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(54) Title: CHEMICAL COMPOUNDS

(57) Abstract: This invention relates to non-steroidal compounds that are modulators of androgen receptor, and also to the methods for the making and use of such compounds.

CHEMICAL COMPOUNDS

FIELD OF THE INVENTION

This invention relates to non-steroidal compounds that are modulators of androgen receptor, and also to the methods for the making and use of such compounds.

BACKGROUND OF THE INVENTION

Nuclear receptors (NRs) are a class of structurally related proteins that modulate gene expression by acting as ligand-dependent transcription factors. The steroid receptors, namely the androgen receptor (AR), the estrogen receptor (ER), the glucocorticoid receptor (GR), the mineralocorticoid receptor (MR), and the progesterone receptor (PR) represent a subclass of the nuclear receptor superfamily. NR ligands in this subclass exert their effects by binding to the corresponding intracellular steroid hormone receptor.

Certain NR ligands are known to exert their action in a tissue selective manner. This selectivity stems from the particular ability of these ligands to function as agonists in some tissues, while having no effect or even an antagonist effect in other tissues. The term “selective receptor modulator” (SRM) has been given to these molecules. A synthetic compound that binds to an intracellular receptor and mimics the effects of the native hormone is referred to as an agonist. A compound that inhibits the effect of the native hormone is called an antagonist. The term “modulators” refers to compounds that have a spectrum of activities ranging from full agonism to partial agonism to full antagonism.

Steroidal NR ligands are known to play important roles in the health of both men and women. In regard to men’s health, testosterone (T) and dihydrotestosterone (DHT) are endogenous steroidal ligands for the AR that likely play a role in every tissue type found in the mammalian body. During the development of the fetus, androgens play a role in sexual differentiation and development of male sexual organs. Further sexual development is mediated by androgens during puberty. Androgens play diverse roles in the adult including stimulation and maintenance of male sexual accessory organs and maintenance of the musculoskeletal system. Cognitive function, sexuality, aggression, and mood

are some of the behavioral aspects mediated by androgens. Androgens affect the skin, bone, and skeletal muscle, as well as blood lipids and blood cells.

The study of androgen action and male reproductive dysfunction continues to expand significantly. In fact, only recently has the definition of a disease state been associated with hormonal changes that occur in aging men. This syndrome, previously referred to as "andropause," has more recently been described as androgen deficiency in the aging male, or "ADAM." The onset of ADAM is unpredictable and its manifestations are subtle and variable. Clinical manifestations of ADAM include fatigue, depression, decreased libido, erectile dysfunction as well as changes in cognition and mood.

Published information indicates that androgen replacement therapy (ART) in men may have benefits in terms of improving body composition parameters (e.g. bone mineral density, lean muscle mass, and strength) as well as improving libido and mood in some men. Andrologists and other specialists are increasingly using ART for the treatment of the symptoms of ADAM. This use is with due caution given potential side effects of androgens. Nonetheless, there is increasing scientific rationale and evidence for androgen deficiency and treatment in the aging male.

In general, current ARTs fail to correctly mimic physiological testosterone levels and have potential side effects including exacerbation of pre-existing sleep apnoea, polycythemia (increased hematocrit), and/or gynaecomastia. Furthermore, the longer-term side effects on target organs such as the prostate or the cardiovascular system are yet to be fully elucidated. Importantly, the potential cancer promoting effects of testosterone on the prostate prevent many physicians from prescribing it to older men (i.e. age > 60 years) who, ironically, stand to benefit most from treatment. The need for a novel selective androgen receptor modulator (SARM) is evidenced by the potential side effect profile manifested by conventional treatments. An ideal SARM has all the beneficial effects of endogenous androgens, while sparing sexual accessory organs, specifically the prostate.

SARMs are currently in the early stages of development. Much of the preclinical and clinical understanding of the therapeutic promise of SARMs stems from work using anabolic steroids. Because of their highly selective anabolic properties and demonstrated prostate sparing activity, SARMs could be used for prevention or treatment of many diseases, including, but not limited to sarcopenia (muscle wasting), osteoporosis, frailty, hypogonadism, and other conditions associated with aging or androgen deficiency. SARMs also show promise in the

areas of hormonal male contraception and benign prostatic hyperplasia (BPH). The therapeutic potential of SARMs for treatment of androgen deficient disorders in women is a far less studied field.

Clinical studies show that ART in men improves body composition parameters such as muscle mass, strength, and bone mineral density. There is also evidence of improvement in less tangible parameters such as libido and mood. Andrologists and other specialists are increasingly using androgens for the treatment of the symptoms of androgen deficiency. ART, using T and its congeners, is available in transdermal, injectable and oral dosage forms. All current treatment options have contraindications (e.g., prostate cancer) and side-effects, such as increased hematocrit, liver toxicity, and sleep apnoea.

Sarcopenia or muscle wasting is the aging-associated decline in neuromuscular function and performance. Skeletal muscle atrophy and weakness are considered major contributing factors to the loss of mobility, independence, and frailty that affect many older adults. Relative muscle loss in aging men and women is similar, but because men start with higher baseline values, their absolute loss of strength is greater. Epidemiological data support the relationship between the fall in testosterone and the decline in muscle mass. As mentioned above, many clinical studies with testosterone have demonstrated significant gains in muscle mass and function along with decreases in visceral fat.

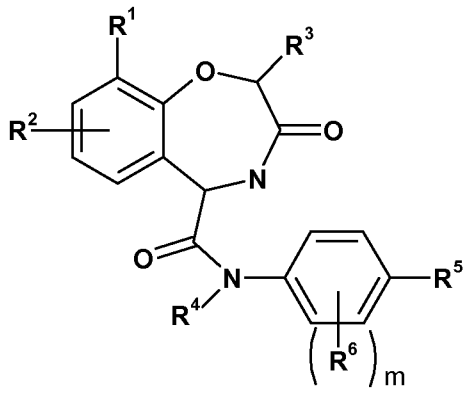
The use of androgens to alleviate the physiological consequences of testosterone deficiency is well recognized in men. The concept of androgen deficiency in women, however, is not readily embraced. The clinical manifestations of T deficiency in women are decreased libido, lowered mood, a diminished sense of well-being, blunted motivation, and persistent fatigue. Clinically, the use of androgens in women has been shown to enhance sexual function, maintain bone mineral density, and increase fat-free mass.

SARMs have the potential to offer the same benefits in women as androgen therapies without the unwanted side effects. Side effects from androgen therapy in women include acne, hirsutism, and lowering of high-density lipoprotein (HDL) cholesterol levels.

Thus, modulators of the androgen receptor that are highly specific for the AR could offer greater benefit with less side effects in the treatment of both female and male related hormone responsive diseases.

BRIEF SUMMARY OF INVENTION

Briefly, in one aspect, the present invention provides compounds of formula (I)



(I)

or a salt or solvate thereof,

wherein:

R^1 is C_{1-2}alkyl, halogen, or CF_3;

R^2 is H, Cl, F, or methyl;

R^3 is H or methyl;

R^4 is H, C_{1-6}alkyl, or benzyl optionally substituted with CF_3;

R^5 is methyl, nitro, halogen, CN, CF_3, or $-C(O)OCH_2CH_3$;

R^6 is Cl, F, or CF_3;

m is 0 or 1;

wherein:

when R^1 is ethyl or CF_3,

R^2 is H;

when R^1 is methyl, R^2 is H, and m is 0,

R^5 is nitro, halogen, CN, CF_3, or $-C(O)OCH_2CH_3$;

when R^1 is methyl, R^2 is H, and m is 1,

R^5 and R^6 are both Cl, or

R^5 is Br and R^6 is Cl or F, or

R^5 is CN and R^6 is CF_3;

when R^1 and R^2 are both methyl,

m is 0 and R^5 is CF_3, Br, nitro, or CN;

when R^1 is methyl, R^2 is F, and m is 0,

R^5 is CN, CF_3, or Br;

when R^1 is methyl, R^2 is F, and m is 1,

R^5 and R^6 are both Cl;

when R^1 is ethyl, R^2 is H, and m is 0,

R^5 is methyl, CF_3, nitro, CN, Br, or $C(O)OCH_2CH_3$;

when R^1 is ethyl, R^2 is H, and m is 1,

R^5 and R^6 are both Cl, or

R^5 is CN and R^6 is CF_3; and

when R^1 and R^2 are both Cl and m is 1,

R^5 and R^6 are both Cl, or

R^5 is CN and R^6 is CF_3

Another aspect of the present invention provides a compound substantially as hereinbefore defined with reference to any one of the Examples.

Another aspect of the present invention provides a pharmaceutical composition comprising a compound of the present invention.

Another aspect of the present invention provides a compound of the present invention for use as an active therapeutic substance.

Another aspect of the present invention provides a compound of the present invention for use in the treatment of hypogonadism, sarcopenia, osteoporosis, muscle wasting, wasting diseases, cancer cachexia, frailty, prostatic hyperplasia, prostate cancer, breast cancer, menopausal and andropausal vasomotor conditions, urinary incontinence, sexual dysfunction, erectile dysfunction, depression, uterine fibroid disease, endometriosis, acne, hirsutism, male contraception, impotence, and in the use as male and female hormone replacement therapy, as a stimulant of hematopoiesis, and as an anabolic agent.

Another aspect of the present invention provides the use of a compound of the present invention in the manufacture of a medicament for use in the treatment of hypogonadism, sarcopenia, osteoporosis, muscle wasting, wasting diseases, cancer cachexia, frailty, prostatic hyperplasia, prostate cancer, breast cancer, menopausal and andropausal vasomotor conditions, urinary incontinence, sexual dysfunction, erectile dysfunction, depression, uterine fibroid disease, endometriosis, acne, hirsutism, male contraception, impotence, and in the use as male and female hormone replacement therapy, as a stimulant of hematopoiesis, and as an anabolic agent.

Another aspect of the present invention provides a method for the treatment of hypogonadism, sarcopenia, osteoporosis, muscle wasting, wasting diseases, cancer cachexia, frailty, prostatic hyperplasia, prostate cancer, breast cancer,

menopausal and andropausal vasomotor conditions, urinary incontinence, sexual dysfunction, erectile dysfunction, depression, uterine fibroid disease, endometriosis, acne, hirsutism, male contraception, impotence, and a method of male and female hormone replacement therapy, stimulation of hematopoiesis, and anabolism, comprising the administration of a compound of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Terms are used within their accepted meanings. The following definitions are meant to clarify, but not limit, the terms defined.

As used herein the term "alkyl" refers to a straight or branched chain hydrocarbon, preferably having from one to six carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, and isopentyl.

As used throughout this specification, the preferred number of atoms, such as carbon atoms, will be represented by, for example, the phrase "C_x-C_y alkyl," which refers to an alkyl group, as herein defined, containing the specified number of carbon atoms. Similar terminology will apply for other preferred terms and ranges as well.

As used herein the term "halogen" refers to fluorine, chlorine, bromine, or iodine.

As used herein the term "nitro" refers to a group -NO_2.

As used herein throughout the present specification, the phrase "optionally substituted" or variations thereof denote an optional substitution, including multiple degrees of substitution, with one or more substituent groups. The phrase should not be interpreted so as to be imprecise or duplicative of substitution patterns herein described or depicted specifically. Rather, those of ordinary skill in the art will appreciate that the phrase is included to provide for obvious modifications, which are encompassed within the scope of the appended claims. Preferably, "one or more substitutents" as used herein refers to one or two substituent groups.

The present invention provides compounds of formula (I) or a salt or solvate thereof as herein before defined.

In one embodiment, R^1 and R^2 are both Cl.

In another embodiment, m is 0.

In another embodiment, m is 1.

In another embodiment R^5 is CF_3.

In one embodiment, R^1 is C_{1-2}alkyl, Cl, or CF_3.

In another embodiment, R^2 is H.

In another embodiment, R^1 is methyl.

In a further embodiment, R^3 is H.

In another embodiment, R^4 is H.

In one embodiment, R^5 is nitro, CF3, Br, Cl, or CN. In a further embodiment, R^5 is nitro.

In another embodiment, m is 1 and the R^6 substituent is ortho to the R5 substituent.

While the embodiments and preferred groups for each variable have generally been listed above separately for each variable, compounds of this invention include those in which several of each variable in formula (I) are selected from the aspects or embodiments, and preferred, more preferred, or most preferred groups for each variable. Therefore, this invention is intended to include all combinations of all aspect, embodiments, and preferred, more preferred, and most preferred groups. Not withstanding, embodiments for each variable have been listed separately above, and necessarily include or exclude certain combinations of variables, as described elsewhere in the specification. For example, in the embodiment above wherein R^5 is CF_3, the specific combination of R^1 is methyl, R^2 is F and m is 1, is excluded.

The compounds of the present invention are believed to modulate the function of one or more nuclear hormone receptor(s). Particularly, the compounds of the present invention modulate the androgen receptor ("AR"). The present invention includes compounds that are selective agonists, partial agonists, antagonists, or partial antagonists of the AR. Compounds of the present invention are useful in the treatment of AR-associated diseases and conditions, for example, a disease or condition that is prevented, alleviated, or cured through the modulation of the function or activity of AR. Such modulation may be isolated within certain tissues or widespread throughout the body of the subject being treated.

As used herein, the term "treatment" refers to alleviating the specified condition, eliminating or reducing the symptoms of the condition, slowing or eliminating the progression of the condition and preventing or delaying the initial occurrence of the condition in a subject, or reoccurrence of the condition in a previously afflicted subject.

One embodiment of the present invention provides compounds of the present invention for use in medical therapy. Particularly, the present invention provides for the treatment of disorders mediated by androgenic activity. More particularly, the present invention provides treatment of disorders responsive to tissue-selective anabolic and or androgenic activity. A further embodiment of the invention provides a method of treatment of a mammal suffering from a disorder mediated by androgenic activity, which includes administering to said subject an effective amount of a compound of the present invention.

One embodiment of the present invention is the use of the compounds of the present invention for the treatment of a variety of disorders including, but not limited to, osteoporosis and/or the prevention of reduced bone mass, density, or growth, osteoarthritis, acceleration of bone fracture repair and healing, acceleration of healing in joint replacement, periodontal disease, acceleration of tooth repair or growth, Paget's disease, osteochondrodysplasias, muscle wasting, the maintenance and enhancement of muscle strength and function, frailty or age-related functional decline ("ARFD"), dry eye, sarcopenia, chronic fatigue syndrome, chronic myaligia, acute fatigue syndrome, acceleration of wound healing, maintenance of sensory function, chronic liver disease, AIDS, weightlessness, burn and trauma recovery, thrombocytopenia, short bowel syndrome, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease and ulcerative colitis, obesity, eating disorders including anorexia associated with cachexia or aging, hypercortisolism and Cushing's syndrome, cardiovascular disease or cardiac dysfunction, congestive heart failure, high blood pressure, malignant tumor cells containing the androgen receptor including breast, brain, skin, ovary, bladder, lymphatic, liver, kidney, uterine, pancreas, endometrium, lung, colon, and prostate, prostatic hyperplasia, hirsutism, acne, seborrhea, androgenic alopecia, anemia, hyperpilosity, adenomas and neoplasis of the prostate, hyperinsulinemia, insulin resistance, diabetes, syndrome X, dyslipidemia, menopausal vasomotor conditions, urinary incontinence, artherosclerosis, libido enhancement, sexual dysfunction, depression, nervousness, irritability, stress, reduced mental energy and low self-esteem, improvement of cognitive function, endometriosis, polycystic ovary syndrome, counteracting preeclampsia, premenstral syndrome, contraception, uterine fibroid disease, aortic smooth muscle cell proliferation, male hormone replacement, or ADAM.

A further embodiment of the invention provides a method of treatment of a mammal requiring the treatment of a variety of disorders including, but not limited to,

osteoporosis and/or the prevention of reduced bone mass, density, or growth, osteoarthritis, acceleration of bone fracture repair and healing, acceleration of healing in joint replacement, periodontal disease, acceleration of tooth repair or growth, Paget's disease, osteochondrodysplasias, muscle wasting, the maintenance and enhancement of muscle strength and function, frailty or age-related functional decline ("ARFD"), dry eye, sarcopenia, chronic fatigue syndrome, chronic myaligia, acute fatigue syndrome, acceleration of wound healing, maintenance of sensory function, chronic liver disease, AIDS, weightlessness, burn and trauma recovery, thrombocytopenia, short bowel syndrome, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease and ulcerative colitis, obesity, eating disorders including anorexia associated with cachexia or aging, hypercortisolism and Cushing's syndrome, cardiovascular disease or cardiac dysfunction, congestive heart failure, high blood pressure, malignant tumor cells containing the androgen receptor including breast, brain, skin, ovary, bladder, lymphatic, liver, kidney, uterine, pancreas, endometrium, lung, colon, and prostate, prostatic hyperplasia, hirsutism, acne, seborrhea, androgenic alopecia, anemia, hyperpilosity, adenomas and neoplasis of the prostate, hyperinsulinemia, insulin resistance, diabetes, syndrome X, dyslipidemia, menopausal vasomotor conditions, urinary incontinence, artherosclerosis, libido enhancement, sexual dysfunction, depression, nervousness, irritability, stress, reduced mental energy and low self-esteem, improvement of cognitive function, endometriosis, polycystic ovary syndrome, counteracting preeclampsia, premenstral syndrome, contraception, uterine fibroid disease, aortic smooth muscle cell proliferation, male hormone replacement, or ADAM. Preferably the compounds of the present invention are used as male and female hormone replacement therapy or for the treatment or prevention of hypogonadism, osteoporosis, muscle wasting, wasting diseases, cancer cachexia, frailty, prostatic hyperplasia, prostate cancer, breast cancer, menopausal and andropausal vasomotor conditions, urinary incontinence, sexual dysfunction, erectile dysfunction, depression, uterine fibroid disease, and/or endometriosis, treatment of acne, hirsutism, stimulation of hematopoiesis, male contraception, impotence, and as anabolic agents, which use includes administering to a subject an effective amount of a compound of the present invention. The mammal requiring treatment with a compound of the present invention is typically a human being.

The compounds of the present invention may crystallize in more than one form, a characteristic known as polymorphism, and such polymorphic forms

("polymorphs") are within the scope of formula (I). Polymorphism generally may occur as a response to changes in temperature, pressure, or both. Polymorphism may also result from variations in the crystallization process. Polymorphs may be distinguished by various physical characteristics known in the art such as x-ray diffraction patterns, solubility, and melting point.

Certain of the compounds described herein contain one or more chiral centers, or may otherwise be capable of existing as multiple stereoisomers. The scope of the present invention includes all mixtures of stereoisomers as well as purified enantiomers or enantiomerically/diastereomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by formula (I), as well as any wholly or partially equilibrated mixtures thereof. The present invention also includes the individual isomers of the compounds represented by the formulas above as mixtures with isomers thereof in which one or more chiral centers are inverted. Those skilled in the art will recognize if a stereocenter exists in compounds of formula (I). When a compound is desired as a single enantiomer, such may be obtained by stereospecific synthesis or by resolution of the final product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be effected by any suitable method known in the art. See, for example, *Stereochemistry of Organic Compounds* by E.L. Eliel, S.H. Wilen, and L.N. Mander (Wiley-Interscience, 1994), incorporated by reference with regard to stereochemistry.

Typically, but not absolutely, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Salts of the compounds of the present invention may comprise acid addition salts. Representative salts include acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, monopotassium maleate, mucate, napsylate, nitrate, N-methylglucamine, oxalate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, potassium, salicylate, sodium, stearate, subacetate, succinate, sulfate, tannate, tartrate,

teoclate, tosylate, triethiodide, trimethylammonium, and valerate salts. Other salts, which are not pharmaceutically acceptable, may be useful in the preparation of compounds of this invention and these should be considered to form a further aspect of the invention.

As used herein, the term “solvate” refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I)) and a solvent. Such solvents, for the purpose of the invention, should not interfere with the biological activity of the solute. Non-limiting examples of suitable solvents include, but are not limited to water, methanol, ethanol, and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Non-limiting examples of suitable pharmaceutically acceptable solvents include water, ethanol, and acetic acid. Most preferably the solvent used is water.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought, for instance, by a researcher or clinician. The biological or medical response may be considered a prophylactic response or a treatment response. The term “therapeutically effective amount” means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function. For use in therapy, therapeutically effective amounts of a compound of formula (I) may be administered as the raw chemical. Additionally, the active ingredient may be presented as a pharmaceutical composition.

Accordingly, the invention further provides pharmaceutical compositions that include effective amounts of compounds of the present invention and one or more pharmaceutically acceptable carriers, diluents, or excipients. The compounds of the present invention are as herein described. The carrier(s), diluent(s) or excipient(s) must be acceptable, in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient of the pharmaceutical composition.

In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical formulation including admixing a

compound of the present invention with one or more pharmaceutically acceptable carriers, diluents or excipients.

