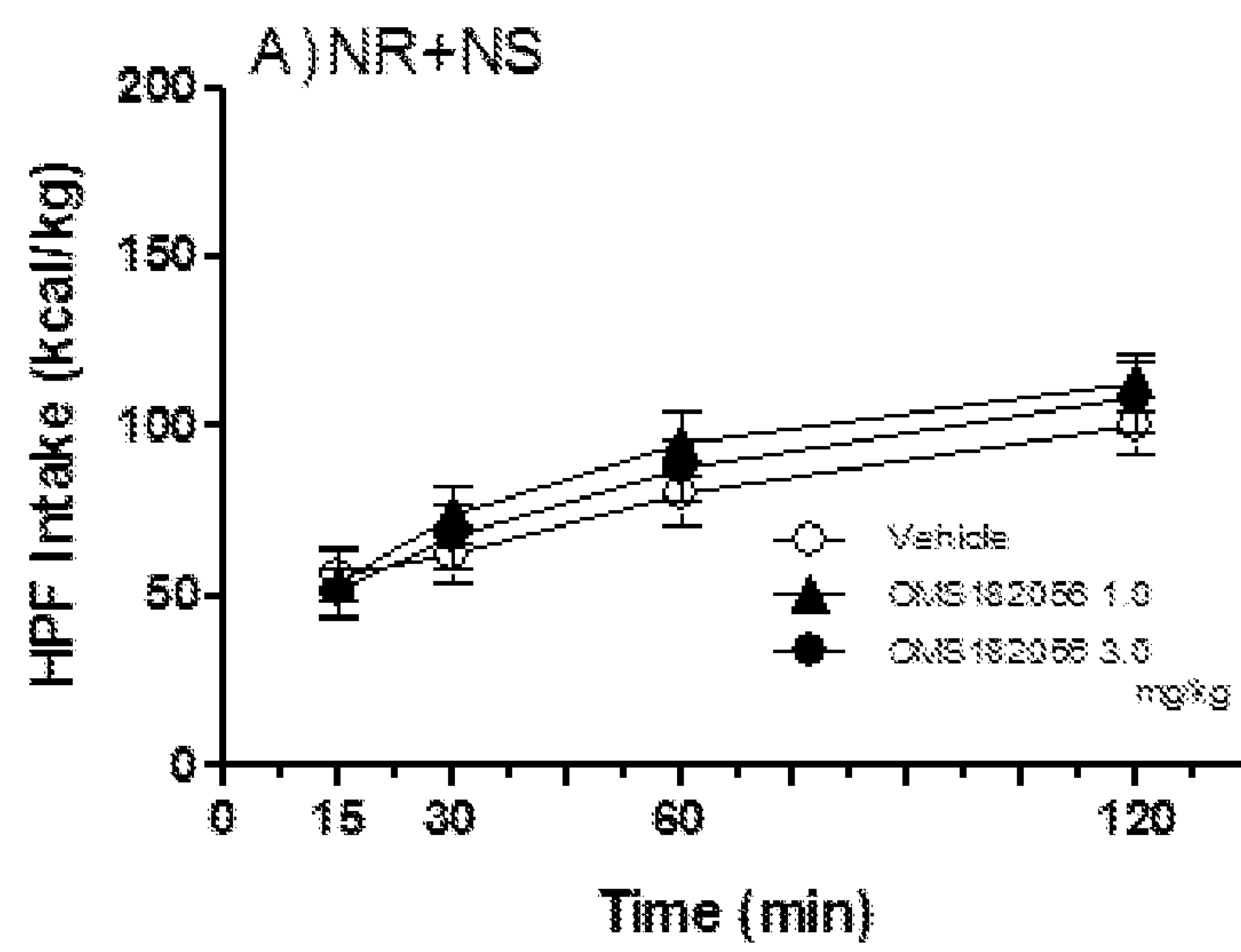
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FIGURE 23D



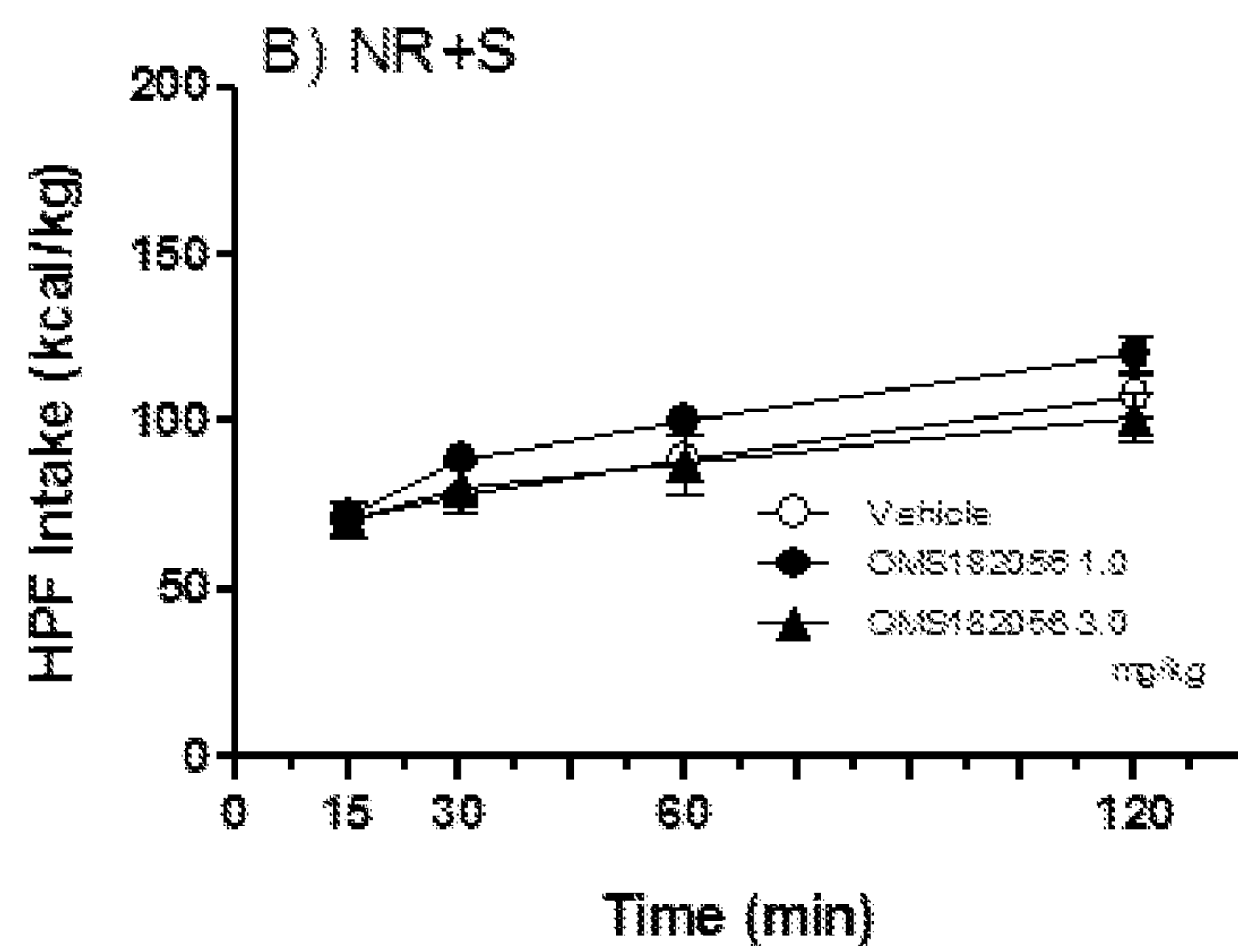
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FIGURE 24A



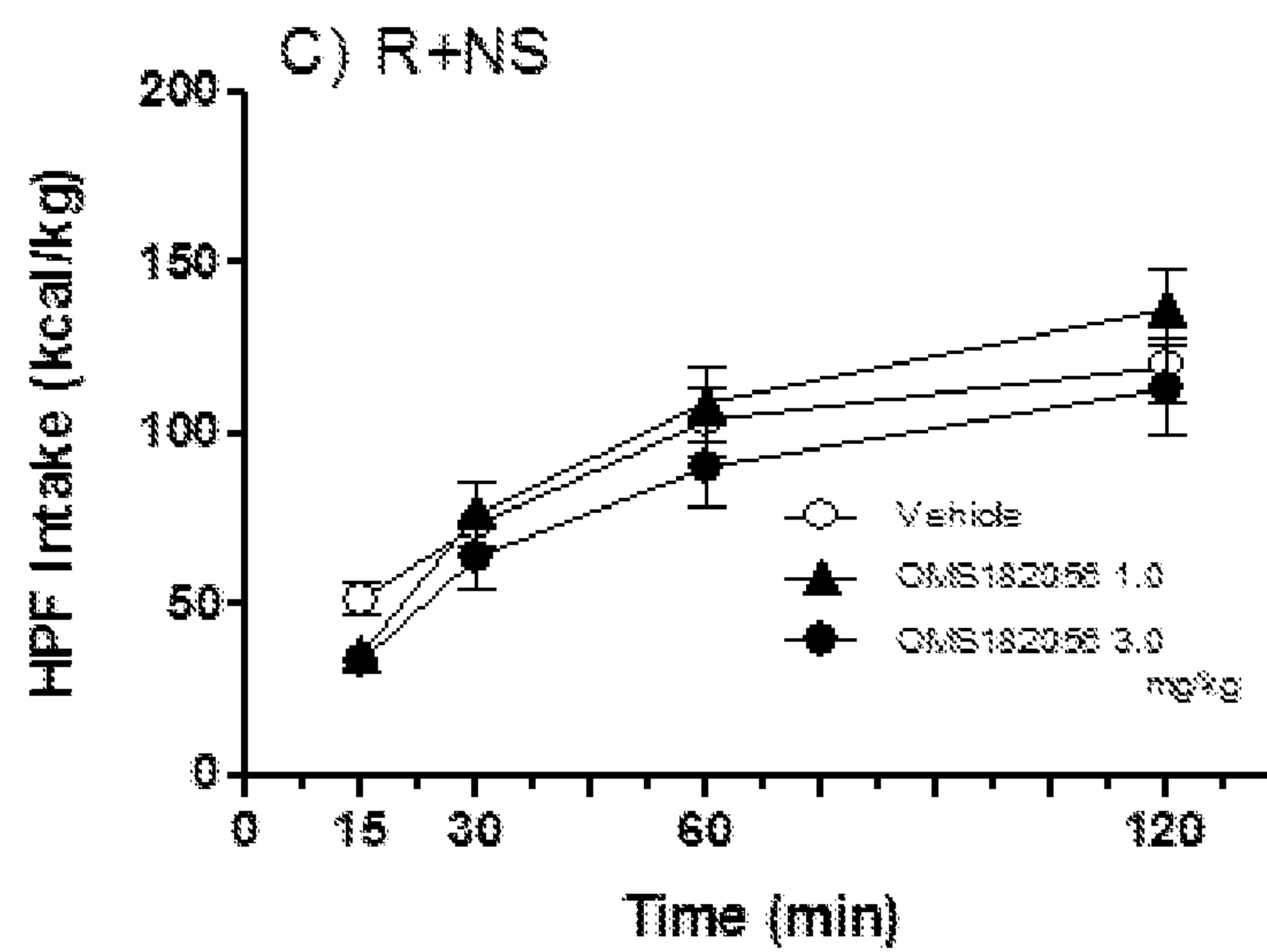
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FIGURE 24B



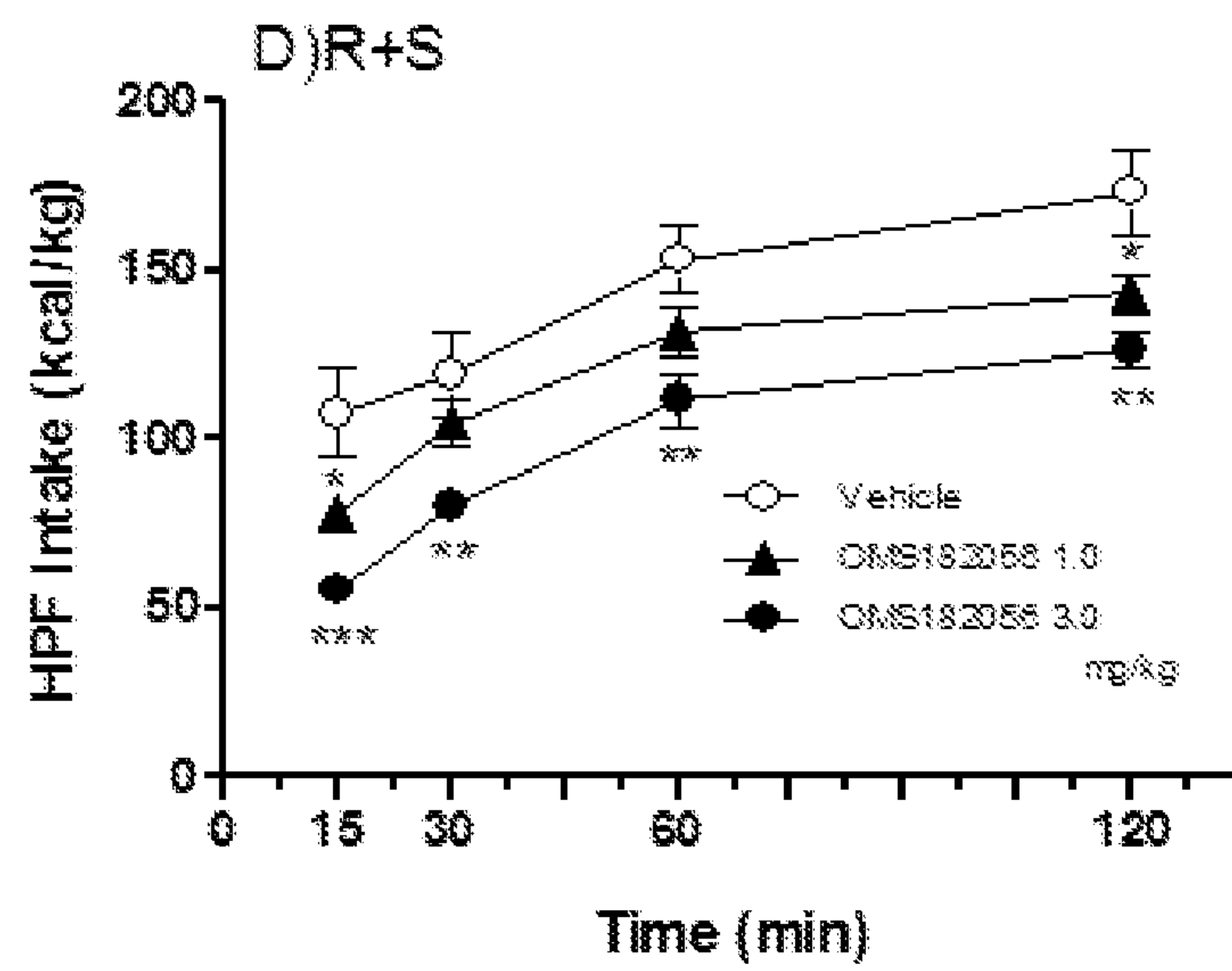
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FIGURE 24C



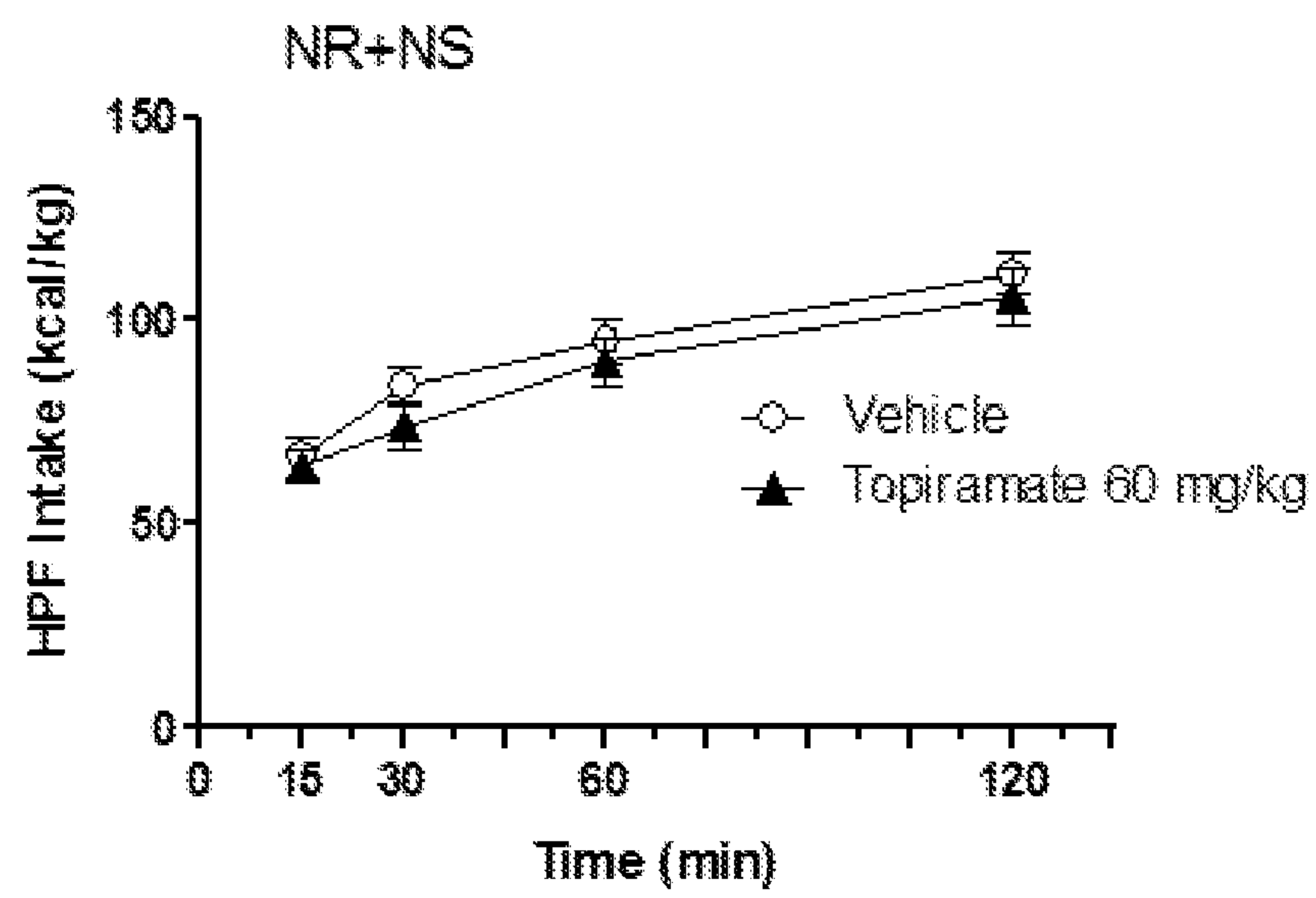
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FIGURE 24D



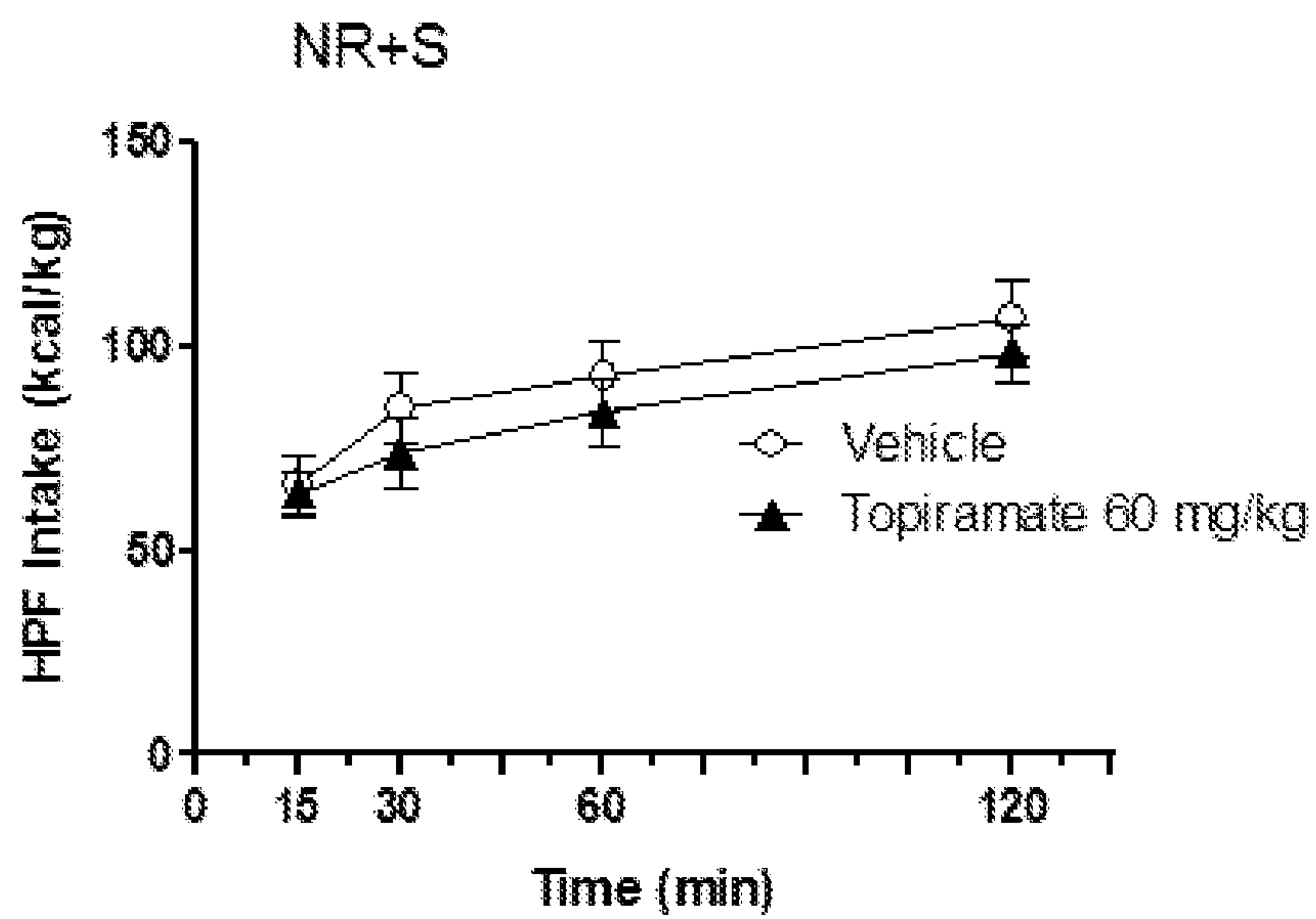
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FIGURE 25A