A therapeutically effective amount of a compound of the present invention will depend upon a number of factors. For example, the species, age, and weight of the recipient, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration are all factors to be considered. The therapeutically effective amount ultimately should be at the discretion of the attendant physician or veterinarian. An effective amount of a compound of the present invention for the treatment of humans suffering from disorders such as frailty, generally, should be in the range of 0.01 to 100 mg/kg body weight of recipient (mammal) per day. More usually the effective amount should be in the range of 0.01 to 30 mg/kg body weight per day. Thus, for a 70 kg adult mammal the actual amount per day would usually be from 0.7 to 700 mg. This amount may be given in a single dose per day or in a number (such as two, three, four, five, or more) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt, solvate, or physiologically functional derivative thereof, may be determined as a proportion of the effective amount of the compound of formula (I) *per se*. Similar dosages should be appropriate for treatment of the other conditions referred to herein.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, as a non-limiting example, 0.1 mg to 1 g of a compound of the present invention, depending on the condition being treated, the route of administration, and the age, weight, and condition of the patient. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Such pharmaceutical formulations may be prepared by any of the methods well known in the pharmacy art.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by an oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal, or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions, each with aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions. For instance, for oral administration in the form of a tablet or capsule, the active drug component may be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Generally, powders are prepared by comminuting the compound to a suitable fine size and mixing with an appropriate pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavorings, preservatives, dispersing agents, and coloring agents may also be present.

Capsules can be made by preparing a powder, liquid, or suspension mixture and encapsulating with gelatin or some other appropriate shell material. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate, or solid polyethylene glycol may be added to the mixture before the encapsulation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate may also be added to improve the availability of the medicament when the capsule is ingested. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents may also be incorporated into the mixture. Examples of suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants useful in these dosage forms include, for example, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

Tablets can be formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant, and pressing into tablets. A powder mixture may be prepared by mixing the compound, suitably comminuted, with a diluent or base as described above. Optional ingredients include binders such as carboxymethylcellulose, aliginates, gelatins, or polyvinyl pyrrolidone, solution retardants such as paraffin, resorption accelerators such as a quaternary salt, and/or absorption agents such as bentonite, kaolin, or dicalcium phosphate. The powder mixture may be wet-granulated with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric

materials, and forcing through a screen. As an alternative to granulating, the powder mixture may be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules may be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention may also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material, and a polish coating of wax may be provided. Dyestuffs may be added to these coatings to distinguish different unit dosages.

Oral fluids such as solutions, syrups, and elixirs may be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups may be prepared, for example, by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions may be formulated generally by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives; flavor additives such as peppermint oil, or natural sweeteners, saccharin, or other artificial sweeteners; and the like may also be added.

Where appropriate, dosage unit formulations for oral administration may be microencapsulated. The formulation may also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The compounds of the present invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes may be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

The compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled.

The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers may include polyvinylpyrrolidone (PVP), pyran copolymer, polyhydroxypropylmethacrylamide–phenol, polyhydroxyethyl-aspartamidephenol, or polyethyleneoxidepolylysine

substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug; for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in *Pharmaceutical Research*, 3(6), 318 (1986), incorporated herein by reference as related to such delivery systems.

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols, or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations may be applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles, and mouthwashes.

Pharmaceutical formulations adapted for nasal administration, where the carrier is a solid, include a coarse powder having a particle size for example in the range 20 to 500 microns. The powder is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or as nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered dose pressurized aerosols, nebulizers, or insufflators.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

In addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question. For example, formulations suitable for oral administration may include flavoring or coloring agents.

The compounds of the present invention or a salt or solvate thereof, may be employed alone or in combination with other therapeutic agents for the treatment of the above-mentioned conditions. The compound(s) of the present invention and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately, administration may occur simultaneously or sequentially, in any order. The amounts of the compound(s) of the present invention and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. The administration in combination of a compound of the present invention with other treatment agents may be in combination by administration concomitantly in: (1) a unitary pharmaceutical composition including both compounds; or (2) separate pharmaceutical compositions each including one of the compounds. Alternatively, the combination may be administered separately in a sequential manner wherein one treatment agent is administered first and the other second or vice versa. Such sequential administration may be close in time or remote in time.

Other potential therapeutic combinations include the compounds of the present invention combined with growth promoting agents, growth hormone secretagogues, growth hormone releasing factor and its analogs, growth hormone and its analogs, somatomedins, alpha-adrenergic agonists, serotonin 5-HT_D agonists, agents that inhibit somatostatin or its release, 5-α-reductase inhibitors, aromatase inhibitors, GnRH agonists or antagonists, parathyroid hormone, bisphosphonates, estrogen, testosterone, SERMs, progesterone receptor agonists or antagonists, and/or with other modulators of nuclear hormone receptors.

The compounds of the present invention may be used in the treatment of a variety of disorders and conditions and, as such, the compounds of the present invention may be used in combination with a variety of other suitable therapeutic agents useful in the treatment of those disorders or conditions. Non-limiting examples include combinations of the present invention with anti-diabetic agents, anti-osteoporosis agents, anti-obesity agents, anti-inflammatory agents, anti-anxiety agents, anti-depressants, anti-hypertensive agents, anti-platelet agents, anti-thrombotic and thrombolytic agents, cardiac glycosides, cholesterol or lipid lowering agents, mineralocorticoid receptor antagonists, phosphodiesterase inhibitors, kinase inhibitors, thyroid mimetics, anabolic agents, viral therapies, cognitive disorder therapies, sleeping disorder therapies, sexual dysfunction therapies, contraceptives, cytotoxic agents, radiation therapy, anti-proliferative agents, and anti-tumor agents. Additionally, the compounds of the present invention may be combined with nutritional supplements such as amino acids, triglycerides, vitamins, minerals, creatine, piloic acid, carnitine, or coenzyme Q10.

In particular, the compounds of the present invention are believed useful, either alone or in combination with other agents, in the treatment of hypogonadism, sarcopenia, osteoporosis, muscle wasting, wasting diseases, cancer cachexia, frailty, prostatic hyperplasia, prostate cancer, breast cancer, menopausal and andropausal vasomotor conditions, urinary incontinence, sexual dysfunction, erectile dysfunction, depression, uterine fibroid disease, endometriosis, acne, hirsutism, male contraception, impotence, and in the use as male and female hormone replacement therapy, as a stimulant of hematopoiesis, and as anabolic agents.

The compounds of this invention may be made by a variety of methods, including well-known standard synthetic methods. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the working Examples.

In all of the schemes described below, protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of synthetic chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T.W. Green and P.G.M. Wuts (1991) *Protecting Groups in Organic Synthesis*, John Wiley & Sons, incorporated by reference with regard to protecting groups). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection of processes as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of formula (I).

Representative compounds according to the current invention include:

9-methyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

7,9-dichloro-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-chloro-*N*-(3,4-dichlorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-chloro-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

7,9-dichloro-*N*-(4-cyanophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-chloro-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-ethyl-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-nitrophenyl)-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(3,4-dichlorophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

7,9-dichloro-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-bromophenyl)-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-ethyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

7,9-dichloro-*N*-(3,4-dichlorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(3,4-dichlorophenyl)-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-bromophenyl)-2,9-dimethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

7,9-dichloro-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-bromophenyl)-9-chloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-methyl-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-bromophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(3,4-dichlorophenyl)-9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-cyanophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

8,9-dichloro-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-chloro-*N*-(4-cyanophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-cyanophenyl)-9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

8,9-dichloro-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-bromophenyl)-8,9-dichloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

ethyl 4-{[(7,9-dichloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)carbonyl]amino}benzoate;

8,9-dichloro-*N*-(3,4-dichlorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

6-fluoro-9-methyl-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-bromophenyl)-6-fluoro-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
N-(4-bromophenyl)-9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
N-(3,4-dichlorophenyl)-6-fluoro-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
N-[4-cyano-3-(trifluoromethyl)phenyl]-9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
8,9-dichloro-*N*-(4-cyanophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
N-(4-bromophenyl)-6,9-dimethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
7,9-dichloro-*N*-(4-fluorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
6,9-dimethyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
6,9-dichloro-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
N-(4-cyanophenyl)-6-fluoro-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
N-[4-cyano-3-(trifluoromethyl)phenyl]-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
N-[4-cyano-3-(trifluoromethyl)phenyl]-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
7,9-dichloro-*N*-(4-methylphenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
6,9-dimethyl-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
2,9-dimethyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
8,9-dichloro-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
N-(4-fluorophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

ethyl 4-{[(9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)carbonyl]amino}benzoate;
9-chloro-*N*-(4-methylphenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
8,9-dichloro-*N*-(4-fluorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
N-(4-fluorophenyl)-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
9-chloro-*N*-(4-fluorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
ethyl 4-{[(9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)carbonyl]amino}benzoate;
9-ethyl-*N*-(4-methylphenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
ethyl 4-{[(8,9-dichloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)carbonyl]amino}benzoate;
8,9-dichloro-*N*-(4-methylphenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
N-(4-bromophenyl)-7,9-dichloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
N-(4-bromo-3-chlorophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
N-(4-bromo-3-fluorophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
N-(4-chlorophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
N-(4-bromo-2-fluorophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
N-(4-bromophenyl)-*N*,9-dimethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
9-methyl-*N*-(3-methylbutyl)-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;
9-methyl-*N*-(4-nitrophenyl)-3-oxo-*N*-{[4-(trifluoromethyl)phenyl]methyl}-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-ethyl-9-methyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-methyl-*N*-(4-nitrophenyl)-3-oxo-*N*-(phenylmethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-methyl-*N*-(4-nitrophenyl)-3-oxo-*N*-propyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-methyl-*N*-(4-nitrophenyl)-3-oxo-*N*-pentyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide; or a salt or solvate thereof.

ABBREVIATIONS

As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, *The Journal of the American Chemical Society or the Journal of Biological Chemistry*. Specifically, the following abbreviations may be used in the examples and throughout the specification:

g (grams); mg (milligrams);
L (liters); ml (milliliters);
µL (microliters); M (molar);
mM (millimolar); Hz (Hertz);
MHz (megahertz); mol (mole(s));
mmol (millimole(s)); RT (room temperature);
eq (equivalent); min (minutes);
hrs (hours); NEt_3 (triethylamine);
TFA (trifluoroacetic acid); THF (tetrahydrofuran);
$CDCl_3$ (deuterated chloroform);
CD_3OD (deuterated methanol);
DMSO (dimethylsulfoxide); d_6-DMSO (hexadeutero-dimethylsulfoxide);
EtOAc (ethyl acetate);
HCl (hydrochloric acid); DCM (methylene chloride);
$CHCl_3$ (chloroform);
DMF (*N*,*N*-dimethylformamide);
AcOH (acetic acid); BOC (*tert*-butyloxycarbonyl);
Me (methyl); Et (ethyl);
EtOH (ethanol); MeOH (methanol);
tBu (tert-butyl); m (multiplet);

ppm (parts-per-million): d (doublet);
t (triplet); q (quartet);
J (coupling constant); dd (doublet of doublets);
ESI (electrospray injection); N (normal);
ES^+ (electrospray ionization in positive mode); m/z (mass-charge ratio);
MS (mass spectrometry); wt% (weight percent);
HPLC (high pressure liquid chromatography); mm (millimeters);
mBar (millibar); NaOH (sodium hydroxide);
HATU (*O*-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate); PS (polystyrene);
DMEM (Dulbecco's modified Eagle's medium); FBS (fetal calf serum);
Pen/Strep (penicillin and streptomycin); PBS (phosphate-buffered saline);
DTT (Dithiothreitol); ip (intraperitoneal);
$MgCl_2$ (Magnesium dichloride) ACN (acetonitrile)
PFA (paraformaldehyde) aq (aqueous)
Et_2O (diethyl ether) Na_2SO_4 (sodium sulfate)
NMR (nuclear magnetic resonance) ^1H (proton)
δ(delta) s (singlet)
br. s. (broad singlet) K_2CO_3 (potassium carbonate)
MOMCl (chloromethylmethyl ether) $MgSO_4$ (magnesium sulfate)
^oC (degrees centigrade) n-BuLi (normal-butyl lithium)
conc. (concentrated)
APCI (atmospheric pressure chemical ionization)
AP^+ (atmospheric pressure chemical ionization in positive mode)
AP^- (atmospheric pressure chemical ionization in negative mode)
Ac_2O (acetic anhydride)
$POCl_3$ (phosphorous oxychloride)
Na_2CO_3 (sodium carbonate)
Hex (hexanes)
DMAP (N,N-dimethylaminopyridine)
Boc_2O (di-*tert*-butyl dicarbonate)
DIEA (diisopropylethylamine)

Unless otherwise indicated, all temperatures are expressed in ^oC (degrees Centigrade).

^{1}H NMR spectra were recorded on a Varian VXR-300, a Varian Unity-300, a Varian Unity-400 instrument, or a General Electric QE-300. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br (broad).

Compounds were analyzed on a Micromass ZMD LC/MS using either Conditions I or Conditions II (below). Retention times were recorded for each compound.

Conditions I: The column was a C18 Phenomenex Luna, 20 x 4.0 mm, 3-micron column 90% H2O, 10% MeOH to 100% MeOH in 3 minutes, holding at 100% MeOH for final 1 minute. Water contained 0.1% v/v formic acid. MeOH contains 0.075% v/v formic acid. The flow rate was 2 ml/min with 3uL of solution injected. Mass spectra were recorded on a Micromass ZMD utilizing electrospray ionization or atmospheric pressure chemical ionization (APCI) switching between positive and negative modes with DAD (Waters 996 DAD) scanning from 210 to 400nm.

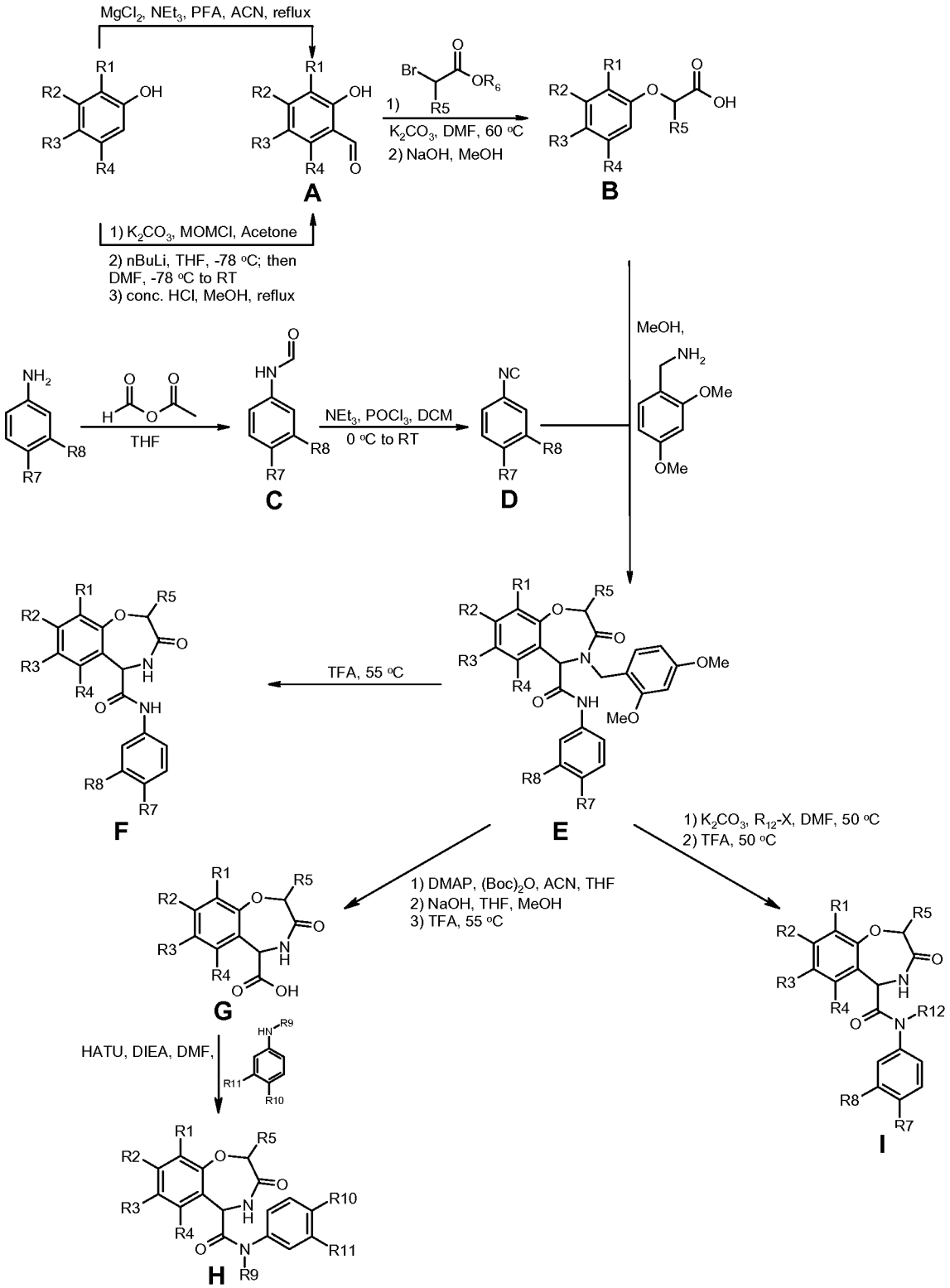
Conditions II: The column was a C18 Phenomenex Luna, 20 x 4.0 mm, 3-micron column 98% H2O, 2% MeOH to 100% MeOH in 3 minutes, holding at 100% MeOH for final 1 minute. Water contained 0.1% v/v formic acid. MeOH contains 0.075% v/v formic acid. The flow rate was 2 ml/min with 3uL of solution injected. Mass spectra were recorded on a Micromass ZMD utilizing electrospray ionization or atmospheric pressure chemical ionization (APCI) switching between positive and negative modes with DAD (Waters 996 DAD) scanning from 210 to 400nm.

Compounds were purified on an Agilent 1100 HPLC using a Phenomenex Luna C-18(2), 75 x 30 mm, 5 micron column; a linear gradient of 10-90% ACN/H2O/0.1% TFA or 30% ACN/H2O/0.1% TFA was run over 11 minutes, followed by 2 minutes at 100% ACN. The flow rate was 35mL/min with DAD at 254nm or 214mm.

The syntheses of compounds of formula (I) proceeded through the key intermediate **E**, which was formed by a 3-component modified Ugi reaction that efficiently assembled the complex 6,7-fused ring system in a single step (Scheme 1). The Ugi reaction precursors, intermediates **B** and **D**, were formed from the alkylation of salicylaldehydes **A** with bromoesters and the dehydration of aniline formamides, respectively. Salicylaldehydes **A** were produced from the corresponding phenols either by Lewis-acid catalyzed formylation using paraformaldehyde or a 3-step ortho-metallation procedure installing the formyl-group

by quenching with DMF. The 2,4-dimethoxybenzyl moiety in intermediate **E** was removed in a TFA-mediated manner to afford products **F**. The aniline-amide portion of intermediate **E** was hydrolyzed via Boc-activation followed by base-mediated hydrolysis of the amide to yield, after the 2,4-dimethoxybenzyl cleavage, carboxylic acid **G**, which underwent smooth conversion to the amide in a HATU-mediated fashion. Secondary amide **E** was also alkylated with alkyl- and benzylic-halides which afforded products **I** after 2,4-dimethoxybenzyl cleavage.

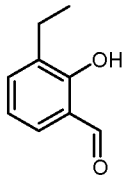
Scheme 1


MgCl2, NEt3, PFA, ACN, reflux
1) K2CO3, DMF, 60 °C
2) NaOH, MeOH
A
B
1) K2CO3, MOMCl, Acetone
2) nBuLi, THF, -78 °C; then DMF, -78 °C to RT
3) conc. HCl, MeOH, reflux
THF
NEt3, POCl3, DCM
0 °C to RT
C
D
MeOH,
TFA, 55 °C
E
F
1) K2CO3, R12-X, DMF, 50 °C
2) TFA, 50 °C
1) DMAP, (Boc)2O, ACN, THF
2) NaOH, THF, MeOH
3) TFA, 55 °C
G
HATU, DIEA, DMF,
H
I

EXAMPLES

Salicylic Aldehyde Synthesis

$MgCl_2$ method

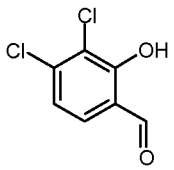


A 3-ethyl-2-hydroxybenzaldehyde (A1)

To a solution of 2-ethylphenol (5g, 41mmol, 1eq) in anhydrous ACN (30ml, 1.4M) was added NEt_3 (22ml, 3.75eq). Anhydrous $MgCl_2$ (6g, 1.5eq) was then added followed by the portionwise addition of PFA (8.3g, 6.75eq). The reaction mixture was heated at reflux for 4hrs, cooled to RT, and poured into a vigorously stirring mixture of 5% HCl (aq, 125ml) and Et_2O (100ml). After stirring for 10min, the phases were separated; the organic fraction was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a quantitative yield of desired product. Because of the difficulties with purification, the product was used without further purification.