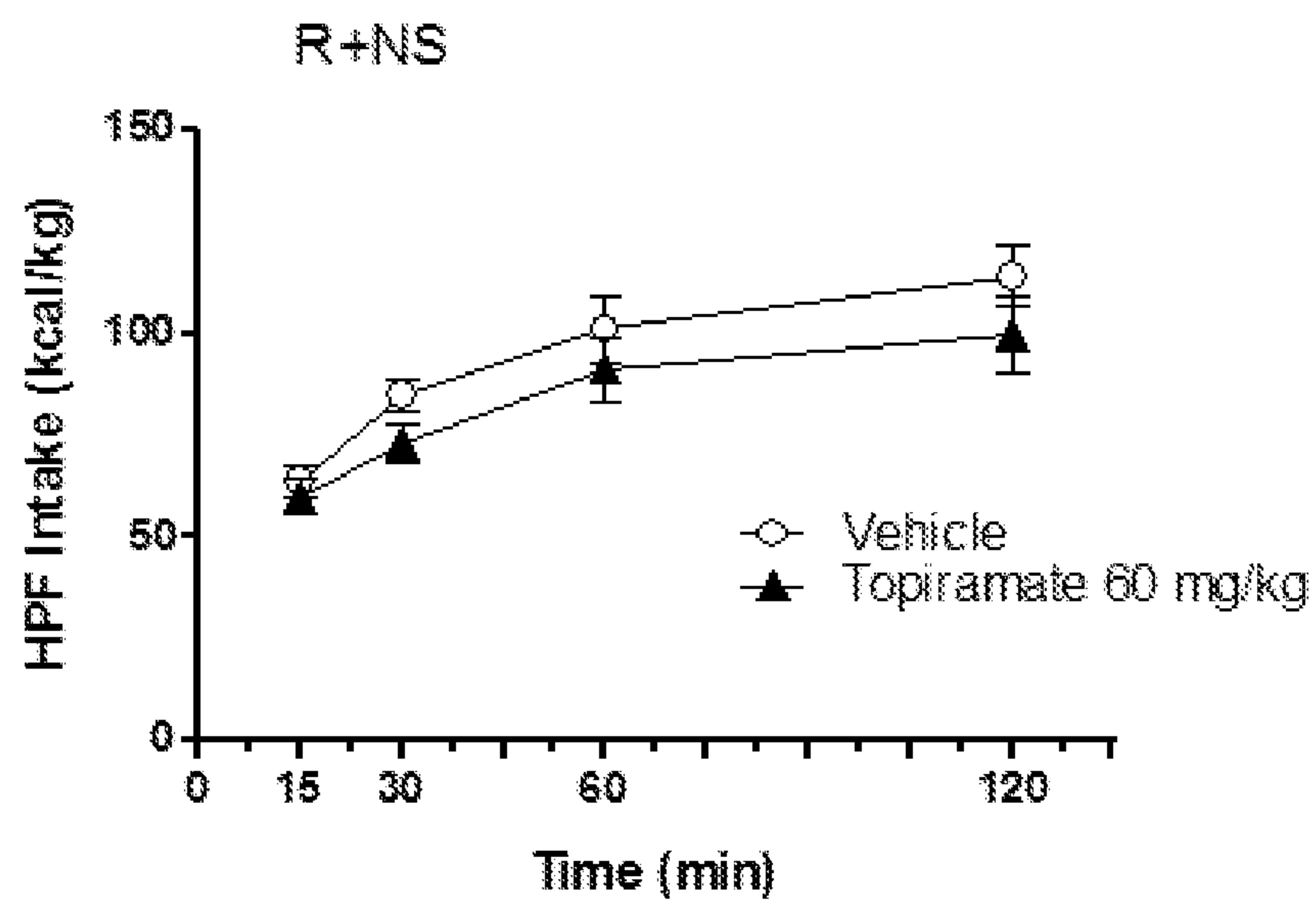
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FIGURE 25B



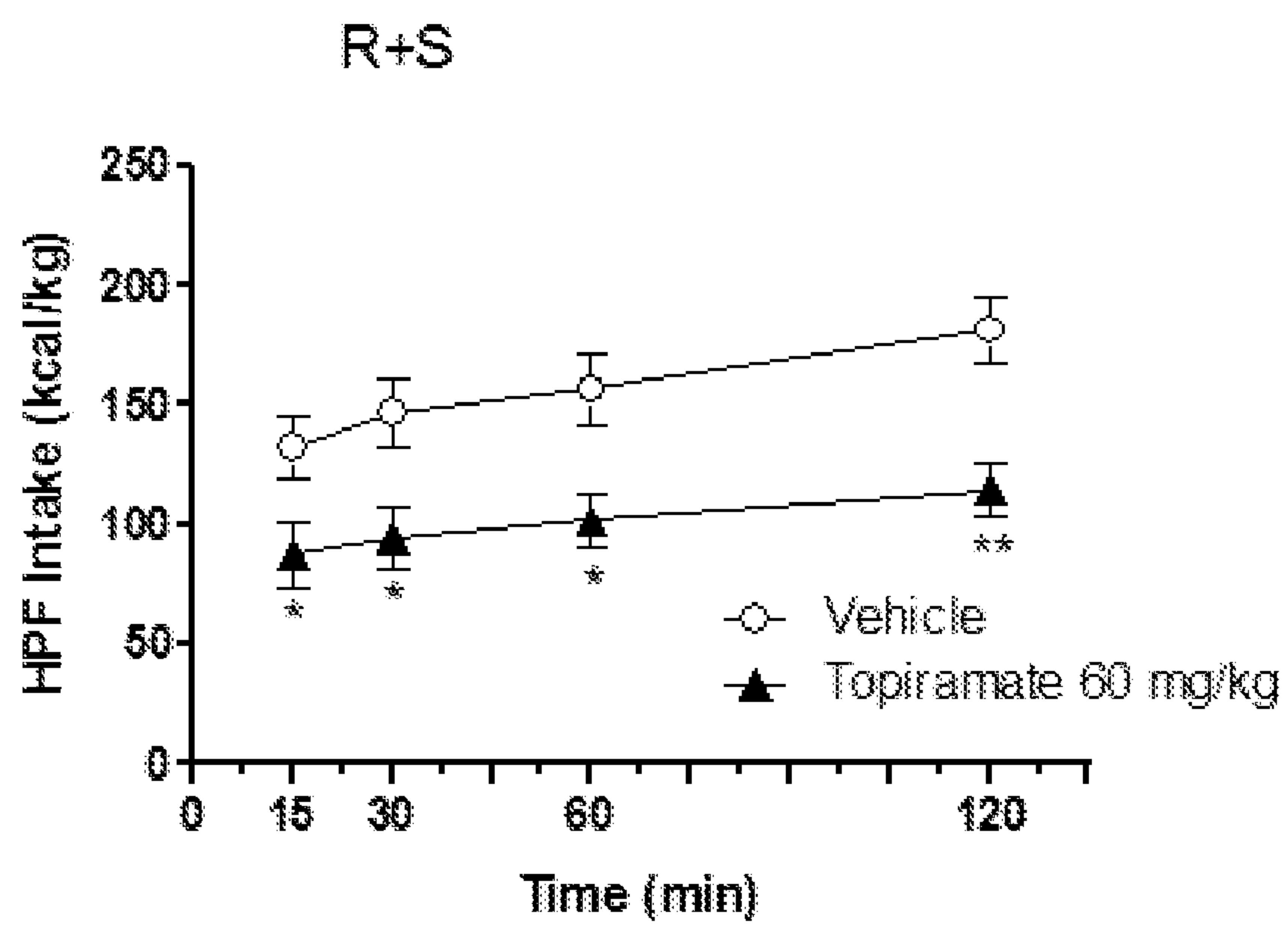
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FIGURE 25C



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FIGURE 25D



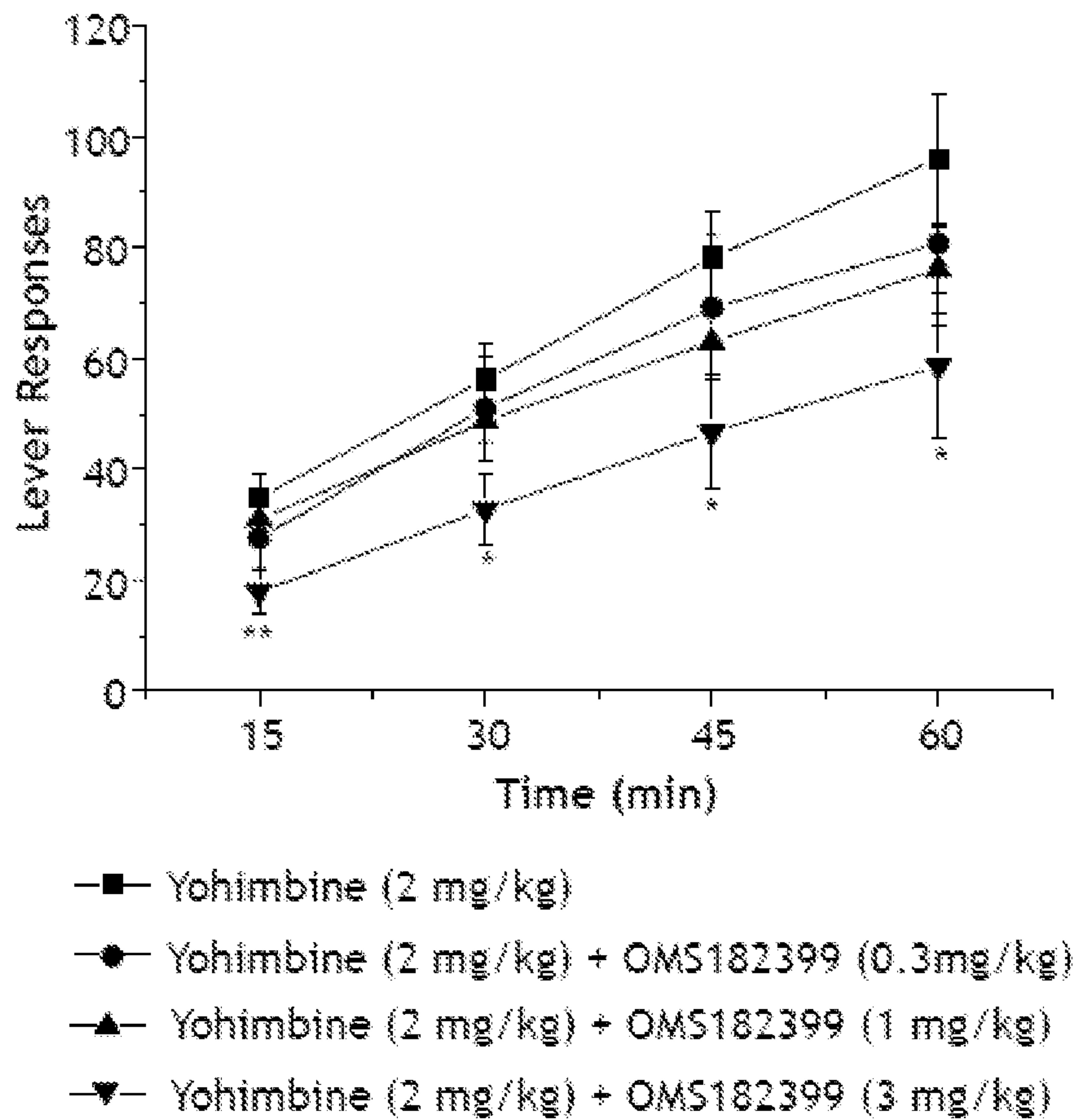
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FIGURE 26

Effect of OMS182399 on yohimbine induced relapse to food seeking

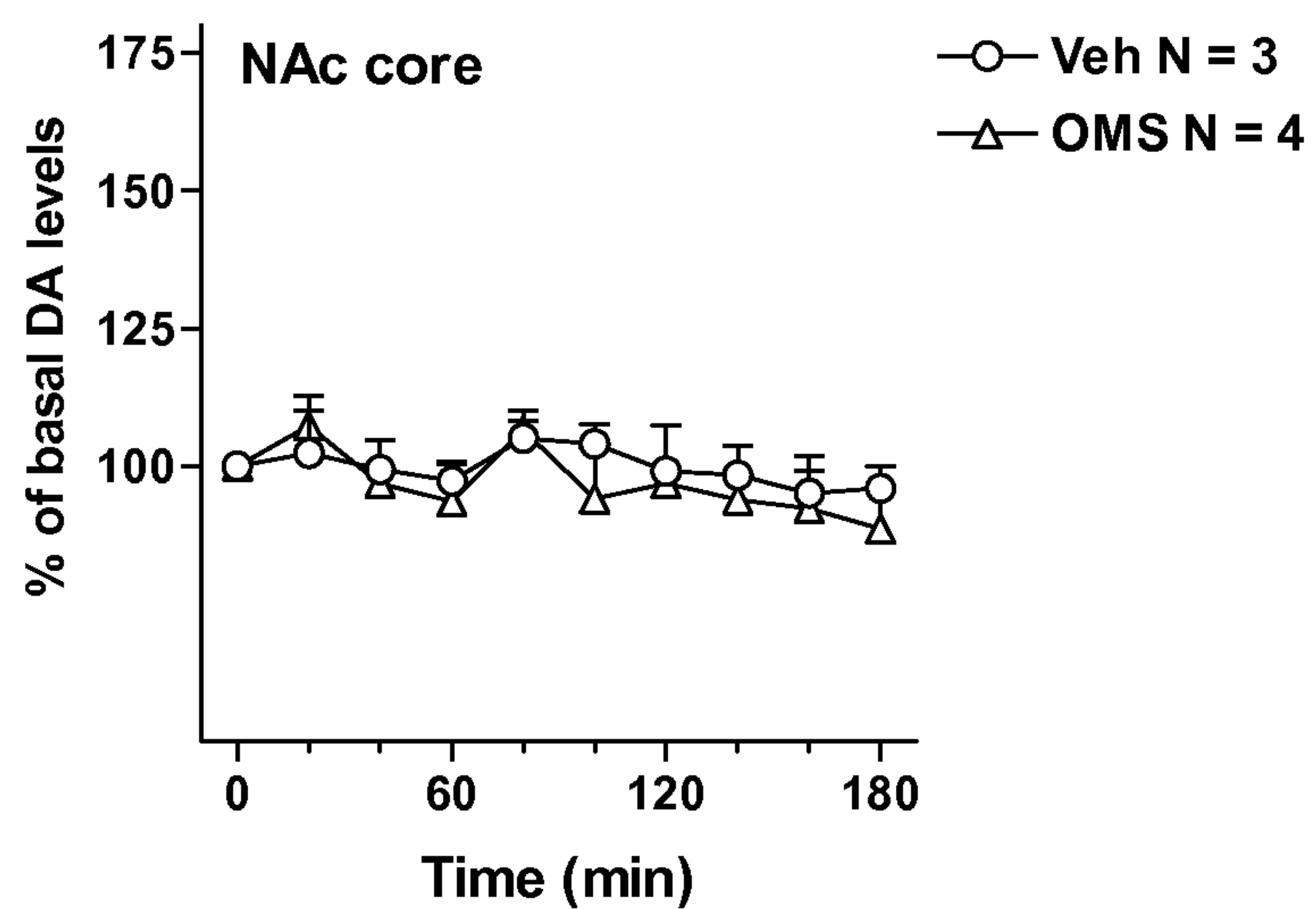
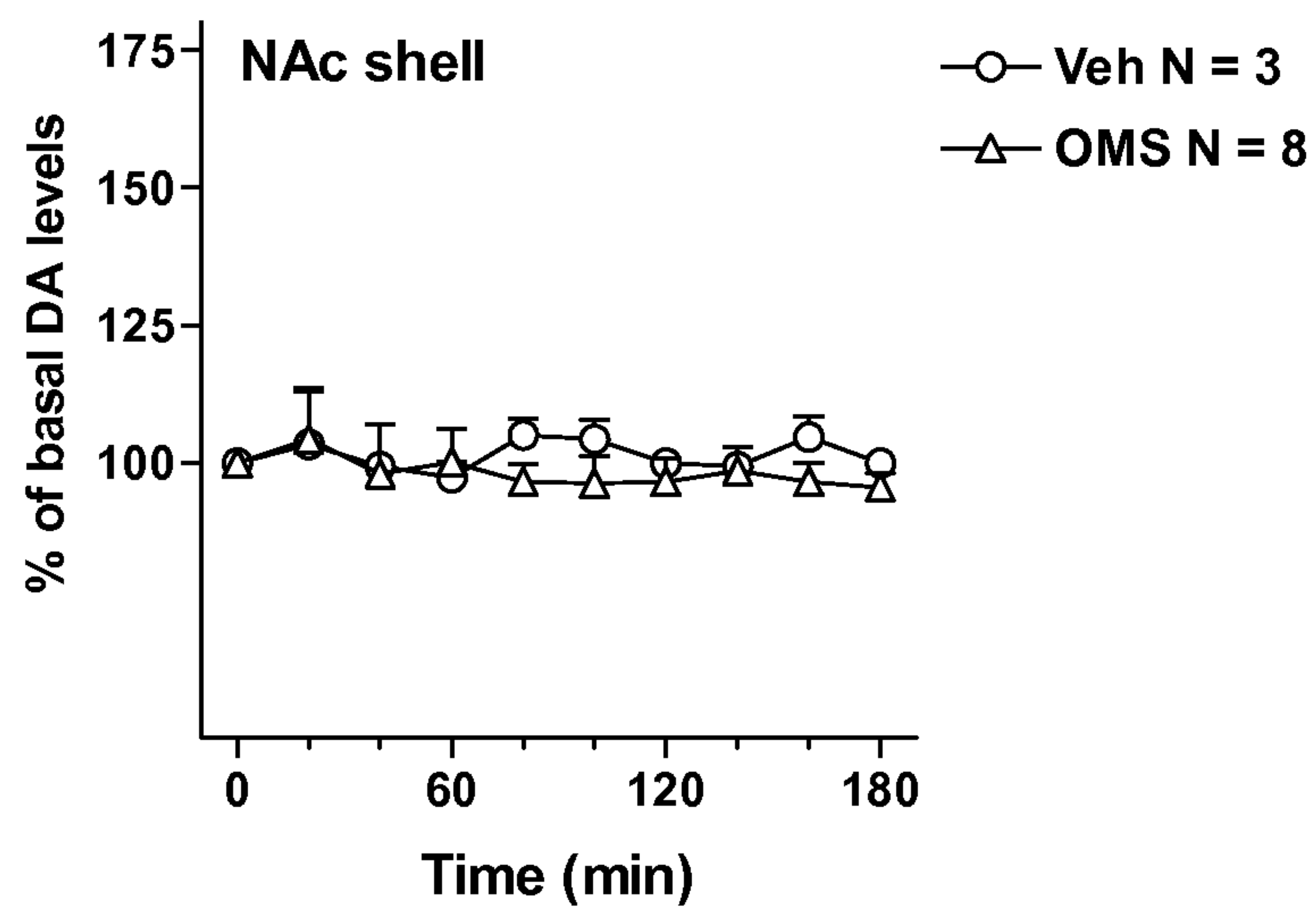
N: 8 Long Evans male rats/group