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.23 (t, *J*=7.57 Hz, 3 H) 2.69 (q, *J*=7.41 Hz, 2 H) 6.95 (t, *J*=7.57 Hz, 1 H) 7.35 - 7.44 (m, 2 H) 9.88 (s, 1 H) 11.27 (s, 1 H)

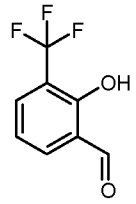
The following compounds were synthesized according to the same general procedure as used for intermediate **A1**:



3,4-dichloro-2-hydroxybenzaldehyde (A2)

From 2,3-dichlorophenol the title compound was afforded.

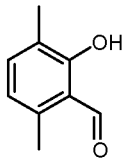
1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.16 (d, *J*=8.55 Hz, 1 H) 7.43 (d, *J*=8.30 Hz, 1 H) 9.87 (s, 1 H) 11.77 (s, 1 H)



2-hydroxy-3-(trifluoromethyl)benzaldehyde (A3)

From 2-trifluoromethylphenol the title compound was afforded as an 80:20 mixture of 2-trifluoromethylphenol : 2-hydroxy-3-(trifluoromethyl)benzaldehyde. The mixture was taken on to the next reaction without purification.

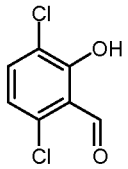
1H NMR (400 MHz, DMSO-d_6) δ ppm 7.20 (t, *J*=8.06 Hz, 1 H) 7.91 (dd, *J*=7.45, 1.83 Hz, 1 H) 8.04 (dd, *J*=7.69, 1.34 Hz, 1 H) 10.09 (s, 1 H) 11.62 (s, 1 H)



2-hydroxy-3,6-dimethylbenzaldehyde (A4)

From 2,5-dimethylphenol the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) δ ppm 2.11 (s, 3 H) 2.53 (s, 3 H) 6.68 (d, *J*=7.57 Hz, 1 H) 7.32 (d, *J*=7.57 Hz, 1 H) 10.26 (s, 1 H) 12.10 (s, 1 H)

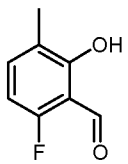


3,6-dichloro-2-hydroxybenzaldehyde (A5)

From 2,5-dichlorophenol the title compound was afforded as a 75:25 mixture of 2,5-dichlorophenol : 3,6-dichloro-2-hydroxybenzaldehyde. The mixture was taken on to the next reaction without purification.

1H NMR (400 MHz, DMSO-d_6) d ppm 7.13 (d, *J*=9.03 Hz, 1 H) 7.76 (d, *J*=9.03 Hz, 1 H) 10.27 (s, 1 H) 12.17 (br. s., 1 H)

o-Metallation method

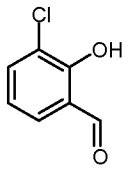


6-fluoro-2-hydroxy-3-methylbenzaldehyde (A6)

To a solution of 2-methyl-5-fluorophenol (0.5g, 3.97mmol, 1eq) in anhydrous acetone (5ml, 0.8M) was added K_2CO_3 (0.22g, 2.5eq) and MOMCl (0.48g, 1.5eq) at

RT. The solution was allowed to stir for 24hrs, at which point, the reaction was partitioned between EtOAc and water. The organic fraction was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield, after silica gel chromatography, 200mg of 4-fluoro-1-methyl-2-{[(methyloxy)methyl]oxy}benzene. To a solution of 4-fluoro-1-methyl-2-{[(methyloxy)methyl]oxy}benzene (200mg, 1.17mmol, 1eq) in anhydrous THF (5ml, 0.25M) cooled to -78°C was added dropwise n-BuLi (0.75ml, 1.6M in hexanes, 1.05eq). After stirring at -78°C, DMF (2ml) was then added and allowed to warm to 0°C over 2hrs. The reaction was then quenched with water (10ml) and the reaction was partitioned between EtOAc and water. The organic fraction was washed with brine, dried over Mg_2SO_4, filtered, and concentrated *in vacuo* to yield, after silica gel chromatography, 90mg of 6-fluoro-3-methyl-2-{[(methyloxy)methyl]oxy}benzaldehyde. To a methanol solution (100ml) of 6-fluoro-3-methyl-2-{[(methyloxy)methyl]oxy}benzaldehyde (1.1g) was added conc. HCl (2 drops) and the reaction was allowed to reflux for 2hrs. After cooling to RT, the reaction was concentrated *in vacuo*. The residue was partitioned between EtOAc and water; the organic fraction was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a quantitative yield of title compound.

The following compounds were synthesized according to the same general procedure as used for intermediate **A6**:

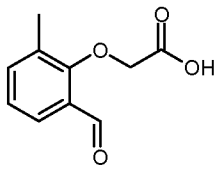


3-chloro-2-hydroxybenzaldehyde (A7)

From 2-chlorophenol the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) □ ppm 7.03 (t, *J*=7.81 Hz, 1 H) 7.60 - 7.75 (m, 2 H) 10.11 (s, 1 H) 11.12 (s, 1 H)

Phenoxyacetic acid- Aldehyde Synthesis



[(2-formyl-6-methylphenyl)oxy]acetic acid (B1)

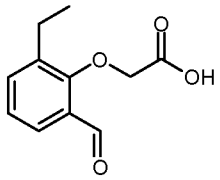
To a solution of 2-hydroxy-3-methylbenzaldehyde (25ml, 0.21mols, 1eq) in anhydrous DMF (600ml, 0.3M) was added K_2CO_3 (32g, 1.1eq) and

methylbromoacetate (19.5ml, 1eq). The reaction mixture was stirred at 60°C for 3hrs. After cooling to RT, the reaction was partitioned between Et_2O/water; the organic fraction was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford a quantitative yield of methyl [(2-formyl-6-methylphenyl)oxy]acetate. The product (0.21mols, 1eq) was dissolved in MeOH (400ml, 0.5M) and to it was added 1N NaOH (410ml, 2eq) and the reaction was stirred at RT for 4hrs. The MeOH was removed *in vacuo*; the residue was partitioned between EtOAc/1N HCl (pH = 2), the organic fraction was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford 29.5g of the title compound.

1H NMR (400 MHz, DMSO-d_6) δ ppm 2.30 (s, 3 H) 4.62 (s, 2 H) 7.19 (t, *J*=7.57 Hz, 1 H) 7.39 - 7.68 (m, 2 H) 10.39 (s, 1 H) 12.95 (br. s., 1 H)

MS (m/z) ESI ES^+ = 195

The following compounds were synthesized according to the same general procedure as used for intermediate **B1**:

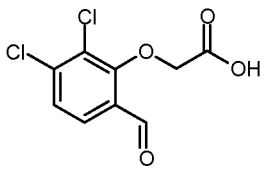


[(2-ethyl-6-formylphenyl)oxy]acetic acid (B2)

From 3-ethyl-2-hydroxybenzaldehyde (A1) the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) δ ppm 1.17 (t, *J*=7.57 Hz, 3 H) 2.69 (q, *J*=7.57 Hz, 2 H) 4.60 (s, 2 H) 7.24 (t, *J*=7.57 Hz, 1 H) 7.49 - 7.67 (m, 2 H) 10.34 (s, 1 H) 12.95 (br. s., 1 H)

MS (m/z) APCI AP^+ = 209

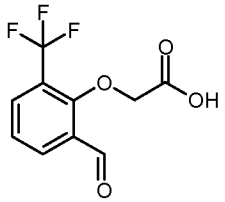


[(2,3-dichloro-6-formylphenyl)oxy]acetic acid (B3)

From 3,4-dichloro-2-hydroxybenzaldehyde (A2) the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) δ ppm 1.17 (t, *J*=7.57 Hz, 3 H) 2.69 (q, *J*=7.57 Hz, 2 H) 4.60 (s, 2 H) 7.24 (t, *J*=7.57 Hz, 1 H) 7.49 - 7.67 (m, 2 H) 10.34 (s, 1 H) 12.95 (br. s., 1 H)

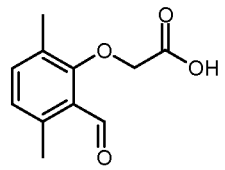
MS (m/z) APCI AP^+ = 249



{[2-formyl-6-(trifluoromethyl)phenyl]oxy}acetic acid (B4)

From an 80:20 mixture of 2-trifluoromethylphenol : 2-hydroxy-3-(trifluoromethyl)benzaldehyde, a 90:10 mixture of {[2-(trifluoromethyl)phenyl]oxy}acetic acid : {[2-formyl-6-(trifluoromethyl)phenyl]oxy}acetic acid was afforded. The mixture was taken on to the next reaction without purification.

1H NMR (400 MHz, DMSO-d_6) δ ppm 4.68 (s, 2 H) 7.52 (t, *J*=7.69 Hz, 1 H) 8.01 (dd, *J*=7.81, 1.71 Hz, 1 H) 8.07 (dd, *J*=7.81, 1.71 Hz, 1 H) 13.11 (br. s., 1 H)

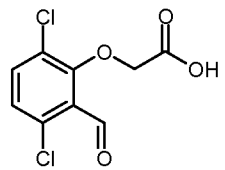


[(2-formyl-3,6-dimethylphenyl)oxy]acetic acid (B5)

From 2-hydroxy-3,6-dimethylbenzaldehyde (A4) the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) δ ppm 2.24 (s, 3 H) 2.43 (s, 3 H) 4.55 (s, 2 H) 6.98 (d, *J*=7.81 Hz, 1 H) 7.37 (d, *J*=7.81 Hz, 1 H) 10.54 (s, 1 H) 13.03 (br. s., 1 H)

MS (m/z) APCI AP^+ = 209

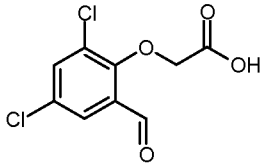


[(3,6-dichloro-2-formylphenyl)oxy]acetic acid (B6)

From a 75:25 mixture of 2,5-dichlorophenol : 3,6-dichloro-2-hydroxybenzaldehyde, a 75:25 mixture of [(2,5-dichlorophenyl)oxy]acetic acid: [(3,6-dichloro-2-formylphenyl)oxy]acetic acid was afforded. The mixture was taken on to the next reaction without purification.

1H NMR (400 MHz, DMSO-d_6) δ ppm 4.72 (s, 2 H) 7.39 (d, *J*=8.79 Hz, 1 H) 7.76 (d, *J*=8.79 Hz, 1 H) 10.38 (s, 1 H) 13.03 (br. s., 1 H)

MS (m/z) ESI ES^+ = 249

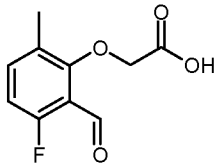


[(2,4-dichloro-6-formylphenyl)oxy]acetic acid (B7)

From 3,5-dichloro-2-hydroxybenzaldehyde the title compound was afforded.

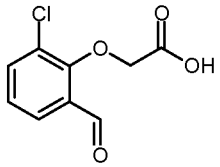
1H NMR (400 MHz, DMSO-d_6) δ ppm 4.80 (s, 2 H) 7.64 (d, *J*=2.69 Hz, 1 H) 8.01 (d, *J*=2.69 Hz, 1 H) 10.35 (s, 1 H) 13.15 (br. s., 1 H)

MS (m/z) APCI AP^+ = 249



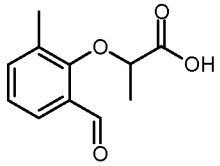
[(3-fluoro-2-formyl-6-methylphenyl)oxy]acetic acid (B8)

From 6-fluoro-2-hydroxy-3-methylbenzaldehyde (A6) the title compound was afforded.



[(2-chloro-6-formylphenyl)oxy]acetic acid (B9)

From 3-chloro-2-hydroxybenzaldehyde (A7) the title compound was afforded.



2-[(2-formyl-6-methylphenyl)oxy]propanoic acid (B10)

To a solution of 2-hydroxy-3-methylbenzaldehyde (1g, 7.5mmols, 1eq) in anhydrous DMF (25ml, 0.3M) was added K_2CO_3 (1.5g, 1.1eq) and methyl 2-bromopropanoate (0.93ml, 1.1eq). The reaction mixture was stirred at 60 °C overnight. After cooling to RT, the reaction was partitioned between Et_2O/water; the organic fraction was washed with water 2x, brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford 1.6g of methyl 2-[(2-formyl-6-methylphenyl)oxy]propanoate.

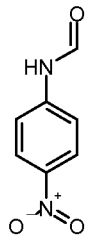
1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.61 (d, *J*=6.84 Hz, 3 H) 2.34 (s, 3 H) 3.71 (s, 3 H) 4.61 (q, *J*=6.75 Hz, 1 H) 7.14 (t, *J*=7.57 Hz, 1 H) 7.42 (dd, *J*=7.45, 1.83 Hz, 1 H) 7.68 (dd, *J*=7.81, 1.71 Hz, 1 H) 10.44 (s, 1 H)

The product (7.2mmols, 1eq) was dissolved in THF (20ml) and MeOH (5ml) and to it was added 5N NaOH (10ml, 5eq) and the reaction was stirred at 60 °C overnight. The volatiles were removed *in vacuo*; the residue was partitioned between EtOAc/1N HCl (pH = 3), the organic fraction was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the title compound in quantitative yield.

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.55 (d, *J*=6.84 Hz, 3 H) 2.10 (s, 3 H) 4.72 (q, *J*=6.84 Hz, 1 H) 7.21 (t, *J*=7.57 Hz, 1 H) 7.47 (d, *J*=7.57 Hz, 1 H) 7.67 (dd, *J*=7.81, 1.46 Hz, 1 H) 10.24 (s, 1 H)

MS (m/z) APCI AP^+ = 209

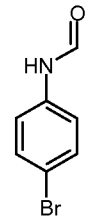
Formamide Synthesis



(4-nitrophenyl)formamide (C1)

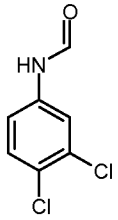
To Ac_2O (49.2ml, 1eq) cooled to 0 °C was added 95% formic acid (25.61ml, 1.25eq). After the addition was complete, the reaction was allowed to warm to RT and subsequently heated to 55 °C for 3hrs. After cooling to RT, anhydrous THF (15ml) was added and this mixture (10ml) was then added to solution of 4-nitroaniline (3g, 22mmol, 1eq) in anhydrous THF (20ml). After stirring overnight the volatiles were removed under reduced pressure and the crude product (3.4g) was used without purification.

The following compounds were synthesized according to the same general procedure as used for intermediate **C1**:



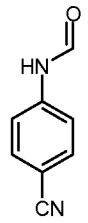
(4-bromophenyl)formamide (C2)

From 4-bromoaniline the title compound was afforded.



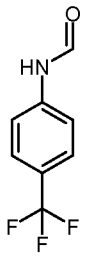
(3,4-dichlorophenyl)formamide (C3)

From 3,4-dichloroaniline the title compound was afforded.



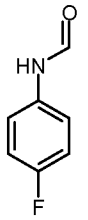
(4-cyanophenyl)formamide (C4)

From 4-cyanoaniline the title compound was afforded.



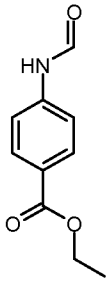
[4-(trifluoromethyl)phenyl]formamide (C5)

From 4-trifluoromethylaniline the title compound was afforded.



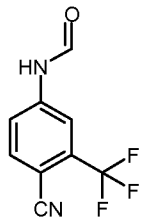
(4-fluorophenyl)formamide (C6)

From 4-fluoroaniline the title compound was afforded.



ethyl 4-(formylamino)benzoate (C7)

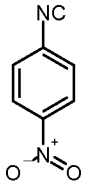
From ethyl 4-aminobenzoate the title compound was afforded.



[4-cyano-3-(trifluoromethyl)phenyl]formamide (C8)

From 4-amino-2-(trifluoromethyl)benzonitrile the title compound was afforded.

Isonitrile Formation: Formamide Dehydration

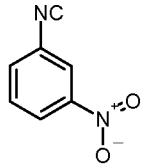


1-isocyano-4-nitrobenzene (D1)

To (4-nitrophenyl)formamide (C1) (2.0g, 12.04mmol, 1eq) dissolved in anhydrous DCM (100ml, 0.12M) in a 125-ml jar was added NEt_3 and shaken on an orbital shaker for 3hrs. After cooling to 0 °C a solution of $POCl_3$ (1.65ml, 1.5eq) in anhydrous DCM (10ml) was slowly added and shaken at RT for 2hrs. Saturated Na_2CO_3 (20ml) and water (10ml) was added and the reaction was shaken vigorously for 3hrs, periodically venting the vessel. The phases were separated and the organic fraction was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford 1.6g of the title compound after silica gel chromatography (10% to 30% EtOAc/Hex). Due to the unstable nature of isonitriles the product was stored at 0 °C.

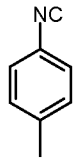
1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.57 (d, *J*=9.03 Hz, 2 H) 8.30 (d, *J*=9.03 Hz, 2 H)

The following compounds were synthesized and stored according to the same general procedure as used for intermediate **D1**:



1-isocyano-3-nitrobenzene (D2)

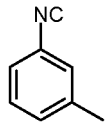
From (3-nitrophenyl)formamide the title compound was afforded.



1-isocyano-4-methylbenzene (D3)

From (4-methylphenyl)formamide the title compound was afforded.

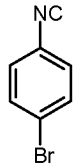
1H NMR (400 MHz, CHLOROFORM-*d*) □ ppm 2.36 (s, 3 H) 7.12 - 7.21 (m, 2 H) 7.21 - 7.30 (m, 2 H)



1-isocyano-3-methylbenzene (D4)

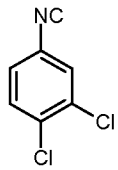
From (3-methylphenyl)formamide the title compound was afforded.

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.35 (s, 3 H) 7.13 - 7.22 (m, 3 H) 7.23 - 7.30 (m, 1 H)



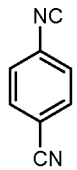
1-bromo-4-isocyanobenzene (D5)

From (4-bromophenyl)formamide (C2) the title compound was afforded.



1,2-dichloro-4-isocyanobenzene (D6)

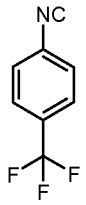
From (3,4-dichlorophenyl)formamide (C3) the title compound was afforded.



4-isocyanobenzonitrile (D7)

From (4-cyanophenyl)formamide (C4) the title compound was afforded.

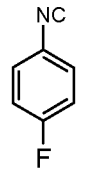
1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.51 (d, *J*=8.30 Hz, 2 H) 7.68 (d, *J*=8.55 Hz, 2 H)



1-isocyano-4-(trifluoromethyl)benzene (D8)

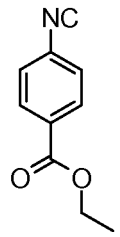
From [4-(trifluoromethyl)phenyl]f`ormamide (C5) the title compound was afforded.

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.50 (d, *J*=8.30 Hz, 1 H) 7.69 - 7.76 (m, 2 H)



1-fluoro-4-isocyanobenzene (D9)

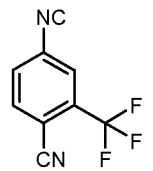
From (4-fluorophenyl)formamide (C6) the title compound was afforded.



ethyl 4-isocyanobenzoate (D10)

From ethyl 4-(formylamino)benzoate (C7) the title compound was afforded.