*p < 0.05; **p < 0.01



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FIGURE 27

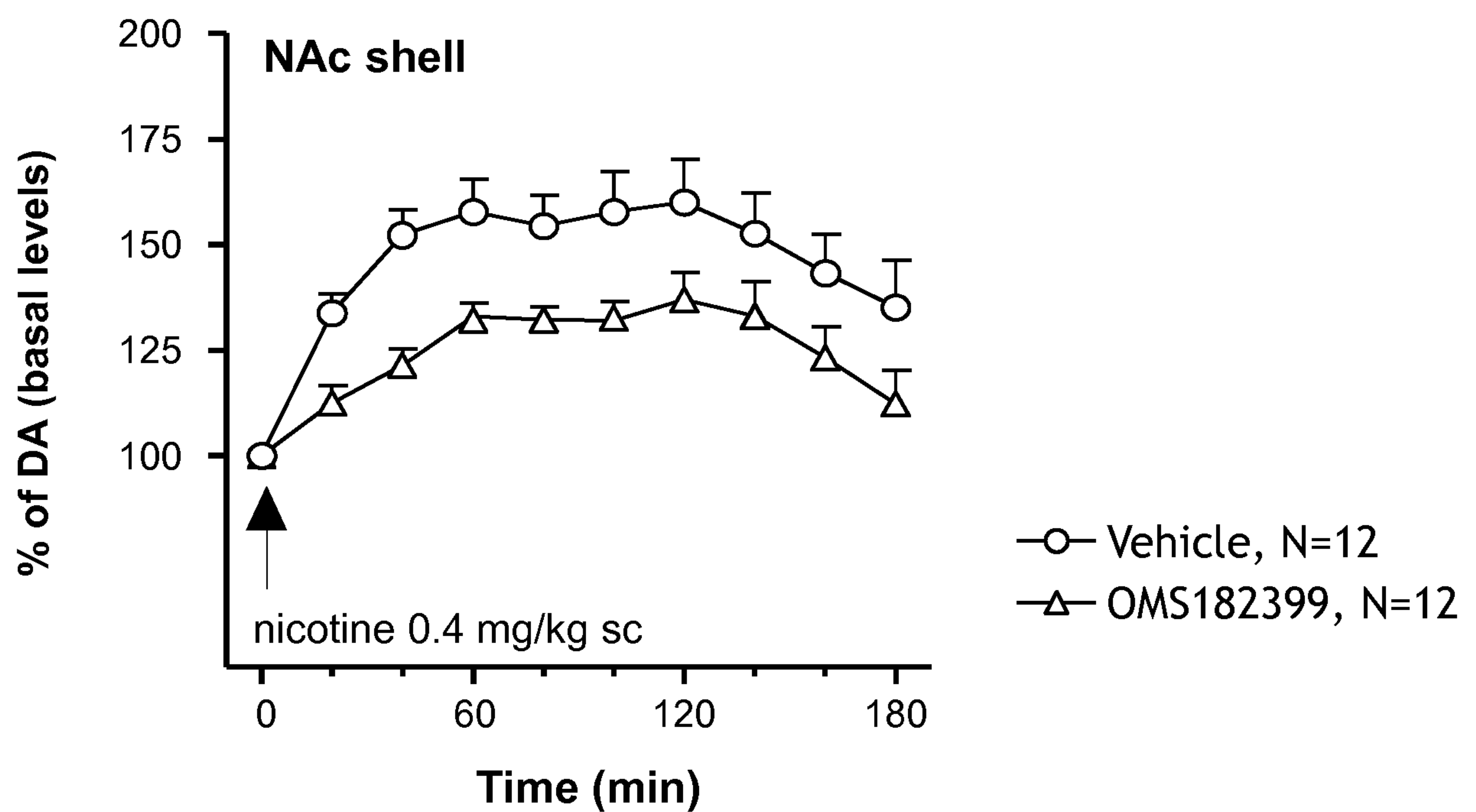


Effect of OMS 182399 (9 mg/kg ip) on NAc shell/core extracellular DA levels

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FIGURE 28

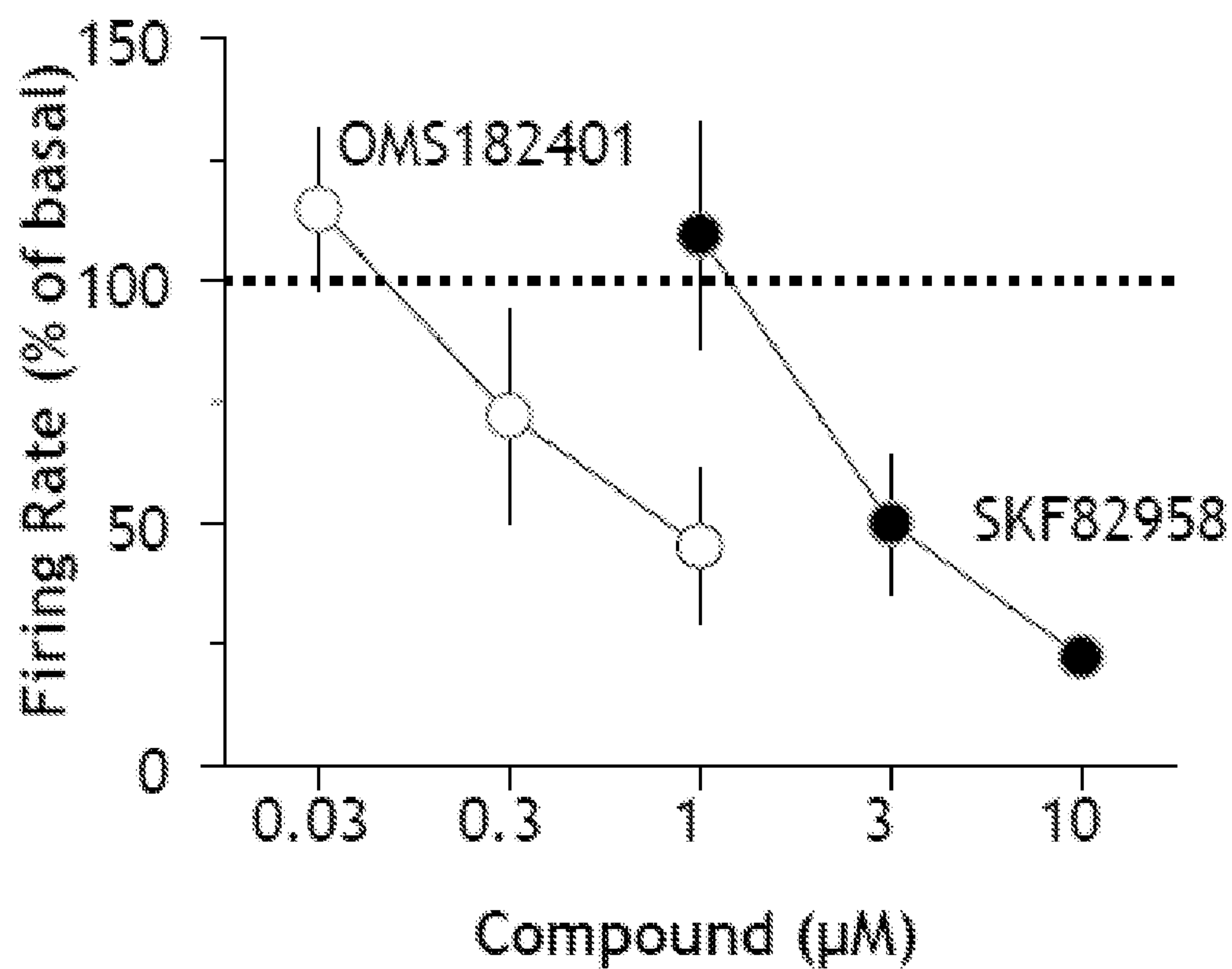
Effect of nicotine (0.4 mg/kg sc) on NAc shell extracellular DA levels in rats pre-treated with OMS182399 (9 mg/kg ip; 10 min before nicotine)



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FIGURE 29A

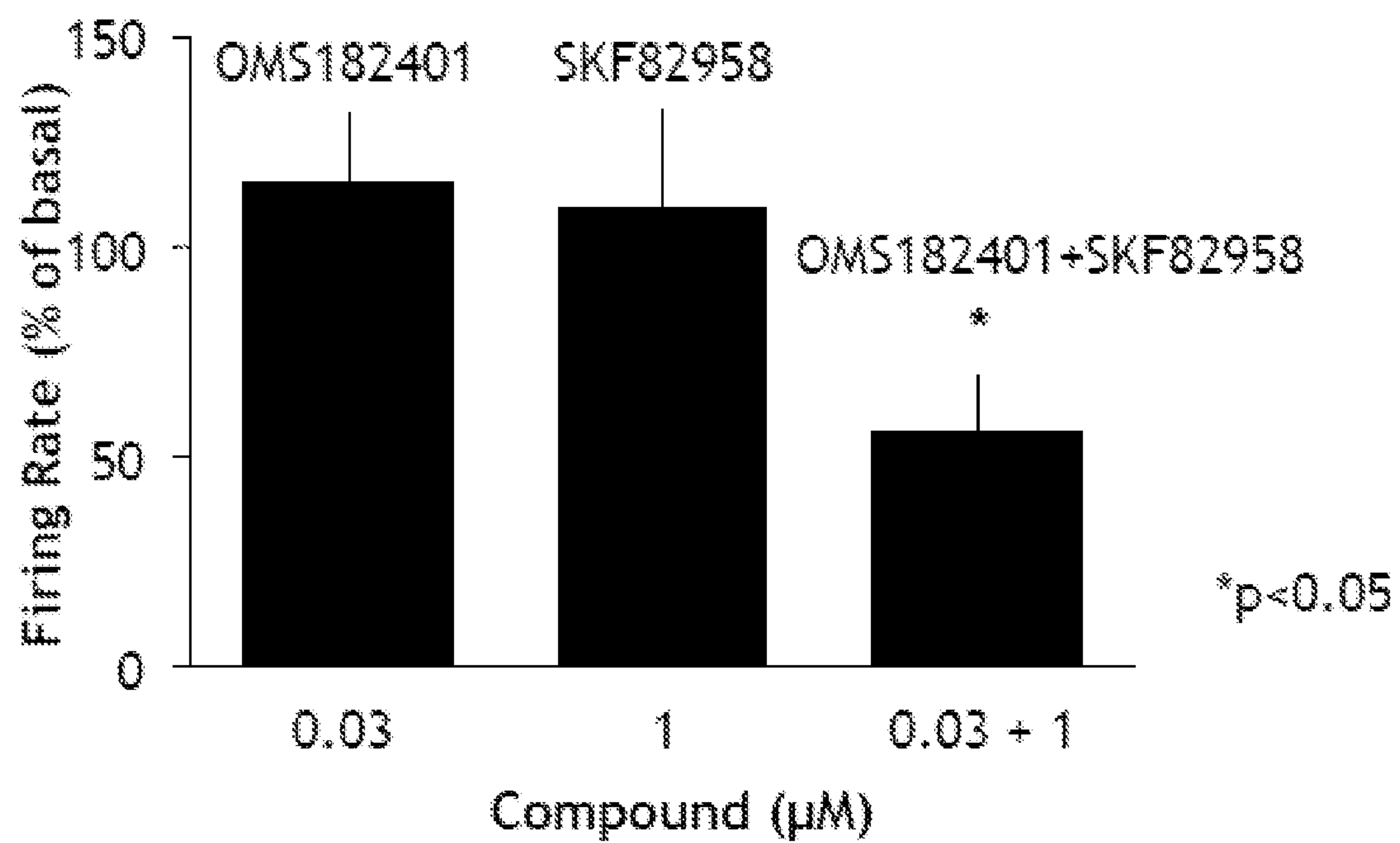
Effect of OMS182401 and SKF82958 on
dopanimergic VTA neurons



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FIGURE 29B

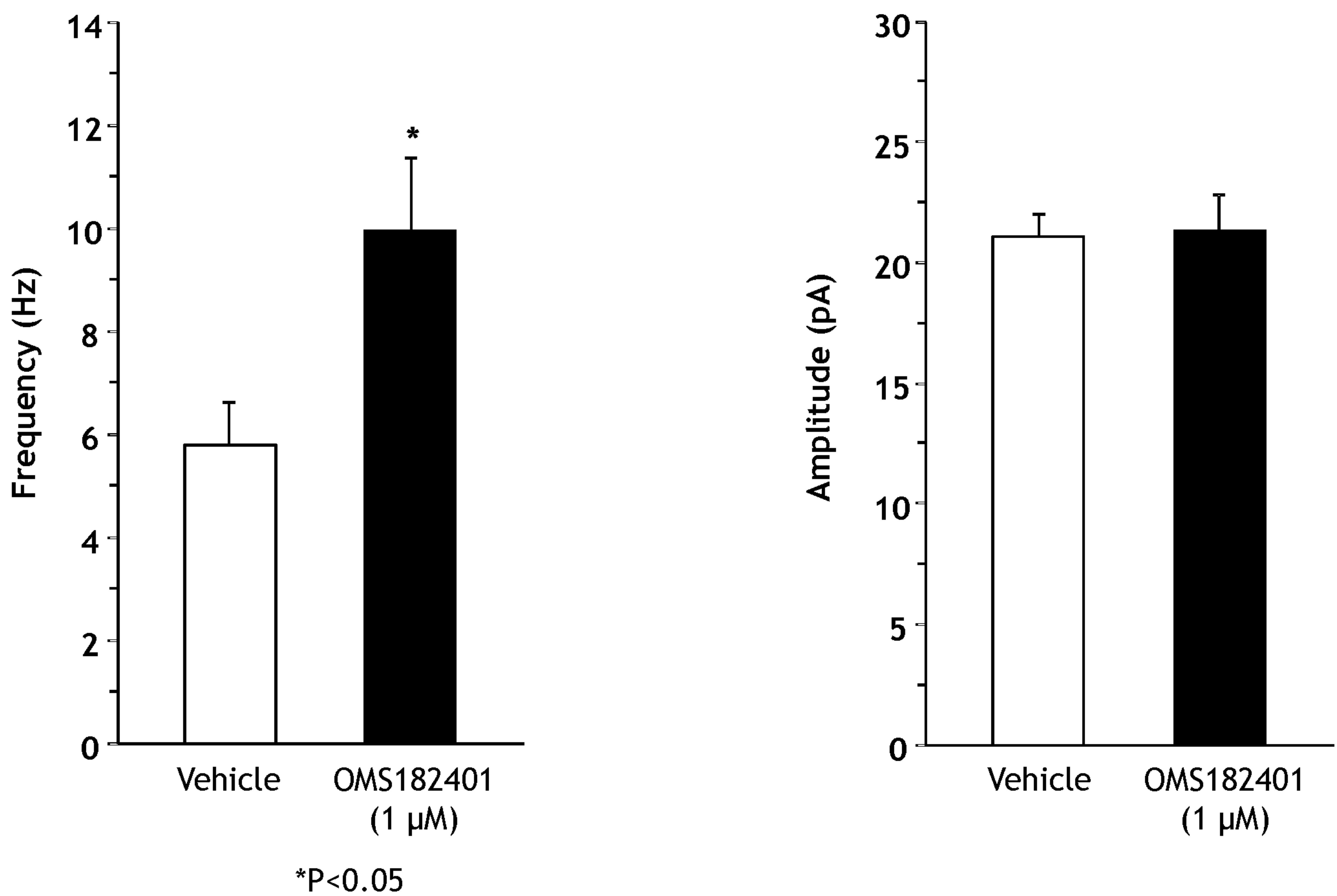
Effect of OMS182401 on dopanimergic VTA neurons



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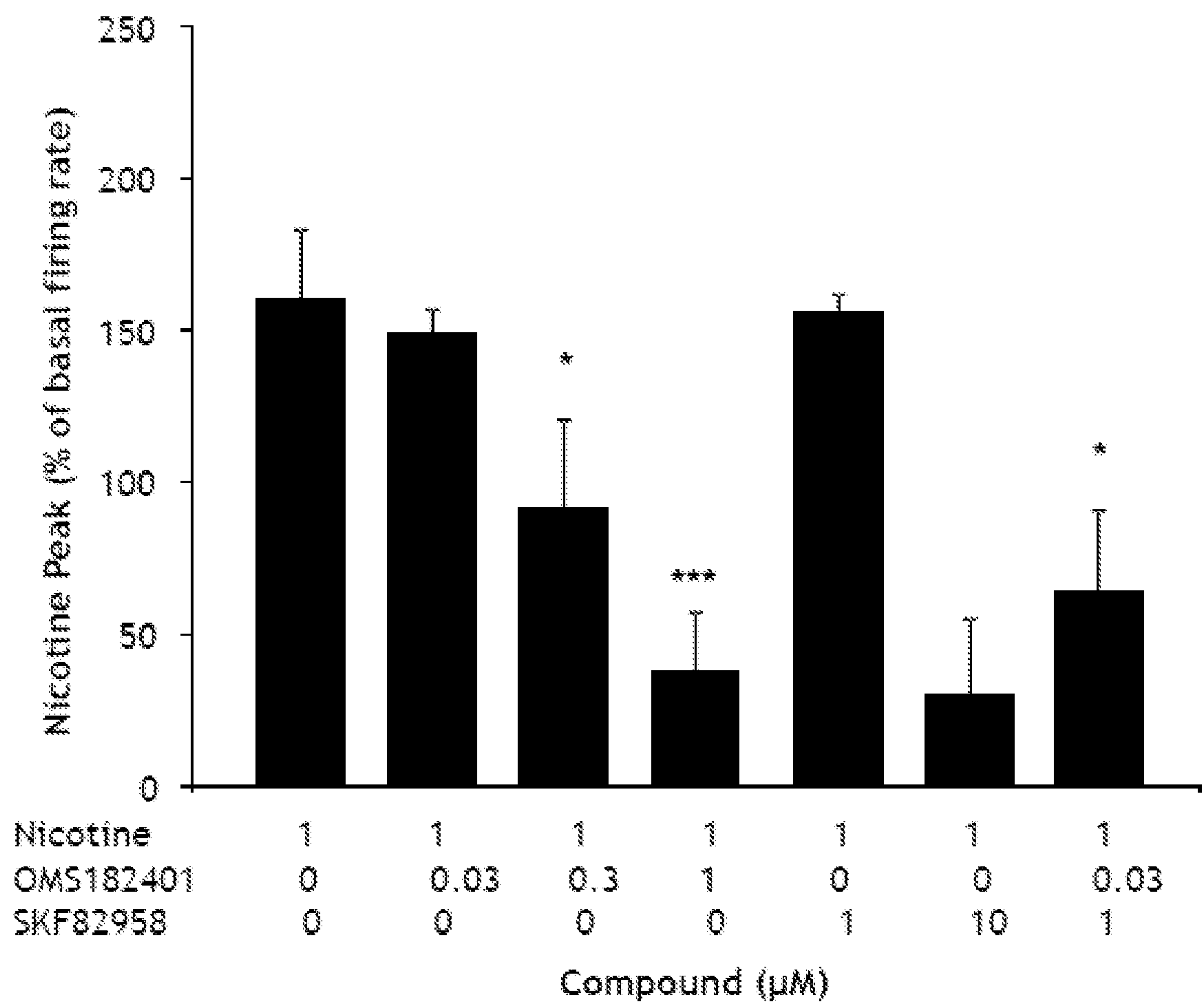
FIGURE 30

Effect of PDE7 Inhibition on VTA GABA Release

Miniature GABA_A Inhibitory Postsynaptic Potentials (mIPSPs)