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.39 (t, *J*=7.20 Hz, 3 H) 4.39 (q, *J*=7.08 Hz, 2 H) 7.43 (d, *J*=8.55 Hz, 2 H) 8.08 (d, *J*=8.55 Hz, 2 H)

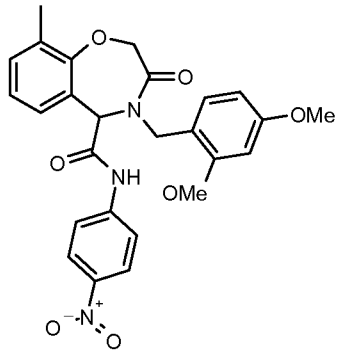


4-isocyano-2-(trifluoromethyl)benzonitrile (D11)

From [4-cyano-3-(trifluoromethyl)phenyl]formamide (C8) the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) δ ppm 8.14 (dd, *J*=8.18, 2.08 Hz, 1 H) 8.29 - 8.37 (m, 2 H)

Ugi Coupling

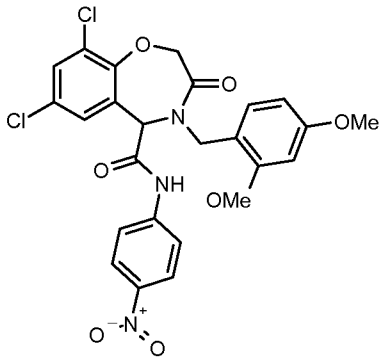


4-{[2,4-bis(methyloxy)phenyl]methyl}-9-methyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E1)

To a solution of [(2-formyl-6-methylphenyl)oxy]acetic acid (B1) (29.5g, 0.15mols, 1eq) in MeOH (500ml) was added 2,4-dimethoxybenzylamine (22.84ml, 1eq). Immediately after the addition is complete a solution of 1-isocyano-4-nitrobenzene(D1) (22.5g, 1eq) in anhydrous THF (100ml) was added all at once. The reaction was allowed to stir at RT overnight, at which point, an off-white solid precipitated. The mixture was filtered to yield 36g of the title compound. During the filtration/drying of the solid, an additional 3g of product was obtained by filtration of the mother liquor. The mother liquor was then concentrated *in vacuo* until additional product began to precipitate. The mother liquor was allowed to sit at RT which yielded an additional 6.5g of product for a total yield of 45.5g (61%) of the title compound.

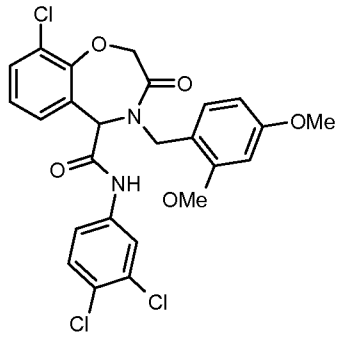
1H NMR (400 MHz, DMSO-d_6) δ ppm 2.14 (s, 3 H) 3.69 (s, 3 H) 3.71 (s, 3 H) 4.16 (d, *J*=14.89 Hz, 1 H) 4.27 (d, *J*=16.36 Hz, 1 H) 4.74 (d, *J*=16.36 Hz, 1 H) 4.94 (d, *J*=14.89 Hz, 1 H) 5.10 - 5.18 (m, 1 H) 6.41 (dd, *J*=8.30, 2.44 Hz, 1 H) 6.51 (d, *J*=2.44 Hz, 1 H) 6.95 - 7.11 (m, 3 H) 7.21 (dd, *J*=7.08, 2.20 Hz, 1 H) 7.77 (d, *J*=9.28 Hz, 2 H) 8.17 (d, *J*=9.52 Hz, 2 H) 9.98 (s, 1 H)

The following compounds were synthesized according to the same general procedure as used for **E1**. If no precipitate formed during the Ugi reaction, then the reaction was simply concentrated and carried on to the next reaction without purification or characterization:



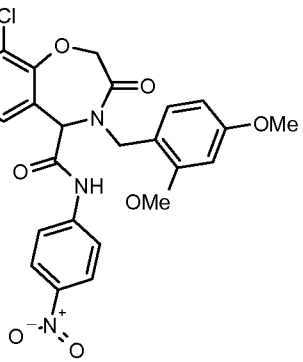
4-{[2,4-bis(methyloxy)phenyl]methyl}-7,9-dichloro-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E2)

From [(2,4-dichloro-6-formylphenyl)oxy]acetic acid (B7) and 1-isocyano-4-nitrobenzene (D1) the title compound was afforded.



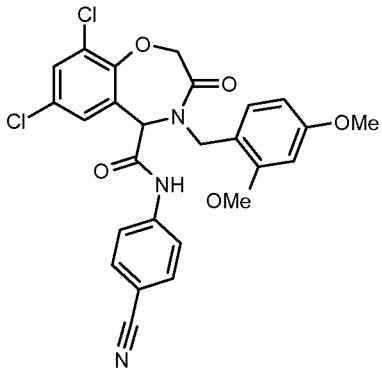
4-{[2,4-bis(methyloxy)phenyl]methyl}-9-chloro-*N*-(3,4-dichlorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E3)

From [(2-chloro-6-formylphenyl)oxy]acetic acid (B9) and 1,2-dichloro-4-isocyanobenzene (D6) the title compound was afforded.



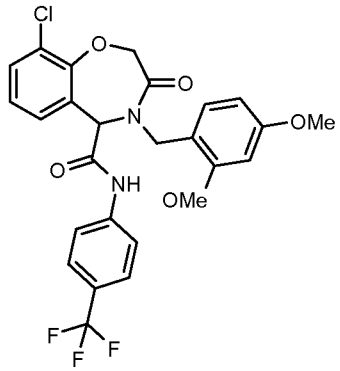
4-{[2,4-bis(methyloxy)phenyl]methyl}-9-chloro-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E4)

From [(2-chloro-6-formylphenyl)oxy]acetic acid (B9) and 1-isocyano-4-nitrobenzene (D1) the title compound was afforded.



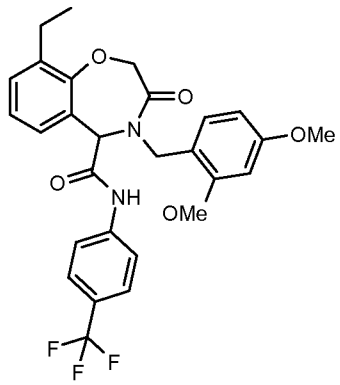
4-{[2,4-bis(methyloxy)phenyl]methyl}-7,9-dichloro-*N*-(4-cyanophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E5)

From [(2,4-dichloro-6-formylphenyl)oxy]acetic acid (B7) and 4-isocyanobenzonitrile (D7) the title compound was afforded.



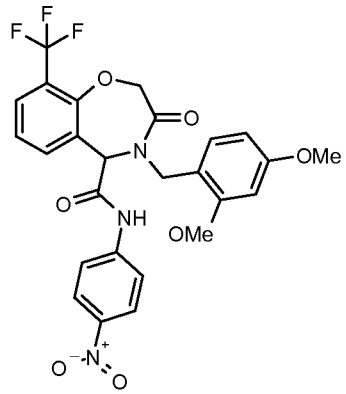
4-{[2,4-bis(methyloxy)phenyl]methyl}-9-chloro-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E6)

From [(2-chloro-6-formylphenyl)oxy]acetic acid (B9) and 1-isocyano-4-(trifluoromethyl)benzene (D8) the title compound was afforded.



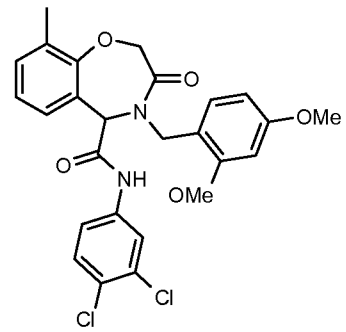
4-{[2,4-bis(methyloxy)phenyl]methyl}-9-ethyl-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E7)

From [(2-ethyl-6-formylphenyl)oxy]acetic acid (B2) and 1-isocyano-4-(trifluoromethyl)benzene (D8) the title compound was afforded.



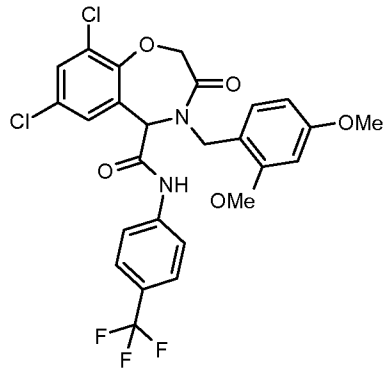
4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-nitrophenyl)-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E8)

From {[2-formyl-6-(trifluoromethyl)phenyl]oxy}acetic acid (B4) and 1-isocyano-4-nitrobenzene (D1) the title compound was afforded.



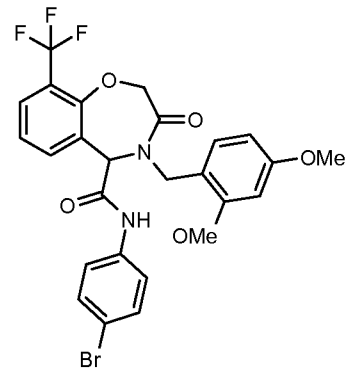
4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(3,4-dichlorophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E9)

From [(2-formyl-6-methylphenyl)oxy]acetic acid (B1) and 1,2-dichloro-4-isocyanobenzene (D6) the title compound was afforded.



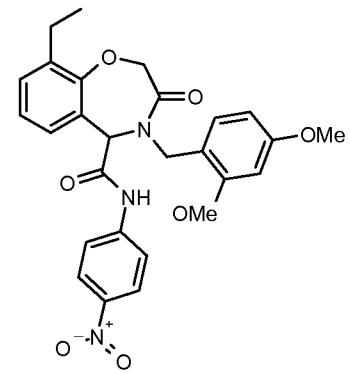
4-{[2,4-bis(methyloxy)phenyl]methyl}-7,9-dichloro-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E10)

From [(2,4-dichloro-6-formylphenyl)oxy]acetic acid (B7) and 1-isocyano-4-(trifluoromethyl)benzene (D8) the title compound was afforded.



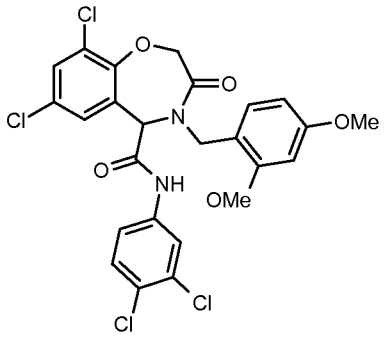
4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-bromophenyl)-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E11)

From {[2-formyl-6-(trifluoromethyl)phenyl]oxy}acetic acid (B4) and 1-bromo-4-isocyanobenzene (D5) the title compound was afforded.



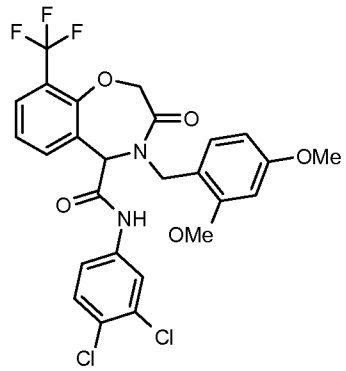
4-{[2,4-bis(methyloxy)phenyl]methyl}-9-ethyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E12)

From [(2-ethyl-6-formylphenyl)oxy]acetic acid (B2) and 1-isocyano-4-nitrobenzene (D1) the title compound was afforded.



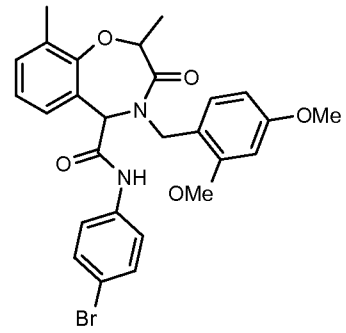
4-{[2,4-bis(methyloxy)phenyl]methyl}-7,9-dichloro-*N*-(3,4-dichlorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E13)

From [(2,4-dichloro-6-formylphenyl)oxy]acetic acid (B7) and 1,2-dichloro-4-isocyanobenzene (D6) the title compound was afforded.



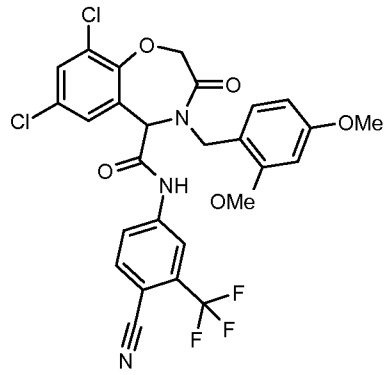
4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(3,4-dichlorophenyl)-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E14)

From {[2-formyl-6-(trifluoromethyl)phenyl]oxy}acetic acid (B4) and 1,2-dichloro-4-isocyanobenzene (D6) the title compound was afforded.



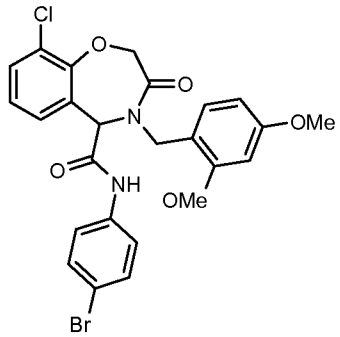
4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-bromophenyl)-2,9-dimethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E15)

From 2-[(2-formyl-6-methylphenyl)oxy]propanoic acid (B10) and 1-bromo-4-isocyanobenzene (D5) the title compound was afforded.



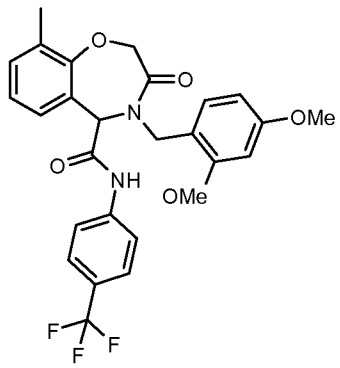
4-{[2,4-bis(methyloxy)phenyl]methyl}-7,9-dichloro-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E16)

From [(2,4-dichloro-6-formylphenyl)oxy]acetic acid (B7) and 4-isocyano-2-(trifluoromethyl)benzonitrile (D11) the title compound was afforded.



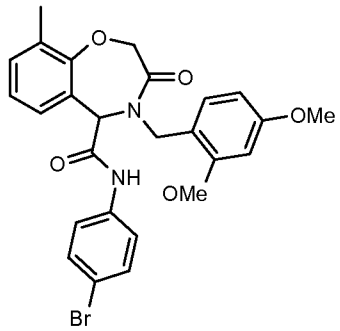
4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-bromophenyl)-9-chloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E17)

From [(2-chloro-6-formylphenyl)oxy]acetic acid (B9) and 1-bromo-4-isocyanobenzene (D5) the title compound was afforded.



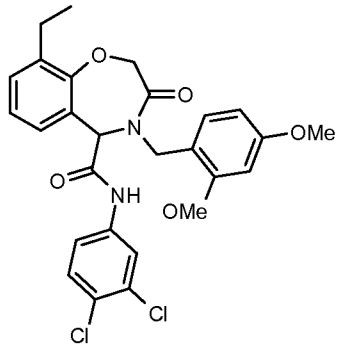
4-{[2,4-bis(methyloxy)phenyl]methyl}-9-methyl-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E18)

From [(2-formyl-6-methylphenyl)oxy]acetic acid (B1) and 1-isocyano-4-(trifluoromethyl)benzene (D8) the title compound was afforded.



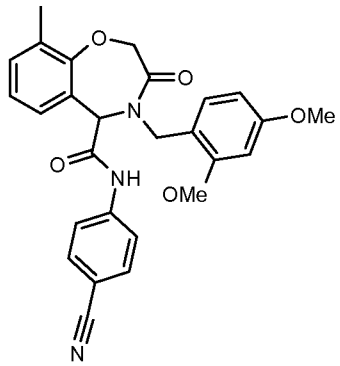
4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-bromophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E19)

From [(2-formyl-6-methylphenyl)oxy]acetic acid (B1) and 1-bromo-4-isocyanobenzene (D5) the title compound was afforded.



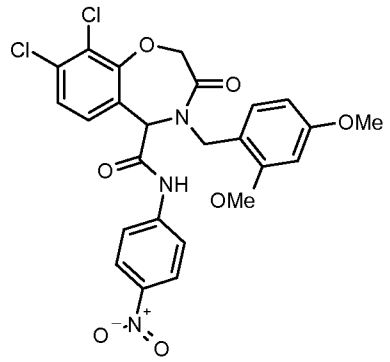
4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(3,4-dichlorophenyl)-9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E20)

From [(2-ethyl-6-formylphenyl)oxy]acetic acid (B2) and 1,2-dichloro-4-isocyanobenzene (D6) the title compound was afforded.



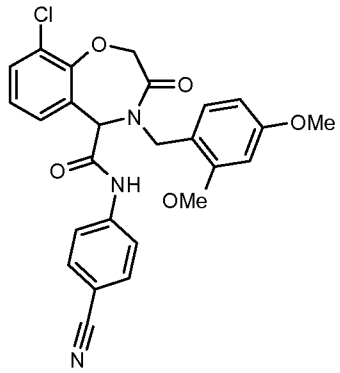
4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-cyanophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E21)

From [(2-formyl-6-methylphenyl)oxy]acetic acid (B1) and 4-isocyanobenzonitrile (D7) the title compound was afforded.



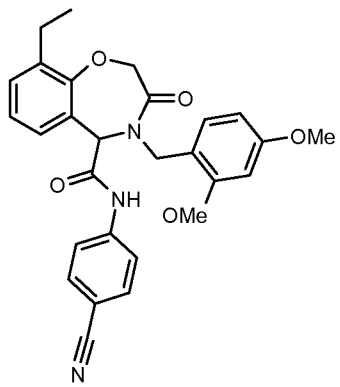
4-{[2,4-bis(methyloxy)phenyl]methyl}-8,9-dichloro-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E22)

From [(2,3-dichloro-6-formylphenyl)oxy]acetic acid (B3) and 1-isocyano-4-nitrobenzene (D1) the title compound was afforded.



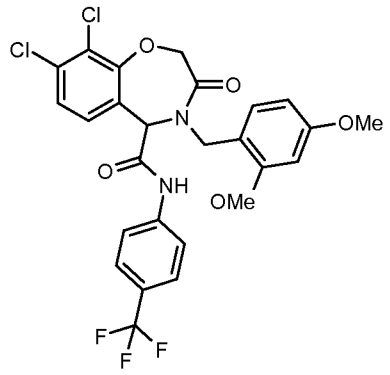
4-{[2,4-bis(methyloxy)phenyl]methyl}-9-chloro-*N*-(4-cyanophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E23)

From [(2-chloro-6-formylphenyl)oxy]acetic acid (B9) and 4-isocyanobenzonitrile (D7) the title compound was afforded.



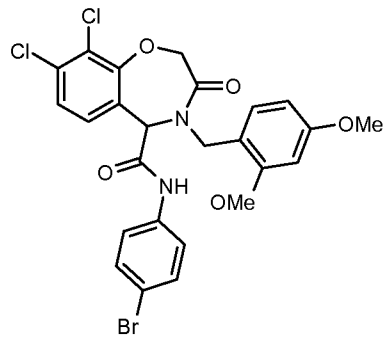
4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-cyanophenyl)-9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E24)

From [(2-ethyl-6-formylphenyl)oxy]acetic acid (B2) and 4-isocyanobenzonitrile (D7) the title compound was afforded.



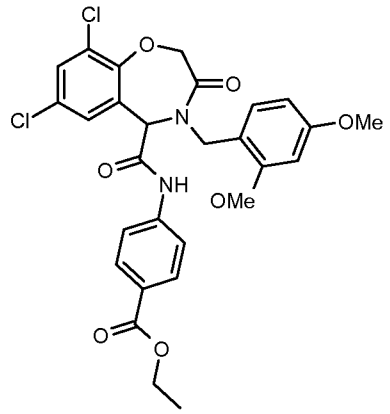
4-{[2,4-bis(methyloxy)phenyl]methyl}-8,9-dichloro-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E25)

From [(2,3-dichloro-6-formylphenyl)oxy]acetic acid (B3) and 1-isocyano-4-(trifluoromethyl)benzene (D8) the title compound was afforded.



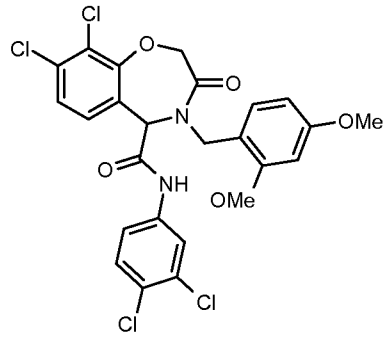
4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-bromophenyl)-8,9-dichloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E26)

From [(2,3-dichloro-6-formylphenyl)oxy]acetic acid (B3) and 1-bromo-4-isocyanobenzene (D5) the title compound was afforded.



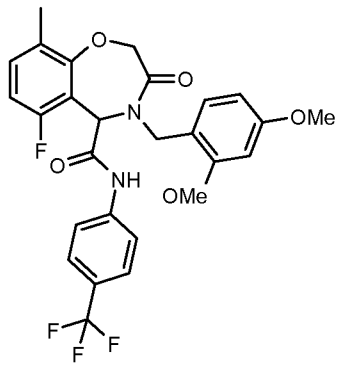
ethyl 4-{[(4-{[2,4-bis(methyloxy)phenyl]methyl}-7,9-dichloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)carbonyl]amino}benzoate (E27)

From [(2,4-dichloro-6-formylphenyl)oxy]acetic acid (B7) and ethyl 4-isocyanobenzoate (D10) the title compound was afforded.