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FIGURE 31

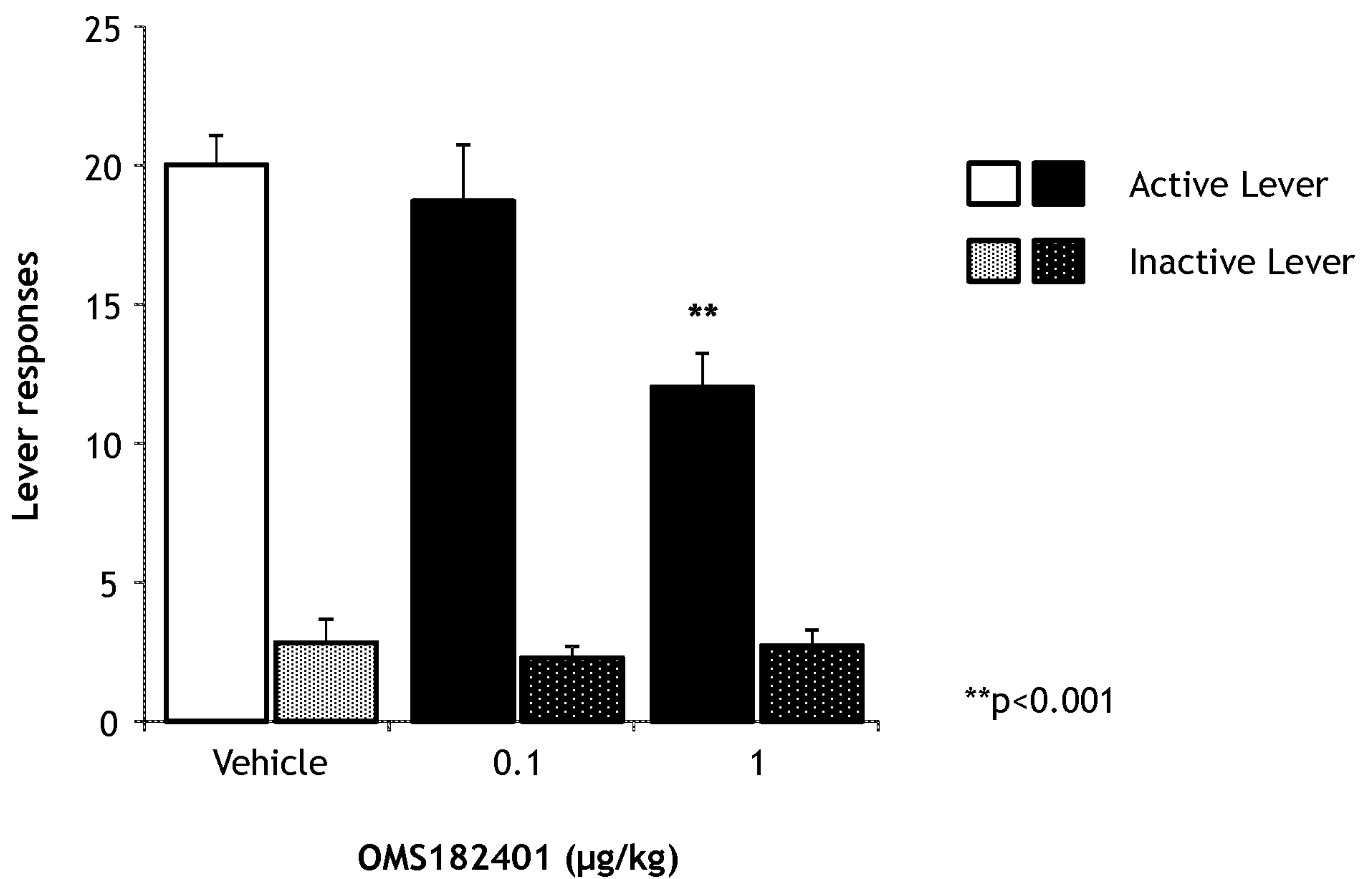


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FIGURE 32

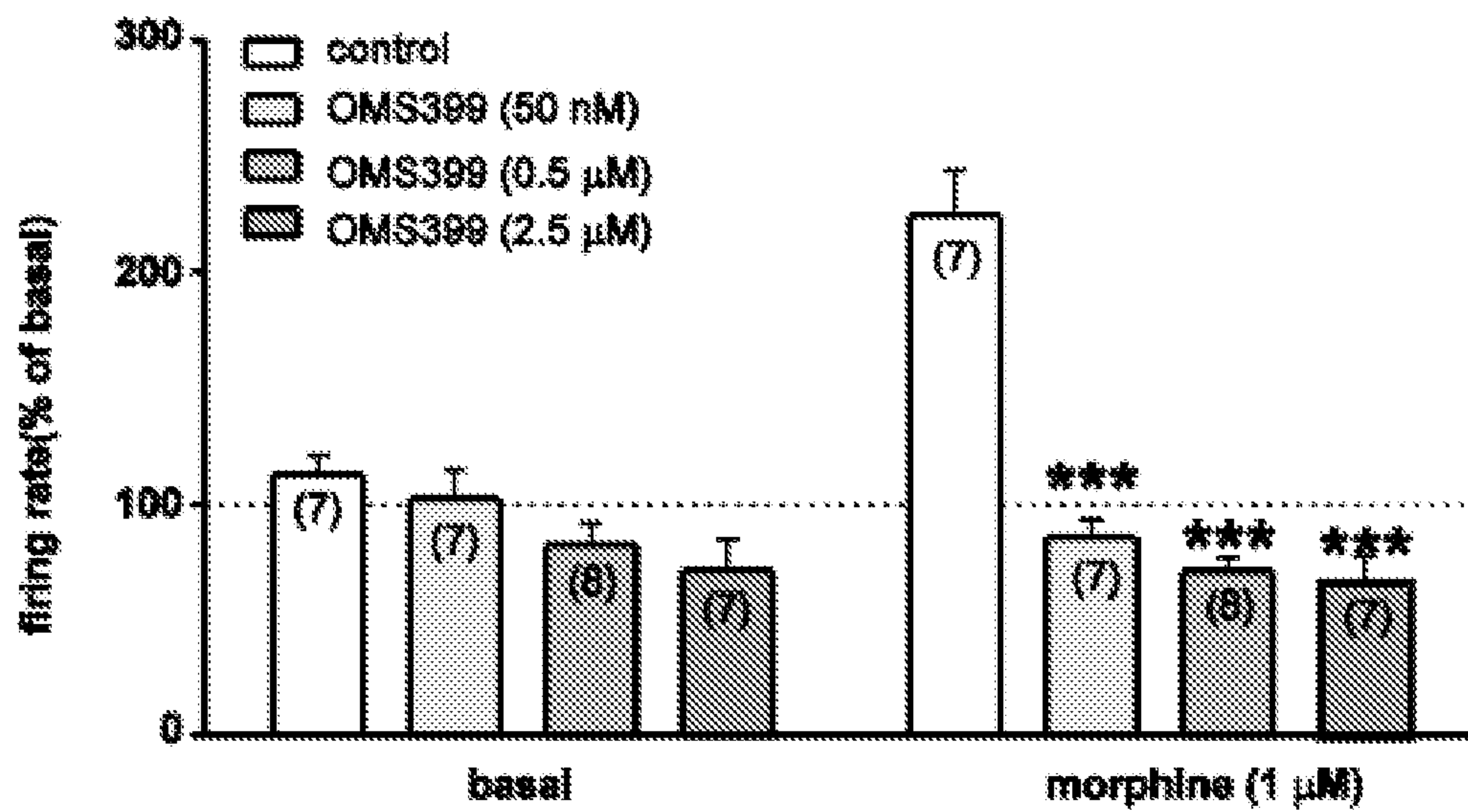
Effects of Direct Administration of PDE7 Inhibitor
into Rat VTA

Nicotine Self-Administration



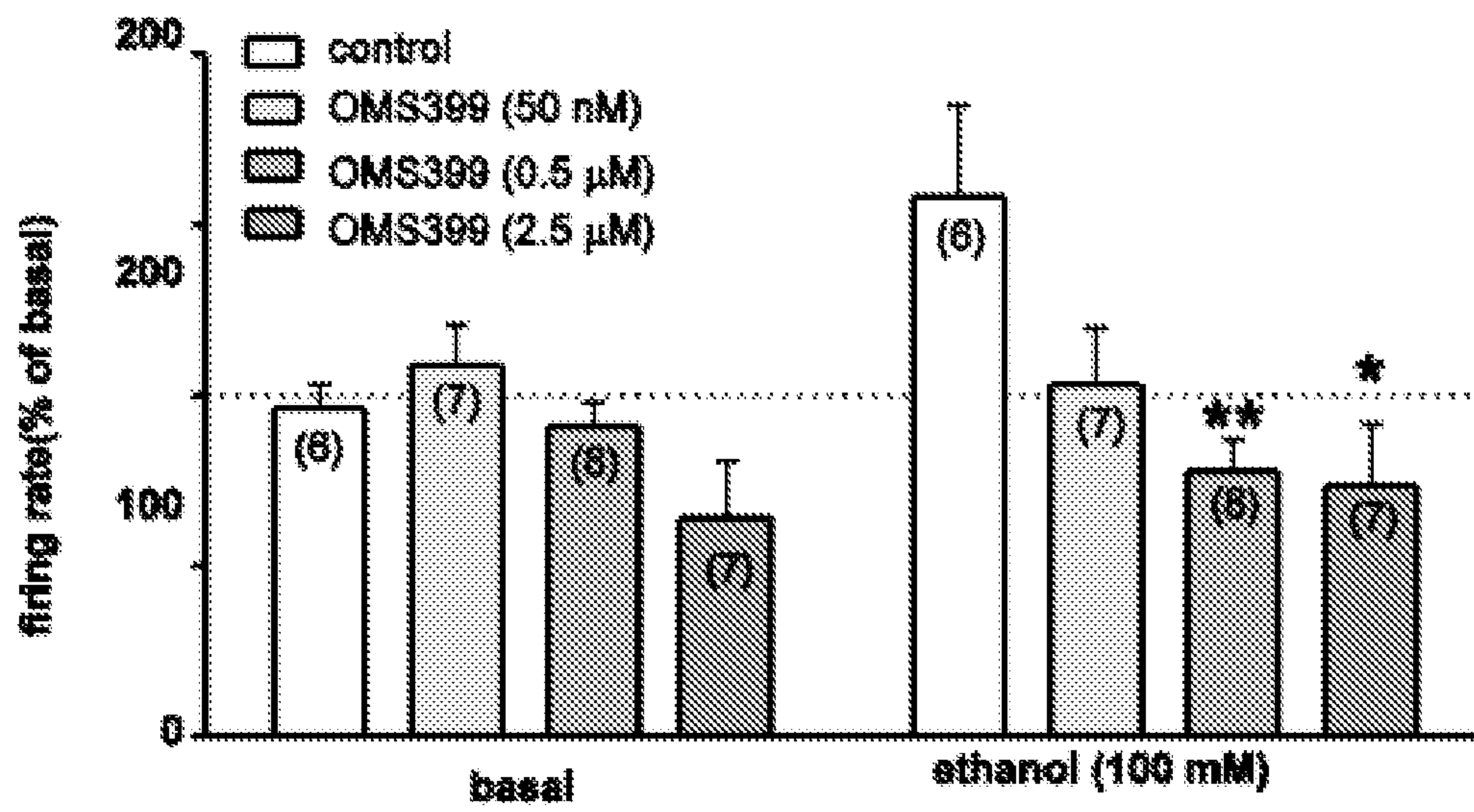
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FIGURE 33



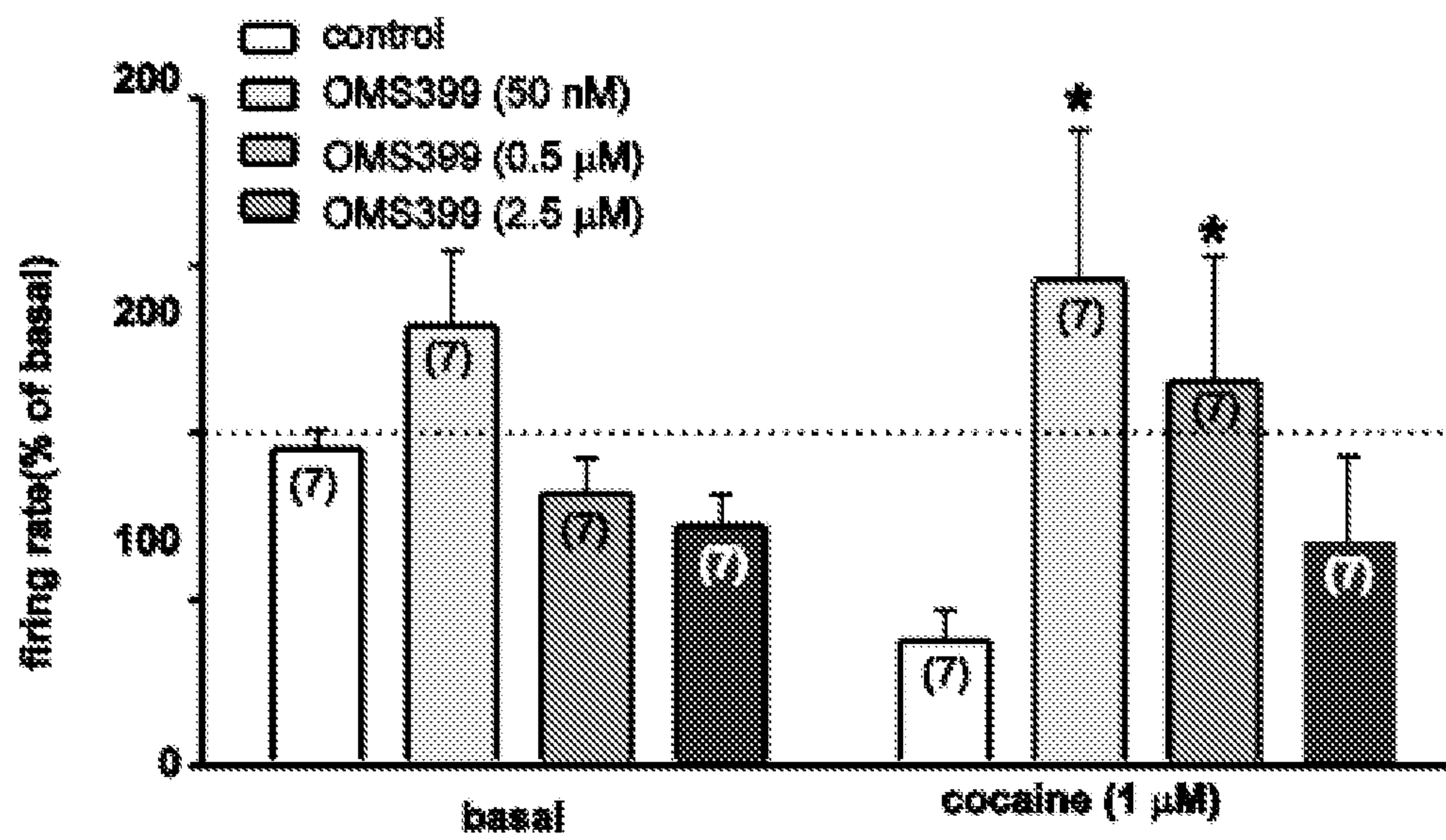
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FIGURE 34



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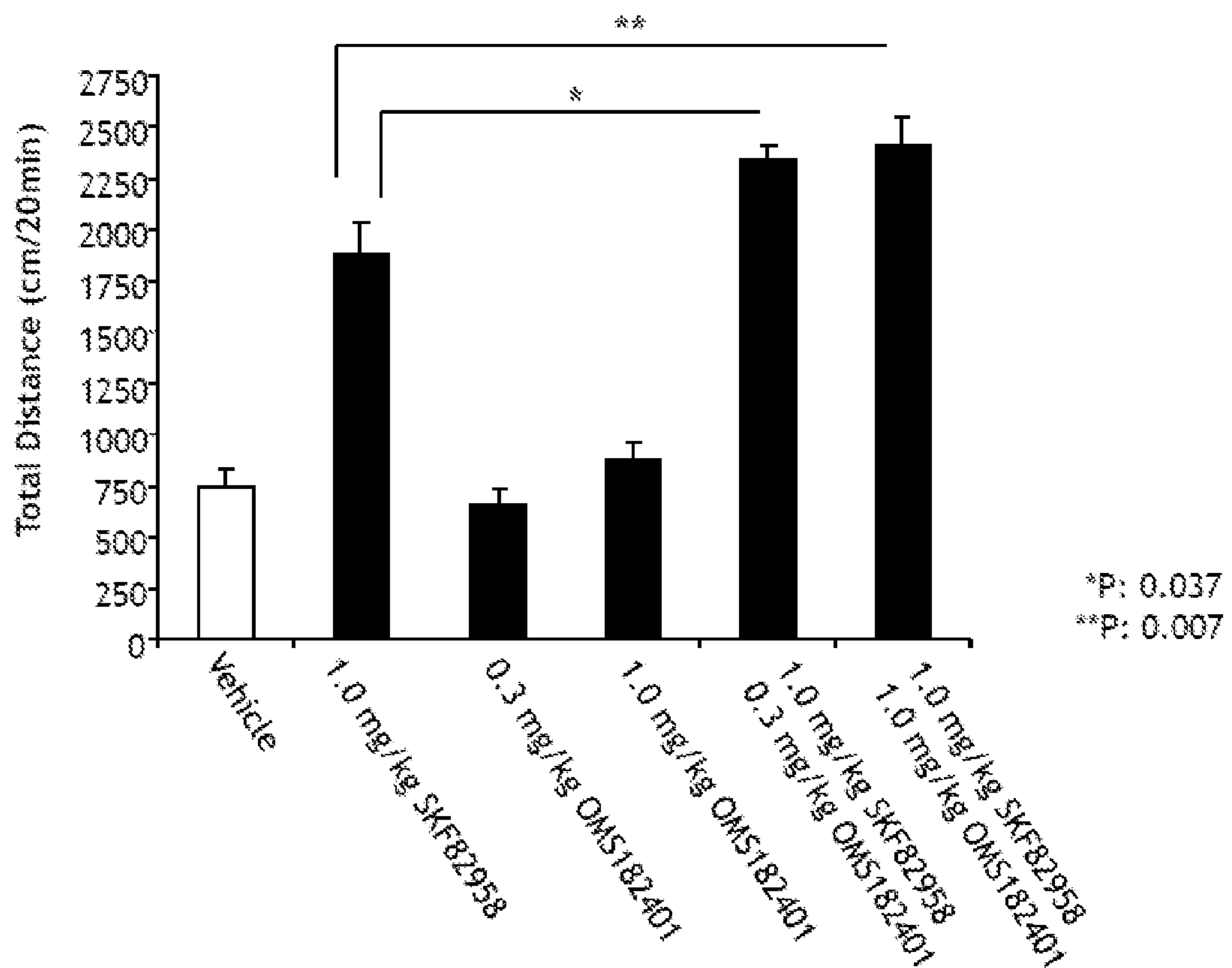
FIGURE 35



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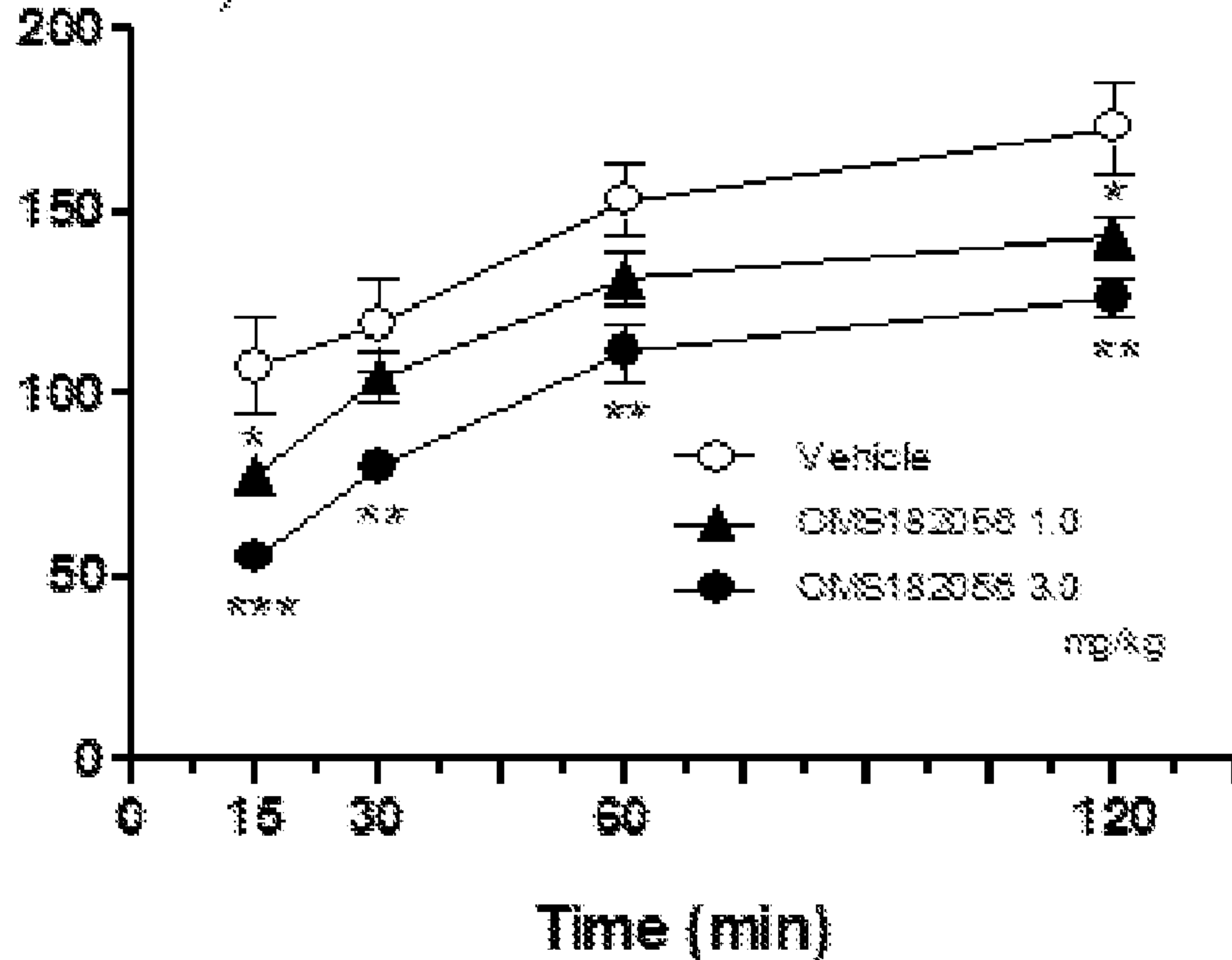
FIGURE 36

Effect of OMS182401 on dopamine D1-mediated stimulation of open field activity



D) R+S

HPF Intake (kcal/kg)



- Vehicle
- ▲ OXB182058 1.0
- OXB182058 3.0

mg/kg