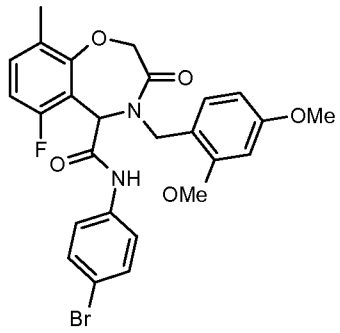
4-{[2,4-bis(methyloxy)phenyl]methyl}-8,9-dichloro-*N*-(3,4-dichlorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E28)

From [(2,3-dichloro-6-formylphenyl)oxy]acetic acid (B3) and 1,2-dichloro-4-isocyanobenzene (D6) the title compound was afforded.



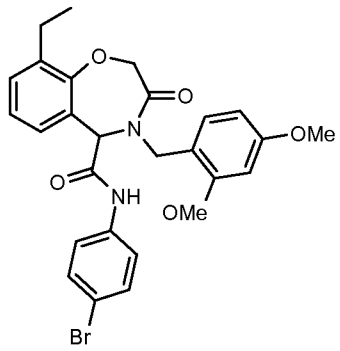
4-{[2,4-bis(methyloxy)phenyl]methyl}-6-fluoro-9-methyl-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E29)

From [(3-fluoro-2-formyl-6-methylphenyl)oxy]acetic acid (B8) and 1-isocyano-4-(trifluoromethyl)benzene (D8) the title compound was afforded.



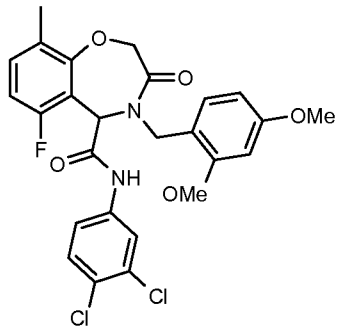
4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-bromophenyl)-6-fluoro-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E30)

From [(3-fluoro-2-formyl-6-methylphenyl)oxy]acetic acid (B8) and 1-bromo-4-isocyanobenzene (D5) the title compound was afforded.



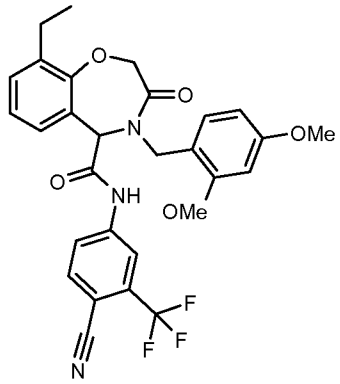
4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-bromophenyl)-9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E31)

From [(2-ethyl-6-formylphenyl)oxy]acetic acid (B2) and 1-bromo-4-isocyanobenzene (D5) the title compound was afforded.



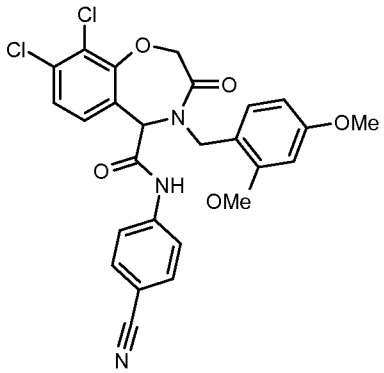
4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(3,4-dichlorophenyl)-6-fluoro-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E32)

From [(3-fluoro-2-formyl-6-methylphenyl)oxy]acetic acid (B8) and 1,2-dichloro-4-isocyanobenzene (D6) the title compound was afforded.



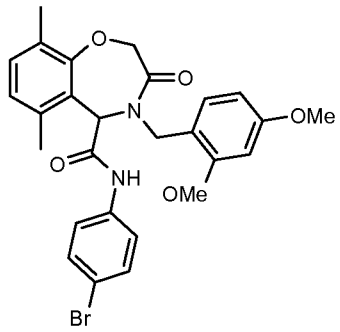
4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E33)

From [(2-ethyl-6-formylphenyl)oxy]acetic acid (B2) and 4-isocyano-2-(trifluoromethyl)benzonitrile (D11) the title compound was afforded.



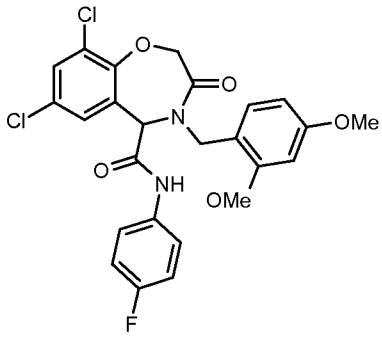
4-{[2,4-bis(methyloxy)phenyl]methyl}-8,9-dichloro-*N*-(4-cyanophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E34)

From [(2,3-dichloro-6-formylphenyl)oxy]acetic acid (B3) and 4-isocyanobenzonitrile (D7) the title compound was afforded.



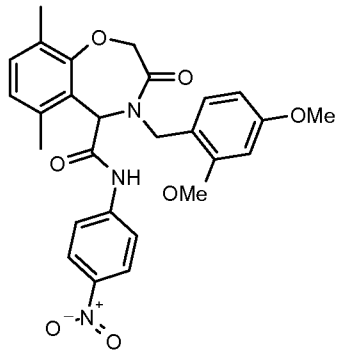
4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-bromophenyl)-6,9-dimethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E35)

From [(2-formyl-3,6-dimethylphenyl)oxy]acetic acid (B5) and 1-bromo-4-isocyanobenzene (D5) the title compound was afforded.



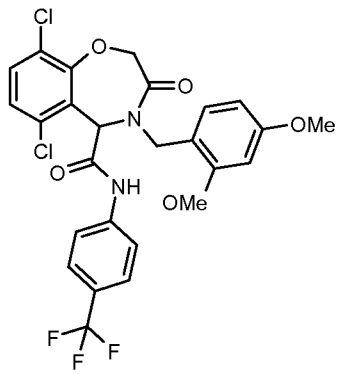
4-{[2,4-bis(methyloxy)phenyl]methyl}-7,9-dichloro-*N*-(4-fluorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E36)

From [(2,4-dichloro-6-formylphenyl)oxy]acetic acid (B7) and 1-fluoro-4-isocyanobenzene (D9) the title compound was afforded.



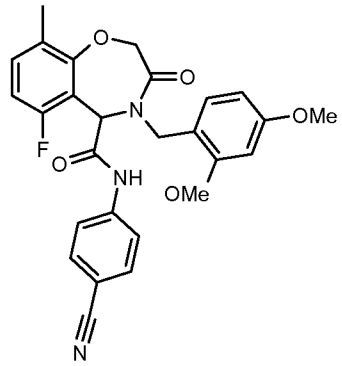
4-{[2,4-bis(methyloxy)phenyl]methyl}-6,9-dimethyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E37)

From [(2-formyl-3,6-dimethylphenyl)oxy]acetic acid (B5) and 1-isocyano-4-nitrobenzene (D1) the title compound was afforded.



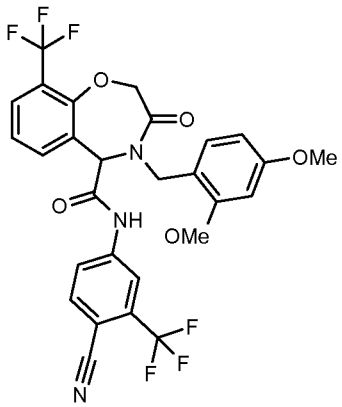
4-{[2,4-bis(methyloxy)phenyl]methyl}-6,9-dichloro-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E38)

From [(3,6-dichloro-2-formylphenyl)oxy]acetic acid (B6) and 1-isocyano-4-(trifluoromethyl)benzene (D8) the title compound was afforded.



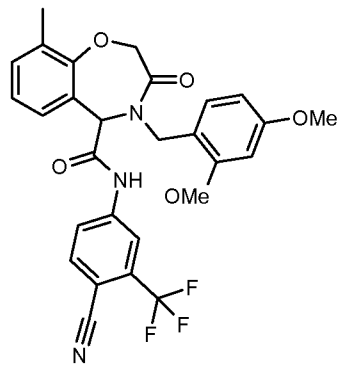
4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-cyanophenyl)-6-fluoro-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E39)

From [(3-fluoro-2-formyl-6-methylphenyl)oxy]acetic acid (B8) and 4-isocyanobenzonitrile (D7) the title compound was afforded.



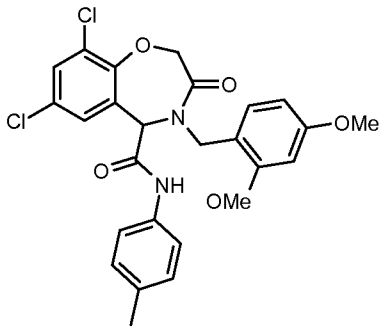
4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E40)

From {[2-formyl-6-(trifluoromethyl)phenyl]oxy}acetic acid (B4) and 4-isocyano-2-(trifluoromethyl)benzonitrile (D11) the title compound was afforded.



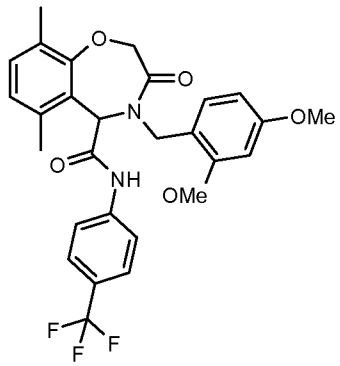
4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E41)

From 2-[(2-formyl-6-methylphenyl)oxy]propanoic acid (B10) and 4-isocyano-2-(trifluoromethyl)benzonitrile (D11) the title compound was afforded.



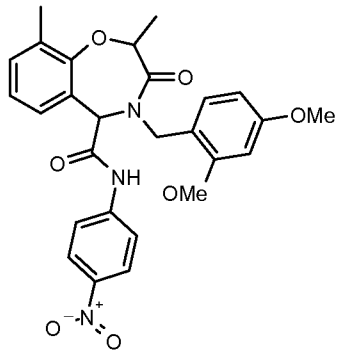
4-{[2,4-bis(methyloxy)phenyl]methyl}-7,9-dichloro-*N*-(4-methylphenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E42)

From [(2,4-dichloro-6-formylphenyl)oxy]acetic acid (B7) and 1-isocyano-4-methylbenzene (D3) the title compound was afforded.



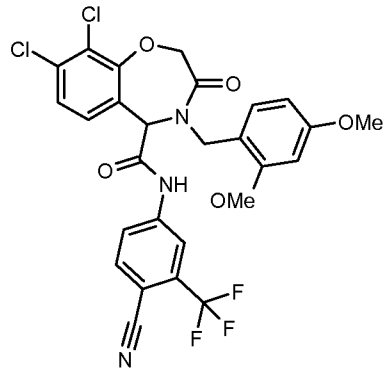
4-{[2,4-bis(methyloxy)phenyl]methyl}-6,9-dimethyl-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E43)

From [(2-formyl-3,6-dimethylphenyl)oxy]acetic acid (B5) and 1-isocyano-4-(trifluoromethyl)benzene (D8) the title compound was afforded.



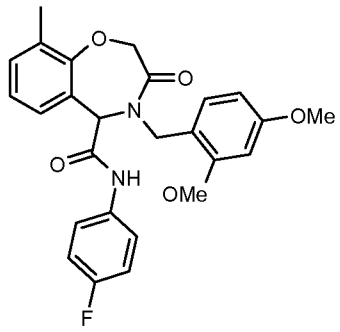
4-{[2,4-bis(methyloxy)phenyl]methyl}-2,9-dimethyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E44)

From 2-[(2-formyl-6-methylphenyl)oxy]propanoic acid (B10) and 1-isocyano-4-nitrobenzene (D1) the title compound was afforded.



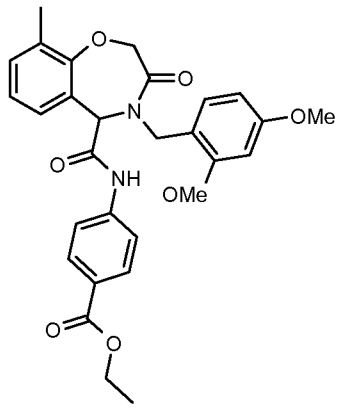
4-{[2,4-bis(methyloxy)phenyl]methyl}-8,9-dichloro-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E45)

From [(2,3-dichloro-6-formylphenyl)oxy]acetic acid (B3) and 4-isocyano-2-(trifluoromethyl)benzonitrile (D11) the title compound was afforded.



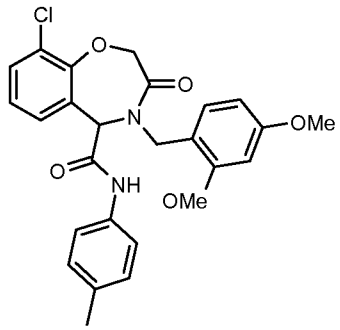
4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-fluorophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E46)

From [(2-formyl-6-methylphenyl)oxy]acetic acid (B1) and 1-fluoro-4-isocyanobenzene (D9) the title compound was afforded.



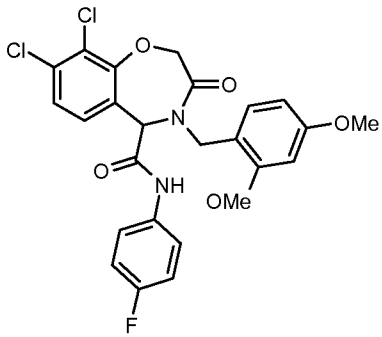
ethyl 4-{[(4-{[2,4-bis(methyloxy)phenyl]methyl}-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)carbonyl]amino}benzoate (E47)

From [(2-formyl-6-methylphenyl)oxy]acetic acid (B1) and ethyl 4-isocyanobenzoate (D10) the title compound was afforded.



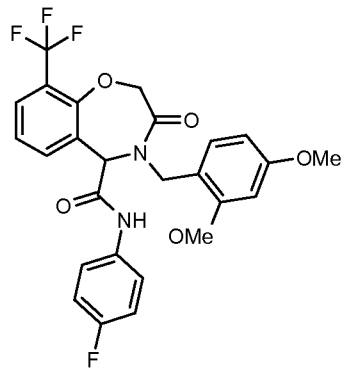
4-{[2,4-bis(methyloxy)phenyl]methyl}-9-chloro-*N*-(4-methylphenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E48)

From [(2-chloro-6-formylphenyl)oxy]acetic acid (B9) and 1-isocyano-4-methylbenzene (D3) the title compound was afforded.



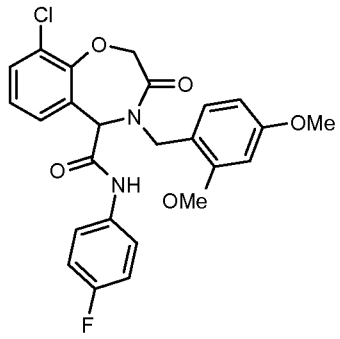
4-{[2,4-bis(methyloxy)phenyl]methyl}-8,9-dichloro-*N*-(4-fluorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E49)

From [(2,3-dichloro-6-formylphenyl)oxy]acetic acid (B3) and 1-fluoro-4-isocyanobenzene (D9) the title compound was afforded.



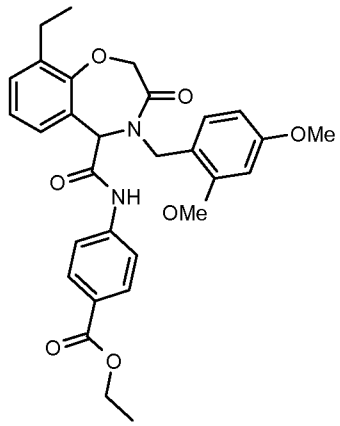
4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-fluorophenyl)-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E50)

From {[2-formyl-6-(trifluoromethyl)phenyl]oxy}acetic acid (B4) and 1-fluoro-4-isocyanobenzene (D9) the title compound was afforded.



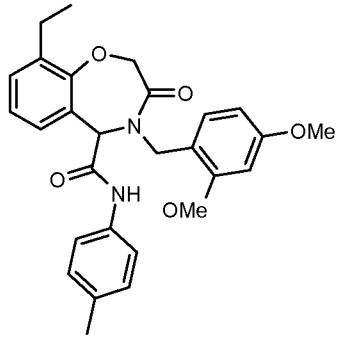
4-{[2,4-bis(methyloxy)phenyl]methyl}-9-chloro-*N*-(4-fluorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E51)

From [(2-chloro-6-formylphenyl)oxy]acetic acid (B9) and 1-fluoro-4-isocyanobenzene (D9) the title compound was afforded.



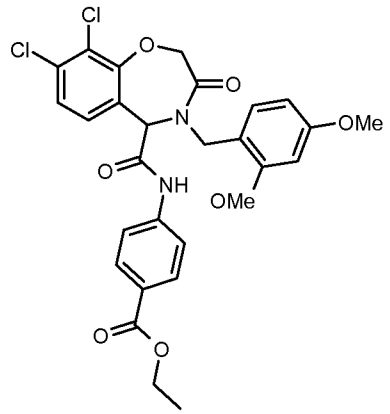
ethyl 4-{[(4-{[2,4-bis(methyloxy)phenyl]methyl}-9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)carbonyl]amino}benzoate (E52)

From [(2-ethyl-6-formylphenyl)oxy]acetic acid (B2) and ethyl 4-isocyanobenzoate (D10) the title compound was afforded.



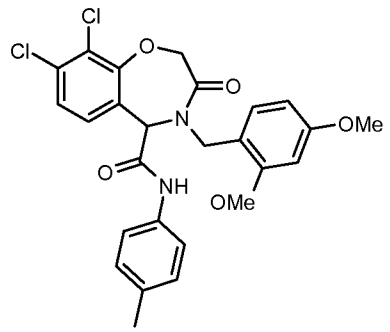
4-{[2,4-bis(methyloxy)phenyl]methyl}-9-ethyl-*N*-(4-methylphenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E53)

From [(2-ethyl-6-formylphenyl)oxy]acetic acid (B2) and 1-isocyano-4-methylbenzene (D3) the title compound was afforded.



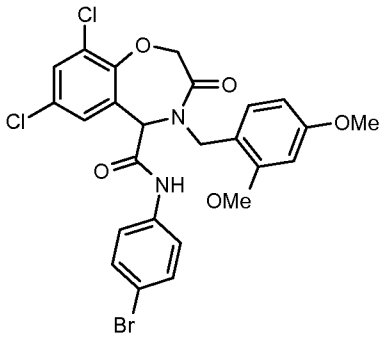
ethyl 4-{[(4-{[2,4-bis(methyloxy)phenyl]methyl}-8,9-dichloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)carbonyl]amino}benzoate (E54)

From [(2,3-dichloro-6-formylphenyl)oxy]acetic acid (B3) and ethyl 4-isocyanobenzoate (D10) the title compound was afforded.



4-{[2,4-bis(methyloxy)phenyl]methyl}-8,9-dichloro-*N*-(4-methylphenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E55)

From [(2,3-dichloro-6-formylphenyl)oxy]acetic acid (B3) and 1-isocyano-4-methylbenzene (D3) the title compound was afforded.

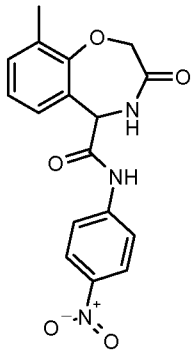


4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-bromophenyl)-7,9-dichloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E56)

The title compound can be synthesized using synthetic procedures similar to those described in the Ugi chemistry section (E1) above, except that [(2,4-dichloro-6-formylphenyl)oxy]acetic acid (B7) and 1-bromo-4-isocyanobenzene (D5) would be used in place of [(2-formyl-6-methylphenyl)oxy]acetic acid (B1) and 1-isocyano-4-nitrobenzene(D1), respectively.

TFA Cleavage of the 2,4-Dimethoxybenzyl Group

Example 1



9-methyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F1)

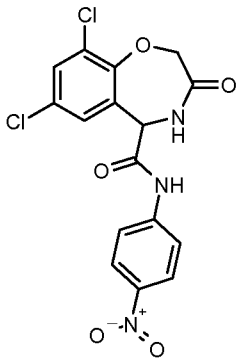
A solution of 4-{[2,4-bis(methyloxy)phenyl]methyl}-9-methyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E1) (600mg) in TFA (15ml) was heated to 55 ^{o}C for 2hrs during which the reaction turned a dark purple color. After cooling to RT, MeOH (1ml) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified via reverse-phase preparatory HPLC (10% to 100% ACN/(water with 0.05% TFA)) to yield 283mg of the desired product.

1H NMR (400 MHz, DMSO-d_6) δ ppm 2.17 (s, 3 H) 4.23 (d, *J*=16.85 Hz, 1 H) 4.62 (d, *J*=16.60 Hz, 1 H) 5.01 (d, *J*=6.84 Hz, 1 H) 7.08 (t, *J*=7.57 Hz, 1 H) 7.23 (d, *J*=7.81 Hz, 1 H) 7.32 (d, *J*=7.32 Hz, 1 H) 7.83 (d, *J*=9.52 Hz, 2 H) 8.19 (d, *J*=9.28 Hz, 2 H) 8.30 (d, *J*=6.84 Hz, 1 H) 10.29 (s, 1 H)

MS (m/z) APCI AP^+ = 342

The following compounds were synthesized according to the same general procedure as used for Example 1:

Example 2



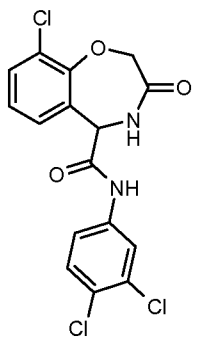
7,9-dichloro-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F2)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-7,9-dichloro-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E2) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 4.26 (d, *J*=16.60 Hz, 1 H) 4.77 (d, *J*=16.60 Hz, 1 H) 5.13 (d, *J*=7.32 Hz, 1 H) 7.65 - 7.73 (m, 1 H) 7.85 (d, *J*=9.28 Hz, 2 H) 8.21 (d, *J*=9.28 Hz, 2 H) 8.58 (d, *J*=7.32 Hz, 1 H) 10.33 (s, 1 H)

MS (m/z) APCI AP^+ = 396

Example 3



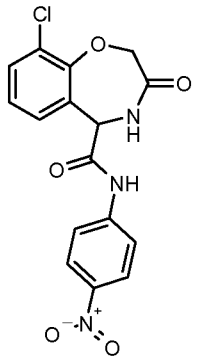
9-chloro-*N*-(3,4-dichlorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F3)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-9-chloro-*N*-(3,4-dichlorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E3) the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) δ ppm 4.23 (d, *J*=16.60 Hz, 1 H) 4.73 (d, *J*=16.60 Hz, 1 H) 5.05 (d, *J*=7.32 Hz, 1 H) 7.22 (t, *J*=7.93 Hz, 1 H) 7.43 - 7.56 (m, 3 H) 7.94 (s, 1 H) 8.43 (d, *J*=7.08 Hz, 1 H) 10.08 (s, 1 H)

MS (m/z) ESI ES^+ = 385

Example 4



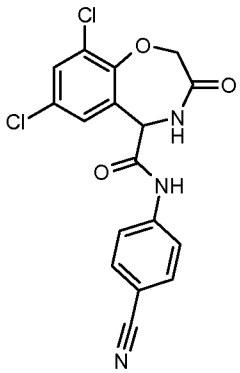
9-chloro-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F4)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-9-chloro-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E4) the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6 δ ppm 4.25 (d, *J*=16.60 Hz, 1 H) 4.73 (d, *J*=16.60 Hz, 1 H) 5.12 (d, *J*=7.08 Hz, 1 H) 7.23 (t, 1 H) 7.52 (d, *J*=8.06 Hz, 1 H) 7.83 (d, *J*=9.28 Hz, 2 H) 8.20 (d, *J*=9.28 Hz, 2 H) 8.44 (d, *J*=7.08 Hz, 1 H) 10.36 (s, 1 H)

MS (m/z) ESI ES^+ = 362

Example 5



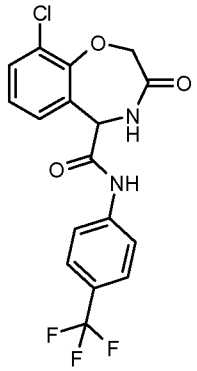
7,9-dichloro-*N*-(4-cyanophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F5)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-7,9-dichloro-*N*-(4-cyanophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E5) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 4.26 (d, *J*=16.60 Hz, 1 H) 4.76 (d, *J*=16.60 Hz, 1 H) 5.11 (d, *J*=7.32 Hz, 1 H) 7.62 - 7.73 (m, 2 H) 7.72 - 7.84 (m, 4 H) 8.56 (d, *J*=7.32 Hz, 1 H) 10.17 (s, 1 H)

MS (m/z) APCI AP^+ = 376

Example 6



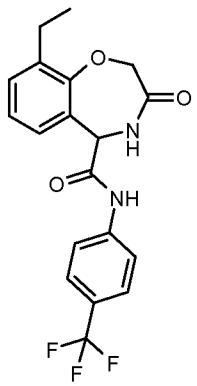
9-chloro-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F6)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-9-chloro-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E6) the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) δ ppm 4.26 (d, *J*=16.60 Hz, 1 H) 4.73 (d, *J*=16.60 Hz, 1 H) 5.10 (d, *J*=6.84 Hz, 1 H) 7.22 (t, *J*=7.81 Hz, 1 H) 7.44 - 7.56 (m, 2 H) 7.65 (d, *J*=8.79 Hz, 2 H) 7.78 (d, *J*=8.55 Hz, 2 H) 8.40 (d, *J*=7.08 Hz, 1 H) 10.15 (s, 1 H)

MS (m/z) ESI ES^+ = 385

Example 7



9-ethyl-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F7)

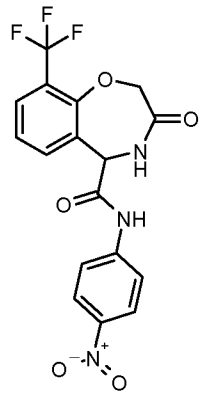
From 4-{[2,4-bis(methyloxy)phenyl]methyl}-9-ethyl-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E7) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.57 Hz, 3 H) 2.50 - 2.70 (m, 2 H) 4.25 (d, *J*=17.09 Hz, 1 H) 4.65 (d, *J*=16.60 Hz, 1 H) 5.06 (d, *J*=6.35 Hz, 1 H) 7.14 (t,

J=7.57 Hz, 1 H) 7.27 (d, *J*=6.84 Hz, 1 H) 7.33 (d, *J*=7.32 Hz, 1 H) 7.66 (d, *J*=8.30 Hz, 2 H) 7.80 (d, *J*=8.30 Hz, 2 H) 8.29 (d, *J*=6.35 Hz, 1 H) 10.13 (s, 1 H)

MS (m/z) APCI AP^+ = 379

Example 8

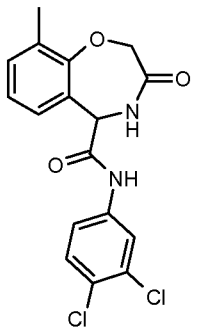


***N*-(4-nitrophenyl)-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F8)**

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-nitrophenyl)-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E8) the title compound was afforded.

MS (m/z) APCI AP^- = 394

Example 9



***N*-(3,4-dichlorophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F9)**

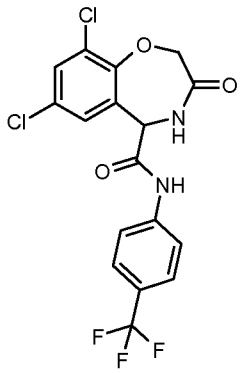
From 4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(3,4-dichlorophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E9) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 2.19 (s, 3 H) 4.22 (d, *J*=17.09 Hz, 1 H) 4.64 (d, *J*=16.60 Hz, 1 H) 4.96 (d, *J*=6.84 Hz, 1 H) 7.10 (t, *J*=7.57 Hz, 1 H) 7.25 (d,

J=7.32 Hz, 1 H) 7.31 (d, *J*=7.32 Hz, 1 H) 7.46 - 7.60 (m, 2 H) 7.96 (s, 1 H) 8.36 (d, *J*=6.84 Hz, 1 H) 10.05 (s, 1 H)

MS (m/z) APCI AP^+ = 365

Example 10



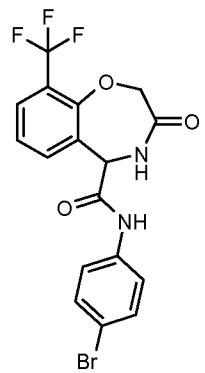
7,9-dichloro-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F10)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-7,9-dichloro-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E10) the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) δ ppm 4.25 (d, *J*=16.60 Hz, 1 H) 4.74 (d, *J*=16.36 Hz, 1 H) 5.08 (d, *J*=7.32 Hz, 1 H) 7.66 (d, *J*=8.79 Hz, 2 H) 7.68 (d, *J*=2.44 Hz, 1 H) 7.71 (d, *J*=2.44 Hz, 1 H) 7.77 (d, *J*=8.79 Hz, 2 H) 8.53 (d, *J*=7.32 Hz, 1 H) 10.08 (s, 1 H)

MS (m/z) APCI AP^+ = 419

Example 11



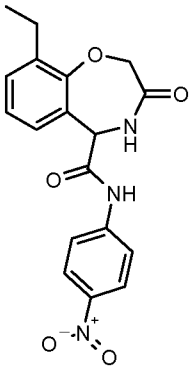
***N*-(4-bromophenyl)-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F11)**

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-bromophenyl)-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E11) the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) δ ppm 4.28 (d, *J*=16.60 Hz, 1 H) 4.76 (d, *J*=16.60 Hz, 1 H) 5.13 (d, *J*=6.84 Hz, 1 H) 7.39 (t, *J*=7.93 Hz, 1 H) 7.44 - 7.55 (m, 4 H) 7.70 (dd, *J*=8.18, 1.10 Hz, 1 H) 7.83 (d, *J*=7.32 Hz, 1 H) 8.44 (d, *J*=6.84 Hz, 1 H) 9.99 (s, 1 H)

MS (m/z) APCI AP^+ = 430

Example 12



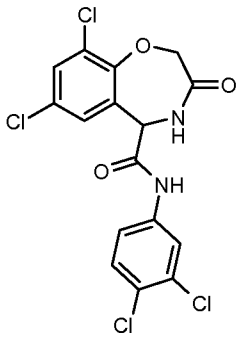
9-ethyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F12)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-9-ethyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E12) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.57 Hz, 3 H) 2.53 - 2.67 (m, 2 H) 4.23 (d, *J*=16.60 Hz, 1 H) 4.66 (d, *J*=17.09 Hz, 1 H) 5.07 (d, *J*=6.84 Hz, 1 H) 7.15 (t, *J*=7.57 Hz, 1 H) 7.28 (d, *J*=6.35 Hz, 1 H) 7.35 (d, *J*=7.32 Hz, 1 H) 7.85 (d, *J*=9.28 Hz, 2 H) 8.21 (d, *J*=8.79 Hz, 2 H) 8.34 (d, *J*=6.84 Hz, 1 H) 10.34 (s, 1 H)

MS (m/z) APCI AP^+ = 356

Example 13



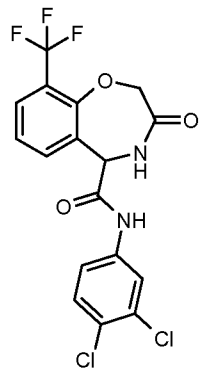
7,9-dichloro-*N*-(3,4-dichlorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F13)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-7,9-dichloro-*N*-(3,4-dichlorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E13) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 4.24 (d, *J*=16.60 Hz, 1 H) 4.77 (d, *J*=16.60 Hz, 1 H) 5.07 (d, *J*=7.32 Hz, 1 H) 7.48 - 7.58 (m, 2 H) 7.64 - 7.76 (m, 2 H) 7.94 (s, 1 H) 8.58 (d, *J*=7.32 Hz, 1 H) 10.04 (s, 1 H)

MS (m/z) APCI AP^+ = 419

Example 14

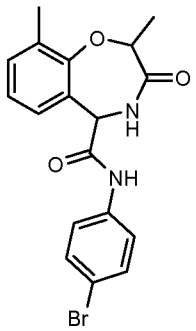


***N*-(3,4-dichlorophenyl)-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F14)**

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(3,4-dichlorophenyl)-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E14) the title compound was afforded.

MS (m/z) APCI AP^+ = 419

Example 15



***N*-(4-bromophenyl)-2,9-dimethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F15)**

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-bromophenyl)-2,9-dimethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E15) the title compound was afforded as 2 diastereomers, which were separated by preparatory HPLC (10% to 100% ACN/water (0.05% TFA)).

Isomer 1

1H NMR (400 MHz, DMSO-d_6) δ ppm 1.55 (d, *J*=6.84 Hz, 3 H) 2.16 (s, 3 H) 4.21 (q, *J*=6.67 Hz, 1 H) 4.79 (d, *J*=7.81 Hz, 1 H) 7.06 (t, *J*=7.45 Hz, 1 H) 7.20 (d, *J*=7.57 Hz, 1 H) 7.31 (d, *J*=7.32 Hz, 1 H) 7.40 - 7.48 (m, 2 H) 7.50 - 7.59 (m, 2 H) 8.25 (d, *J*=8.06 Hz, 1 H) 9.71 (s, 1 H)

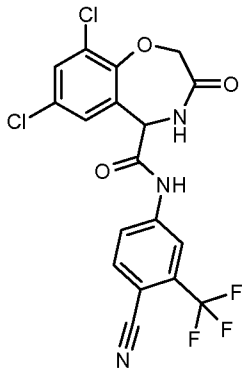
MS (m/z) APCI AP^+ = 390

Isomer 2

1H NMR (400 MHz, DMSO-d_6) □ ppm 1.44 (d, *J*=7.08 Hz, 3 H) 2.19 (s, 3 H) 4.79 (q, *J*=6.84 Hz, 1 H) 5.28 (d, *J*=5.62 Hz, 1 H) 6.99 (t, *J*=7.57 Hz, 1 H) 7.12 (d, *J*=7.57 Hz, 1 H) 7.19 (d, *J*=7.57 Hz, 1 H) 7.45 - 7.52 (m, 2 H) 7.52 - 7.60 (m, 2 H) 7.77 (d, *J*=5.62 Hz, 1 H) 10.33 (s, 1 H)

MS (m/z) APCI AP^+ = 390

Example 16



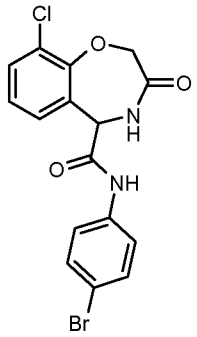
7,9-dichloro-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F16)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-7,9-dichloro-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E16) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 4.24 (d, *J*=16.60 Hz, 1 H) 4.79 (d, *J*=16.60 Hz, 1 H) 5.14 (d, *J*=7.32 Hz, 1 H) 7.61 - 7.85 (m, 2 H) 7.99 - 8.41 (m, 3 H) 8.67 (d, *J*=7.32 Hz, 1 H) 10.48 (s, 1 H)

MS (m/z) APCI AP^+ = 444

Example 17



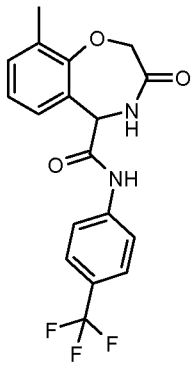
***N*-(4-bromophenyl)-9-chloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F17)**

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-bromophenyl)-9-chloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E17) the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) δ ppm 4.26 (d, *J*=16.60 Hz, 1 H) 4.72 (d, *J*=16.60 Hz, 1 H) 5.06 (d, *J*=7.08 Hz, 1 H) 7.21 (t, *J*=7.93 Hz, 1 H) 7.37 - 7.59 (m, 6 H) 8.37 (d, *J*=6.84 Hz, 1 H) 9.95 (s, 1 H)

MS (m/z) ESI ES^- = 394

Example 18



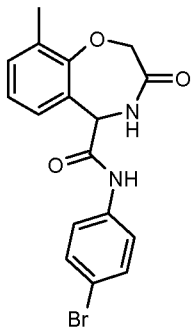
9-methyl-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F18)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-9-methyl-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E18) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 2.20 (s, 3 H) 4.27 (d, *J*=16.60 Hz, 1 H) 4.64 (d, *J*=16.60 Hz, 1 H) 5.03 (d, *J*=6.84 Hz, 1 H) 7.10 (t, *J*=7.57 Hz, 1 H) 7.25 (d, *J*=7.32 Hz, 1 H) 7.33 (d, *J*=7.32 Hz, 1 H) 7.66 (d, *J*=8.30 Hz, 2 H) 7.81 (d, *J*=8.30 Hz, 2 H) 8.30 (d, *J*=6.84 Hz, 1 H) 10.11 (s, 1 H)

MS (m/z) APCI AP^+ = 365

Example 19



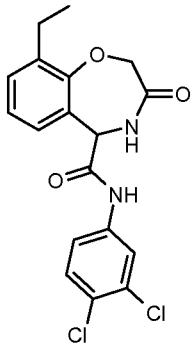
***N*-(4-bromophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F19)**

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-bromophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E19) the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) δ ppm 2.17 (s, 3 H) 4.25 (d, *J*=16.60 Hz, 1 H) 4.60 (d, *J*=16.60 Hz, 1 H) 4.97 (d, *J*=6.59 Hz, 1 H) 7.06 (t, *J*=7.57 Hz, 1 H) 7.22 (d, *J*=7.57 Hz, 1 H) 7.28 (d, *J*=7.57 Hz, 1 H) 7.41 - 7.49 (m, 2 H) 7.51 - 7.58 (m, 2 H) 8.22 (d, *J*=6.59 Hz, 1 H) 9.88 (s, 1 H)

MS (m/z) APCI AP^+ = 376

Example 20



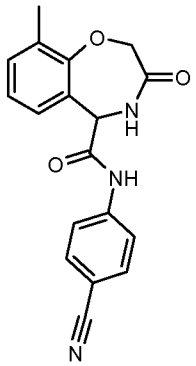
***N*-(3,4-dichlorophenyl)-9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F20)**

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(3,4-dichlorophenyl)-9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E20) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.57 Hz, 3 H) 2.53 - 2.67 (m, 2 H) 4.22 (d, *J*=16.60 Hz, 1 H) 4.65 (d, *J*=16.60 Hz, 1 H) 5.00 (d, *J*=6.35 Hz, 1 H) 7.14 (t, *J*=7.57 Hz, 1 H) 7.27 (d, *J*=6.84 Hz, 1 H) 7.31 (d, *J*=7.32 Hz, 1 H) 7.49 - 7.58 (m, 2 H) 7.96 (s, 1 H) 8.33 (d, *J*=6.84 Hz, 1 H) 10.06 (s, 1 H)

MS (m/z) APCI AP^+ = 379

Example 21



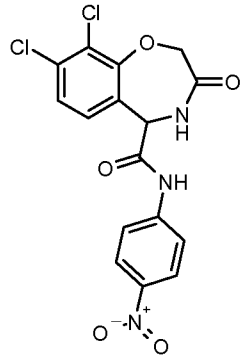
***N*-(4-cyanophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F21)**

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-cyanophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E21) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 2.19 (s, 3 H) 4.25 (d, *J*=17.09 Hz, 1 H) 4.63 (d, *J*=16.60 Hz, 1 H) 5.02 (d, *J*=6.84 Hz, 1 H) 7.10 (t, *J*=7.57 Hz, 1 H) 7.25 (d, *J*=7.81 Hz, 1 H) 7.33 (d, *J*=7.32 Hz, 1 H) 7.69 - 7.83 (m, 4 H) 8.32 (d, *J*=6.84 Hz, 1 H) 10.16 (s, 1 H)

MS (m/z) APCI AP^+ = 322

Example 22



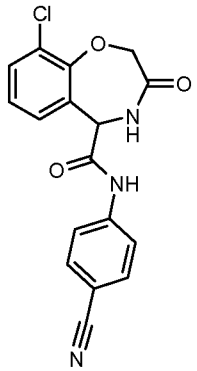
8,9-dichloro-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F22)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-8,9-dichloro-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E22) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 4.34 (d, *J*=16.60 Hz, 1 H) 4.79 (d, *J*=16.60 Hz, 1 H) 5.16 (d, *J*=7.32 Hz, 1 H) 7.49 - 7.55 (m, 1 H) 7.56 - 7.61 (m, 1 H) 7.84 (d, *J*=9.28 Hz, 2 H) 8.21 (d, *J*=9.28 Hz, 2 H) 8.53 (d, *J*=7.32 Hz, 1 H) 10.37 (s, 1 H)

MS (m/z) APCI AP^+ = 396

Example 23



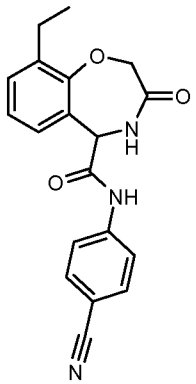
9-chloro-*N*-(4-cyanophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F23)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-9-chloro-*N*-(4-cyanophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E23) the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) δ ppm 4.25 (d, *J*=16.60 Hz, 1 H) 4.72 (d, *J*=16.60 Hz, 1 H) 5.10 (d, *J*=7.08 Hz, 1 H) 7.22 (t, *J*=7.81 Hz, 1 H) 7.46 - 7.55 (m, 2 H) 7.72 - 7.78 (m, 4 H) 8.41 (d, *J*=7.08 Hz, 1 H) 10.21 (s, 1 H)

MS (m/z) ESI ES^+ = 342

Example 24



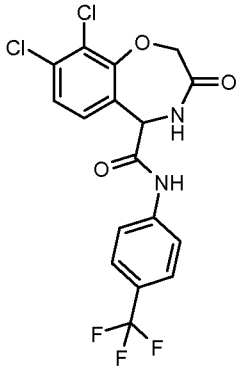
***N*-(4-cyanophenyl)-9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F24)**

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-cyanophenyl)-9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E24) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.57 Hz, 3 H) 2.53 - 2.67 (m, 2 H) 4.24 (d, *J*=16.60 Hz, 1 H) 4.64 (d, *J*=16.60 Hz, 1 H) 5.05 (d, *J*=6.84 Hz, 1 H) 7.14 (t, *J*=7.57 Hz, 1 H) 7.27 (d, *J*=7.32 Hz, 1 H) 7.33 (d, *J*=7.32 Hz, 1 H) 7.68 - 7.83 (m, 4 H) 8.31 (d, *J*=6.84 Hz, 1 H) 10.19 (s, 1 H)

MS (m/z) APCI AP^+ = 336

Example 25



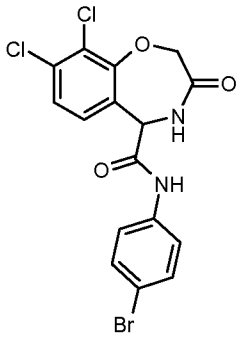
8,9-dichloro-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F25)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-8,9-dichloro-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E25) the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) δ ppm 4.33 (d, *J*=16.60 Hz, 1 H) 4.76 (d, *J*=16.60 Hz, 1 H) 5.12 (d, *J*=7.08 Hz, 1 H) 7.48 - 7.58 (m, 2 H) 7.65 (d, *J*=8.55 Hz, 2 H) 7.77 (d, *J*=8.55 Hz, 2 H) 8.46 (d, *J*=7.32 Hz, 1 H) 10.12 (s, 1 H)

MS (m/z) APCI AP^+ = 419

Example 26



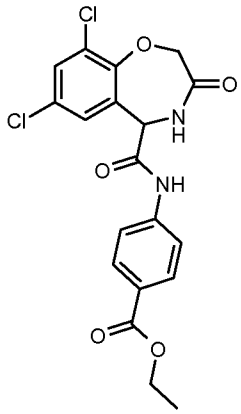
***N*-(4-bromophenyl)-8,9-dichloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F26)**

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-bromophenyl)-8,9-dichloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E26) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 4.34 (d, *J*=16.60 Hz, 1 H) 4.78 (d, *J*=16.60 Hz, 1 H) 5.10 (d, *J*=7.32 Hz, 1 H) 7.42 - 7.59 (m, 6 H) 8.47 (d, *J*=6.84 Hz, 1 H) 9.95 (s, 1 H)

MS (m/z) APCI AP^+ = 430

Example 27



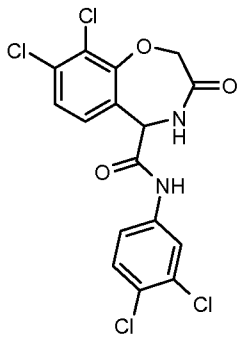
ethyl 4-{[(7,9-dichloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)carbonyl]amino}benzoate (F27)

From ethyl 4-{[(4-{[2,4-bis(methyloxy)phenyl]methyl}-7,9-dichloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)carbonyl]amino}benzoate (E27) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 1.31 (t, *J*=7.08 Hz, 3 H) 4.19 - 4.33 (m, 3 H) 4.77 (d, *J*=16.60 Hz, 1 H) 5.10 (d, *J*=7.32 Hz, 1 H) 7.62 - 7.78 (m, 4 H) 7.91 (d, *J*=8.79 Hz, 2 H) 8.54 (d, *J*=7.32 Hz, 1 H) 10.09 (s, 1 H)

MS (m/z) APCI AP^+ = 423

Example 28



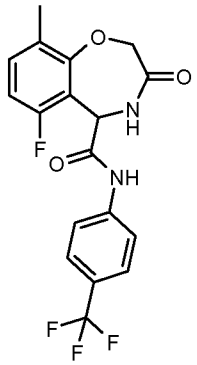
8,9-dichloro-*N*-(3,4-dichlorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F28)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-8,9-dichloro-*N*-(3,4-dichlorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E28) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 4.32 (d, *J*=16.60 Hz, 1 H) 4.79 (d, *J*=16.60 Hz, 1 H) 5.10 (d, *J*=6.84 Hz, 1 H) 7.46 - 7.61 (m, 4 H) 7.94 (s, 1 H) 8.52 (d, *J*=7.32 Hz, 1 H) 10.08 (s, 1 H)

MS (m/z) APCI AP^+ = 419

Example 29



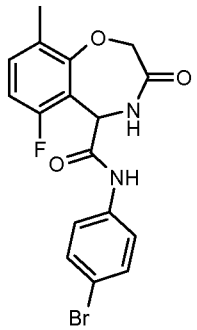
6-fluoro-9-methyl-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F29)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-6-fluoro-9-methyl-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E29) the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) δ ppm 2.13 (s, 3 H) 4.20 (d, *J*=16.85 Hz, 1 H) 4.71 (d, *J*=16.85 Hz, 1 H) 5.15 (d, *J*=7.81 Hz, 1 H) 7.03 (t, *J*=8.67 Hz, 1 H) 7.22 - 7.31 (m, 1 H) 7.65 (d, *J*=9.03 Hz, 2 H) 7.83 (d, *J*=8.79 Hz, 2 H) 8.46 (d, *J*=7.57 Hz, 1 H) 10.14 (s, 1 H)

MS (m/z) ESI ES^+ = 383

Example 30

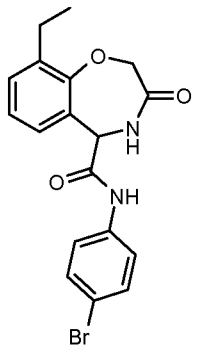


***N*-(4-bromophenyl)-6-fluoro-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F30)**

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-bromophenyl)-6-fluoro-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E30) the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) δ ppm 2.13 (s, 3 H) 4.19 (d, *J*=16.60 Hz, 1 H) 4.71 (d, *J*=16.85 Hz, 1 H) 5.10 (d, *J*=7.57 Hz, 1 H) 7.01 (t, *J*=8.79 Hz, 1 H) 7.22 - 7.29 (m, 1 H) 7.46 (d, *J*=9.03 Hz, 2 H) 7.57 (d, *J*=9.03 Hz, 2 H) 8.44 (d, *J*=7.57 Hz, 1 H) 9.92 (s, 1 H)

Example 31



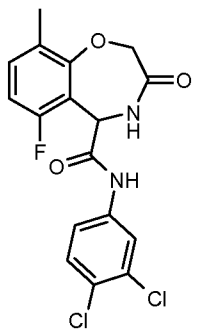
***N*-(4-bromophenyl)-9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F31)**

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-bromophenyl)-9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E31) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.57 Hz, 3 H) 2.52 - 2.72 (m, 2 H) 4.26 (d, *J*=16.60 Hz, 1 H) 4.63 (d, *J*=17.09 Hz, 1 H) 5.03 (d, *J*=6.35 Hz, 1 H) 7.13 (t, *J*=7.57 Hz, 1 H) 7.22 - 7.35 (m, 2 H) 7.47 (d, *J*=8.79 Hz, 2 H) 7.56 (d, *J*=8.79 Hz, 2 H) 8.25 (d, *J*=6.35 Hz, 1 H) 9.93 (s, 1 H)

MS (m/z) APCI AP^+ = 390

Example 32

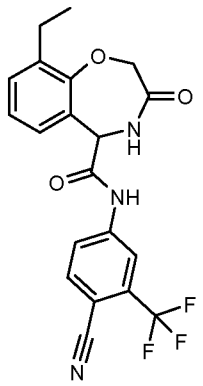


***N*-(3,4-dichlorophenyl)-6-fluoro-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F32)**

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(3,4-dichlorophenyl)-6-fluoro-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E32) the title compound was afforded.

MS (m/z) ESI ES^+ = 383

Example 33

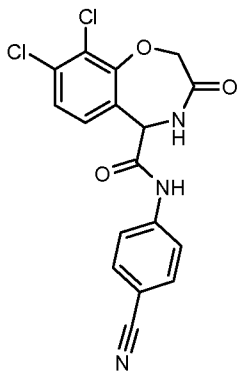


***N*-[4-cyano-3-(trifluoromethyl)phenyl]-9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F33)**

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E33) the title compound was afforded.

MS (m/z) APCI AP^+ = 403

Example 34

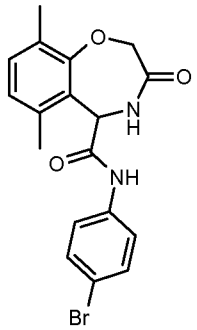


8,9-dichloro-*N*-(4-cyanophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F34)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-8,9-dichloro-*N*-(4-cyanophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E34) the title compound was afforded.

MS (m/z) APCI AP^+ = 376

Example 35

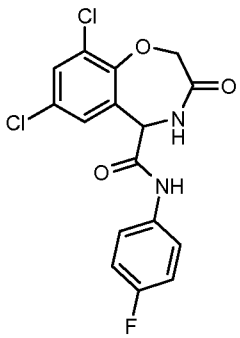


***N*-(4-bromophenyl)-6,9-dimethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F35)**

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-bromophenyl)-6,9-dimethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E35) the title compound was afforded.

MS (m/z) APCI AP^+ = 390

Example 36



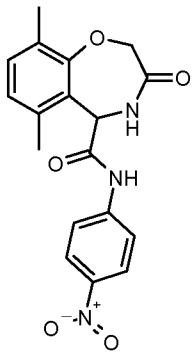
7,9-dichloro-*N*-(4-fluorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F36)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-7,9-dichloro-*N*-(4-fluorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E36) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 4.26 (d, *J*=16.60 Hz, 1 H) 4.77 (d, *J*=16.60 Hz, 1 H) 5.05 (d, *J*=7.32 Hz, 1 H) 7.08 - 7.19 (m, 2 H) 7.52 - 7.61 (m, 2 H) 7.63 - 7.73 (m, 2 H) 8.55 (d, *J*=6.84 Hz, 1 H) 9.86 (s, 1 H)

MS (m/z) APCI AP^+ = 369

Example 37

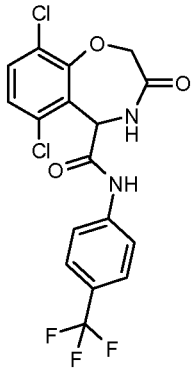


6,9-dimethyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F37)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-6,9-dimethyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E37) the title compound was afforded.

MS (m/z) APCI AP^+ = 356

Example 38



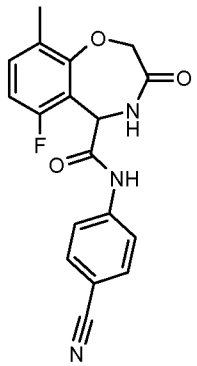
6,9-dichloro-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F38)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-6,9-dichloro-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E38) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 4.22 (d, *J*=16.65 Hz, 1 H) 4.85 (d, *J*=16.65 Hz, 1 H) 5.37 (d, *J*=8.19 Hz, 1 H) 7.45 (d, *J*=8.72 Hz, 1 H) 7.60 (d, *J*=8.72 Hz, 1 H) 7.67 (d, *J*=8.72 Hz, 2 H) 7.86 (d, *J*=8.72 Hz, 2 H) 8.72 (d, *J*=8.19 Hz, 1 H) 10.20 (s, 1 H)

MS (m/z) ESI ES^+ = 419

Example 39



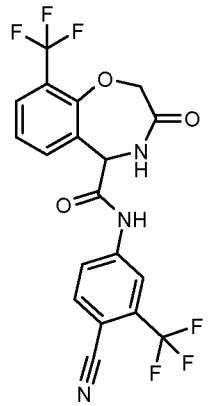
***N*-(4-cyanophenyl)-6-fluoro-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F39)**

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-cyanophenyl)-6-fluoro-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E39) the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) δ ppm 2.13 (s, 3 H) 4.20 (d, *J*=16.60 Hz, 1 H) 4.70 (d, *J*=16.85 Hz, 1 H) 5.15 (d, *J*=7.57 Hz, 1 H) 7.03 (t, *J*=8.79 Hz, 1 H) 7.23 - 7.33 (m, 1 H) 7.71 - 7.78 (m, 2 H) 7.79 - 7.86 (m, 2 H) 8.46 (d, *J*=7.57 Hz, 1 H) 10.19 (s, 1 H)

MS (m/z) ESI ES^+ = 340

Example 40

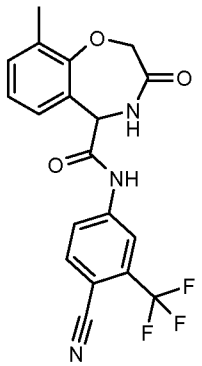


***N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F40)**

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E40) the title compound was afforded.

MS (m/z) ESI ES^+ = 444

Example 41



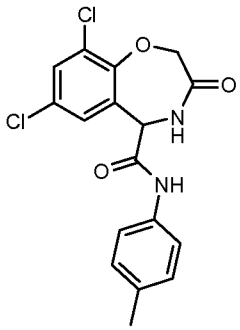
***N*-[4-cyano-3-(trifluoromethyl)phenyl]-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F41)**

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E41) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 2.19 (s, 3 H) 4.22 (d, *J*=17.09 Hz, 1 H) 4.67 (d, *J*=16.60 Hz, 1 H) 5.01 (d, *J*=7.32 Hz, 1 H) 7.12 (t, *J*=7.57 Hz, 1 H) 7.26 (d, *J*=7.81 Hz, 1 H) 7.36 (d, *J*=7.32 Hz, 1 H) 8.03 - 8.10 (m, 1 H) 8.11 - 8.17 (m, 1 H) 8.29 (s, 1 H) 8.44 (d, *J*=6.84 Hz, 1 H) 10.47 (s, 1 H)

MS (m/z) APCI AP^+ = 390

Example 42

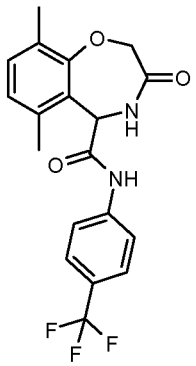


7,9-dichloro-*N*-(4-methylphenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F42)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-7,9-dichloro-*N*-(4-methylphenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E42) the title compound was afforded.

MS (m/z) APCI AP^+ = 365

Example 43

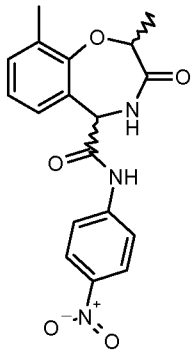


6,9-dimethyl-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F43)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-6,9-dimethyl-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E43) the title compound was afforded.

MS (m/z) APCI AP^+ = 379

Example 44



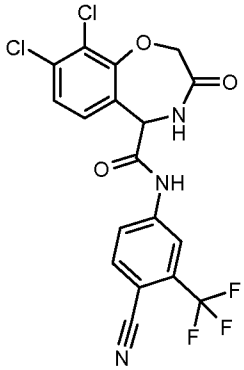
2,9-dimethyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F44)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-2,9-dimethyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E44) the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) δ ppm 1.56 (d, *J*=6.84 Hz, 3 H) 2.16 (s, 3 H) 4.14 - 4.29 (m, 1 H) 4.87 (d, *J*=7.81 Hz, 1 H) 7.08 (t, *J*=7.57 Hz, 1 H) 7.22 (d, *J*=6.84 Hz, 1 H) 7.35 (dd, *J*=8.06, 1.22 Hz, 1 H) 7.86 (d, *J*=9.28 Hz, 2 H) 8.19 (d, *J*=9.28 Hz, 2 H) 8.30 (d, *J*=7.57 Hz, 1 H) 10.17 (s, 1 H)

MS (m/z) APCI AP^+ = 356

Example 45



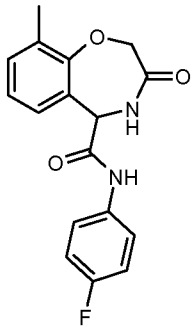
8,9-dichloro-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F45)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-8,9-dichloro-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E45) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 4.31 (d, *J*=16.60 Hz, 1 H) 4.80 (d, *J*=17.09 Hz, 1 H) 5.16 (d, *J*=7.32 Hz, 1 H) 7.51 - 7.57 (m, 1 H) 7.57 - 7.63 (m, 1 H) 8.05 - 8.15 (m, 2 H) 8.21 - 8.27 (m, 1 H) 8.62 (d, *J*=7.32 Hz, 1 H) 10.51 (s, 1 H)

MS (m/z) APCI AP^+ = 444

Example 46



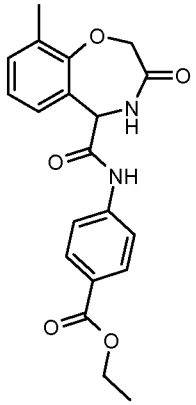
***N*-(4-fluorophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F46)**

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-fluorophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E46) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 2.20 (s, 3 H) 4.27 (d, *J*=16.60 Hz, 1 H) 4.63 (d, *J*=16.60 Hz, 1 H) 5.00 (d, *J*=6.84 Hz, 1 H) 7.03 - 7.17 (m, 3 H) 7.24 (d, *J*=7.81 Hz, 1 H) 7.29 (d, *J*=7.32 Hz, 1 H) 7.52 - 7.65 (m, 2 H) 8.26 (d, *J*=6.84 Hz, 1 H) 9.85 (s, 1 H)

MS (m/z) APCI AP^+ = 315

Example 47



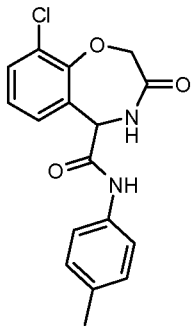
ethyl 4-{[(9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)carbonyl]amino}benzoate (F47)

From ethyl 4-{[(4-{[2,4-bis(methyloxy)phenyl]methyl}-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)carbonyl]amino}benzoate (E47) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 1.30 (t, *J*=7.08 Hz, 3 H) 2.20 (s, 3 H) 4.19 - 4.33 (m, 3 H) 4.64 (d, *J*=16.60 Hz, 1 H) 5.03 (d, *J*=6.84 Hz, 1 H) 7.10 (t, *J*=7.57 Hz, 1 H) 7.25 (d, *J*=6.84 Hz, 1 H) 7.33 (d, *J*=7.32 Hz, 1 H) 7.73 (d, *J*=8.79 Hz, 2 H) 7.90 (d, *J*=8.79 Hz, 2 H) 8.29 (d, *J*=6.84 Hz, 1 H) 10.07 (s, 1 H)

MS (m/z) APCI AP^+ = 369

Example 48



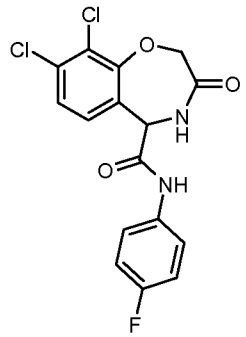
9-chloro-*N*-(4-methylphenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F48)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-9-chloro-*N*-(4-methylphenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E48) the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) δ ppm 2.22 (s, 3 H) 4.29 (d, *J*=16.36 Hz, 1 H) 4.71 (d, *J*=16.36 Hz, 1 H) 5.06 (d, *J*=6.59 Hz, 1 H) 7.08 (d, *J*=8.55 Hz, 2 H) 7.20 (t, *J*=7.93 Hz, 1 H) 7.42 (d, *J*=8.55 Hz, 2 H) 7.44 - 7.54 (m, 2 H) 8.32 (d, *J*=6.84 Hz, 1 H) 9.75 (s, 1 H)

MS (m/z) ESI ES^+ = 331

Example 49



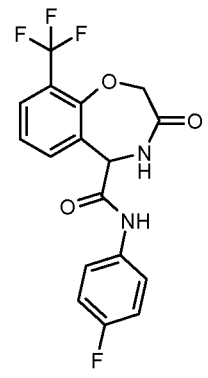
8,9-dichloro-*N*-(4-fluorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F49)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-8,9-dichloro-*N*-(4-fluorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E49) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 4.34 (d, *J*=16.11 Hz, 1 H) 4.78 (d, *J*=16.11 Hz, 1 H) 5.09 (d, *J*=6.84 Hz, 1 H) 7.07 - 7.18 (m, 2 H) 7.45 - 7.61 (m, 4 H) 8.47 (d, *J*=6.84 Hz, 1 H) 9.89 (s, 1 H)

MS (m/z) APCI AP^+ = 369

Example 50

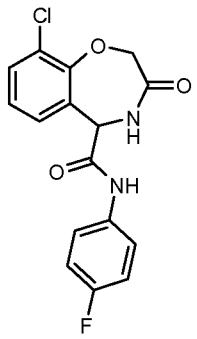


***N*-(4-fluorophenyl)-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F50)**

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-fluorophenyl)-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E50) the title compound was afforded.

MS (m/z) APCI AP^+ = 369

Example 51



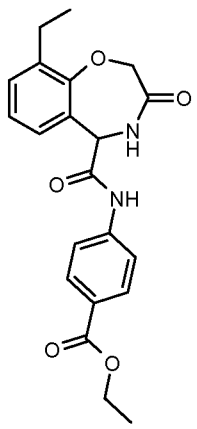
9-chloro-*N*-(4-fluorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F51)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-9-chloro-*N*-(4-fluorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E51) the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) d ppm 4.27 (d, *J*=16.60 Hz, 1 H) 4.72 (d, *J*=16.36 Hz, 1 H) 5.05 (d, *J*=6.84 Hz, 1 H) 7.07 - 7.26 (m, 3 H) 7.42 - 7.60 (m, 4 H) 8.37 (d, *J*=6.84 Hz, 1 H) 9.89 (s, 1 H)

MS (m/z) ESI ES^+ = 335

Example 52



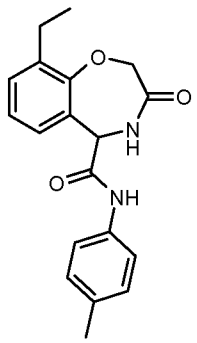
ethyl 4-{[(9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)carbonyl]amino}benzoate (F52)

From ethyl 4-{[(4-{[2,4-bis(methyloxy)phenyl]methyl}-9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)carbonyl]amino}benzoate (E52) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.57 Hz, 3 H) 1.30 (t, *J*=7.08 Hz, 3 H) 2.53 - 2.66 (m, 2 H) 4.20 - 4.31 (m, 3 H) 4.65 (d, *J*=16.60 Hz, 1 H) 5.06 (d, *J*=6.35 Hz, 1 H) 7.14 (t, *J*=7.57 Hz, 1 H) 7.27 (d, *J*=6.84 Hz, 1 H) 7.33 (d, *J*=7.32 Hz, 1 H) 7.72 (d, *J*=8.79 Hz, 2 H) 7.90 (d, *J*=8.79 Hz, 2 H) 8.29 (d, *J*=6.84 Hz, 1 H) 10.10 (s, 1 H)

MS (m/z) APCI AP^+ = 383

Example 53



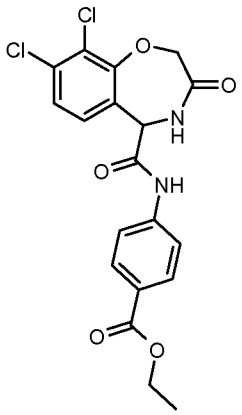
9-ethyl-*N*-(4-methylphenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F53)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-9-ethyl-*N*-(4-methylphenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E53) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 1.13 (t, *J*=7.57 Hz, 3 H) 2.24 (s, 3 H) 2.53 - 2.68 (m, 2 H) 4.29 (d, *J*=16.60 Hz, 1 H) 4.62 (d, *J*=16.60 Hz, 1 H) 5.05 (d, *J*=6.35 Hz, 1 H) 7.05 - 7.16 (m, 3 H) 7.21 - 7.32 (m, 2 H) 7.45 (d, *J*=8.30 Hz, 2 H) 8.19 (d, *J*=5.86 Hz, 1 H) 9.75 (s, 1 H)

MS (m/z) APCI AP^+ = 325

Example 54



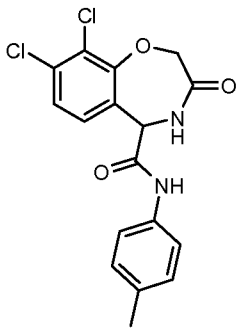
ethyl 4-{[(8,9-dichloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)carbonyl]amino}benzoate (F54)

From ethyl 4-{[(4-{[2,4-bis(methyloxy)phenyl]methyl}-8,9-dichloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)carbonyl]amino}benzoate (E54) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) □ ppm 1.30 (t, *J*=7.08 Hz, 3 H) 4.21 - 4.31 (m, 2 H) 4.34 (d, *J*=16.60 Hz, 1 H) 4.79 (d, *J*=16.60 Hz, 1 H) 5.13 (d, *J*=6.84 Hz, 1 H) 7.46 - 7.54 (m, 1 H) 7.54 - 7.60 (m, 1 H) 7.71 (d, *J*=8.79 Hz, 2 H) 7.91 (d, *J*=8.79 Hz, 2 H) 8.49 (d, *J*=6.84 Hz, 1 H) 10.13 (s, 1 H)

MS (m/z) APCI AP^+ = 423

Example 55



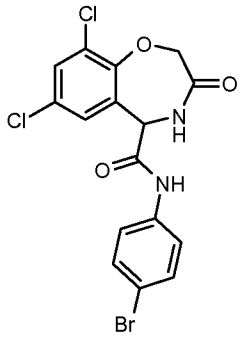
8,9-dichloro-*N*-(4-methylphenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F55)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-8,9-dichloro-*N*-(4-methylphenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E55) the title compound was afforded.

1H NMR (500 MHz, DMSO-d_6) δ ppm 2.24 (s, 3 H) 4.35 (d, *J*=16.60 Hz, 1 H) 4.78 (d, *J*=16.11 Hz, 1 H) 5.09 (d, *J*=6.84 Hz, 1 H) 7.10 (d, *J*=8.30 Hz, 2 H) 7.42 (d, *J*=8.30 Hz, 2 H) 7.47 - 7.57 (m, 2 H) 8.43 (d, *J*=6.84 Hz, 1 H) 9.76 (s, 1 H)

MS (m/z) APCI AP^+ = 365

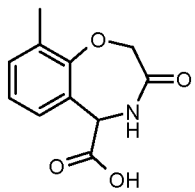
Example 56



***N*-(4-bromophenyl)-7,9-dichloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (F56)**

The title compound can be synthesized using synthetic procedures similar to those described for **F1,** except that 4-{[2,4-bis(methyloxy)phenyl]methyl}-*N*-(4-bromophenyl)-7,9-dichloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E56) would be used in place of 4-{[2,4-bis(methyloxy)phenyl]methyl}-9-methyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E1) .

Nitro-aniline-amide Hydrolysis



9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxylic acid (G1)

To a solution of 4-{[2,4-bis(methyloxy)phenyl]methyl}-9-methyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E1) (45.5g, 92.6mmols,1.0eq) in dry ACN (300ml) was added DMAP (12.44g, 1.1eq) all at once as a solid followed by the dropwise addition of Boc_2O (20.2g, 1eq) in dry THF (400ml). After stirring for 1hr at RT, the volatiles were removed *in vacuo*. The residue was partitioned between EtOAc/0.1N HCl. During the extraction a small amount of a white precipitate would not fully dissolve. The biphasic mixture was filtered and the white solid was determined to be product and was put aside. The phases were separated and the organic fraction was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield, when combined with the above

solids isolated after the filtration, 61.78g (>100%) of clean 1,1-dimethylethyl [(4-{[2,4-bis(methyloxy)phenyl]methyl}-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)carbonyl](4-nitrophenyl)carbamate contaminated with DMAP.

1H NMR (400 MHz, DMSO-d_6) δ ppm 1.11 (s, 9 H) 2.25 (s, 3 H) 3.73 (s, 3 H) 3.79 (s, 3 H) 4.20 (d, *J*=14.40 Hz, 1 H) 4.27 (d, *J*=16.85 Hz, 1 H) 4.55 (d, *J*=16.85 Hz, 1 H) 4.89 (d, *J*=14.65 Hz, 1 H) 6.23 (s, 1 H) 6.43 (dd, *J*=8.30, 2.44 Hz, 1 H) 6.55 - 6.57 (m, 1 H) 6.92 (dd, *J*=7.69, 1.10 Hz, 1 H) 7.00 (t, *J*=7.57 Hz, 1 H) 7.07 (d, *J*=8.30 Hz, 1 H) 7.19 - 7.33 (m, 3 H) 8.23 (d, *J*=9.03 Hz, 2 H)

MS (m/z) ESI ES^+ = 592

1,1-dimethylethyl [(4-{[2,4-bis(methyloxy)phenyl]methyl}-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)carbonyl](4-nitrophenyl)carbamate (61.78g) contaminated with DMAP was dissolved in THF (150ml) and MeOH (100ml) followed by the addition of 1N NaOH (100ml). After allowing the reaction mixture to stir at RT overnight, the MeOH and THF were removed *in vacuo*. The residue was partitioned between EtOAc/1N HCl; the organic fraction was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield, after silica gel purification (DCM to 20% MeOH/DCM with 1% AcOH), 34.85g of 4-{[2,4-bis(methyloxy)phenyl]methyl}-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxylic acid.

1H NMR (400 MHz, DMSO-d_6) δ ppm 2.17 (s, 3 H) 3.70 (s, 3 H) 3.74 (s, 3 H) 4.13 (d, *J*=15.14 Hz, 1 H) 4.26 (d, *J*=16.60 Hz, 1 H) 4.66 (d, *J*=16.60 Hz, 1 H) 4.93 (d, *J*=14.89 Hz, 1 H) 5.03 (s, 1 H) 6.37 (dd, *J*=8.30, 2.44 Hz, 1 H) 6.52 (d, *J*=2.44 Hz, 1 H) 6.89 - 6.95 (m, 2 H) 6.99 (t, *J*=7.45 Hz, 1 H) 7.18 (d, *J*=8.55 Hz, 1 H) 12.89 (br. s., 1 H)

MS (m/z) ESI ES^+ = 372

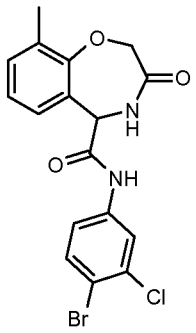
4-{[2,4-bis(methyloxy)phenyl]methyl}-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxylic acid (30g) was dissolved in neat TFA (120ml) and heated to 55 ^oC for 4hrs. After cooling to RT, MeOH (400ml) was added which affected the precipitation of purple solids. This solid was washed with hot DCM/MeOH (10:1) and filtered. The filtrate was concentrated *in vacuo* to yield 8.5g of the title compound, which was put aside. The remaining solids were again washed with DCM/MeOH (10:1), which removed the purple impurity to yield 1.0g of the desired product. The two batches were combined to afford 9.5g (60%) of the title compound.

1H NMR (400 MHz, DMSO-d_6) δ ppm 2.17 (s, 3 H) 4.13 (d, *J*=16.85 Hz, 1 H) 4.57 (d, *J*=16.85 Hz, 1 H) 4.73 (d, *J*=7.32 Hz, 1 H) 7.03 (t, *J*=7.45 Hz, 1 H) 7.19 (dd, *J*=7.93, 1.34 Hz, 1 H) 7.26 (dd, *J*=7.20, 1.10 Hz, 1 H) 8.52 (d, *J*=7.57 Hz, 1 H) 12.79 (s, 1 H)

MS (m/z) ESI ES^+ = 222

HATU-mediated Amide Coupling

Example 57



***N*-(4-bromo-3-chlorophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (H1)**

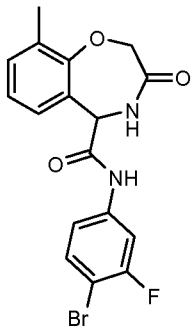
To a solution of 9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxylic acid (G1) (50mg, 0.23mmols, 1.0eq) in dry DMF (1ml) was added DIEA (0.045ml, 1.1eq) followed by HATU (100mg, 1.1eq). After stirring for 30min at RT, 4-bromo-3-chloroaniline was added and the reaction was allowed to stir at RT overnight. The reaction was directly purified via reverse phase preparatory HPLC (20% to 100% ACN/water with 0.05% TFA) to afford 13mg of the title compound.

1H NMR (400 MHz, DMSO-d_6) δ ppm 2.17 (s, 3 H) 4.22 (d, *J*=16.77 Hz, 1 H) 4.62 (d, *J*=16.77 Hz, 1 H) 4.94 (d, *J*=6.96 Hz, 1 H) 7.08 (t, *J*=7.58 Hz, 1 H) 7.20 - 7.25 (m, 1 H) 7.30 (dd, *J*=7.40, 1.52 Hz, 1 H) 7.47 (dd, *J*=8.92, 2.50 Hz, 1 H) 7.66 (d, *J*=8.92 Hz, 1 H) 7.96 (d, *J*=2.50 Hz, 1 H) 8.30 (d, *J*=6.96 Hz, 1 H) 10.02 (s, 1 H)

MS (m/z) ESI ES^- = 408

The following compounds were synthesized according to the same general procedure as used for Example 57:

Example 58

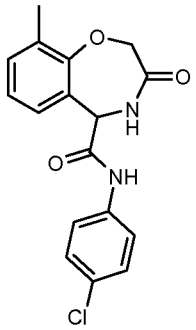


***N*-(4-bromo-3-fluorophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (H2)**

From 9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxylic acid (G1) and 4-bromo-3-fluoroaniline the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) δ ppm 2.17 (s, 3 H) 4.23 (d, *J*=16.77 Hz, 1 H) 4.62 (d, *J*=16.77 Hz, 1 H) 4.96 (d, *J*=6.96 Hz, 1 H) 7.08 (t, *J*=7.49 Hz, 1 H) 7.23 (dd, *J*=7.67, 0.89 Hz, 1 H) 7.30 (dd, *J*=7.58, 1.16 Hz, 1 H) 7.34 (dd, *J*=8.92, 2.14 Hz, 1 H) 7.56 - 7.65 (m, 1 H) 7.72 (dd, *J*=11.50, 2.41 Hz, 1 H) 8.28 (d, *J*=6.96 Hz, 1 H) 10.05 (s, 1 H)

Example 59



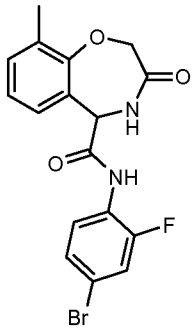
***N*-(4-chlorophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (H3)**

From 9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxylic acid (G1) and 4-chloroaniline the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) δ ppm 2.17 (s, 3 H) 4.25 (d, *J*=16.59 Hz, 1 H) 4.61 (d, *J*=16.59 Hz, 1 H) 4.97 (d, *J*=6.78 Hz, 1 H) 7.07 (t, *J*=7.58 Hz, 1 H) 7.20 - 7.25 (m, 1 H) 7.26 - 7.30 (m, 1 H) 7.34 (d, *J*=8.92 Hz, 2 H) 7.59 (d, *J*=8.92 Hz, 2 H) 8.23 (d, *J*=6.78 Hz, 1 H) 9.89 (s, 1 H)

MS (m/z) ESI ES^+ = 331

Example 60

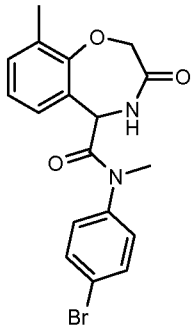


***N*-(4-bromo-2-fluorophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (H4)**

From 9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxylic acid (G1) and 4-bromo-2-fluoroaniline the title compound was afforded.

1H NMR (400 MHz, DMSO-d_6) δ ppm 2.18 (s, 3 H) 4.23 (d, *J*=16.77 Hz, 1 H) 4.62 (d, *J*=16.77 Hz, 1 H) 5.06 (d, *J*=6.96 Hz, 1 H) 7.07 (t, *J*=7.58 Hz, 1 H) 7.20 - 7.26 (m, 1 H) 7.33 (d, *J*=7.13 Hz, 2 H) 7.35 - 7.39 (m, 1 H) 7.57 (dd, *J*=10.35, 2.14 Hz, 1 H) 8.40 (d, *J*=6.96 Hz, 1 H) 9.56 (s, 1 H)

Example 61



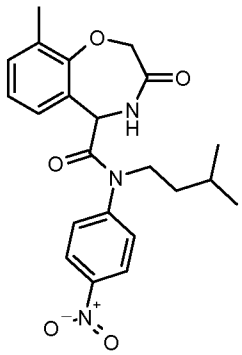
***N*-(4-bromophenyl)-*N*,9-dimethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (H5)**

From 9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxylic acid (G1) and N-methyl-4-bromoaniline the title compound was afforded.

MS (m/z) ESI ES^+ = 390

Tertiary Aniline-Amide Synthesis

Example 62



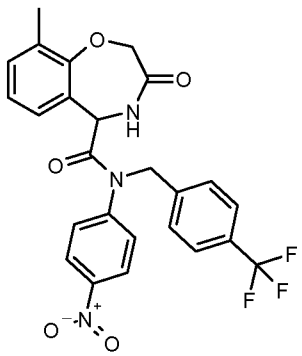
9-methyl-*N*-(3-methylbutyl)-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (I1)

To a solution 4-{[2,4-bis(methyloxy)phenyl]methyl}-9-methyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E1) (50mg, 0.10mmols, 1.0eq) in dry DMF (1ml) was added K_2CO_3 (70mg, 5.0eq) followed by 1-bromo-3-methylbutane (0.061ml, 5.0eq). After stirring for 48hrs at RT, the reaction was allowed to stir at 50 ^oC for 8hrs. After cooling to RT, the reaction was filtered followed by the addition of TFA (2ml) and heated to 50 ^oC for 12hrs. The reaction was concentrated *in vacuo* and the residue was purified via reverse phase preparatory HPLC to afford 7mg of the title compound.

MS (m/z) ESI ES^+ = 412

The following compounds were synthesized according to the same general procedure as used for Example 62:

Example 63

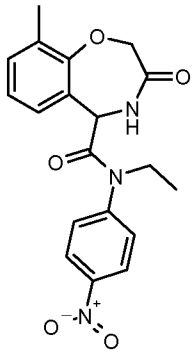


9-methyl-*N*-(4-nitrophenyl)-3-oxo-*N*-{[4-(trifluoromethyl)phenyl]methyl}-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (I2)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-9-methyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E1) and 4-trifluoromethylbenzyl bromide the title compound was afforded.

MS (m/z) ESI ES^+ = 500

Example 64

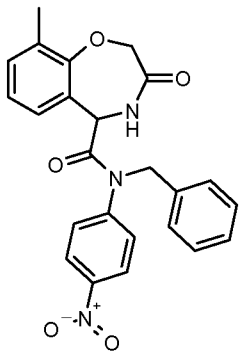


***N*-ethyl-9-methyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (I3)**

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-9-methyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E1) and iodoethane the title compound was afforded.

MS (m/z) ESI ES^+ = 370

Example 65

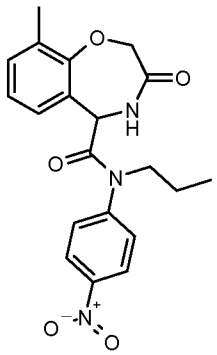


9-methyl-*N*-(4-nitrophenyl)-3-oxo-*N*-(phenylmethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (I4)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-9-methyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E1) and benzylbromide the title compound was afforded.

MS (m/z) ESI ES^+ = 432

Example 66



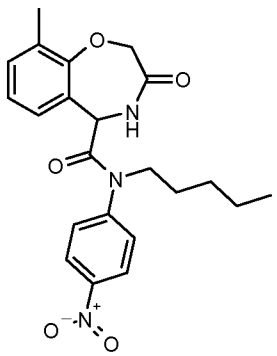
9-methyl-*N*-(4-nitrophenyl)-3-oxo-*N*-propyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (I5)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-9-methyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E1) and 1-bromopropane the title compound was afforded.

1H NMR (400 MHz, METHANOL-d_4) δ ppm 0.86 (t, *J*=7.40 Hz, 3 H) 1.35 - 1.62 (m, 2 H) 2.22 (s, 3 H) 3.41 - 3.54 (m, 1 H) 3.82 - 3.96 (m, 1 H) 4.22 (d, *J*=16.94 Hz, 1 H) 4.60 (d, *J*=16.77 Hz, 1 H) 5.12 (br. s., 1 H) 6.20 (br. s., 1 H) 6.56 - 6.76 (m, 1 H) 7.01 - 7.30 (m, 3 H) 8.10 (d, *J*=8.92 Hz, 2 H)

MS (m/z) ESI ES^+ = 384

Example 67



9-methyl-*N*-(4-nitrophenyl)-3-oxo-*N*-pentyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (I6)

From 4-{[2,4-bis(methyloxy)phenyl]methyl}-9-methyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide (E1) and 1-bromopentane the title compound was afforded.

MS (m/z) ESI ES^+ = 412

BIOLOGICAL SECTION

Compounds of the current invention are modulators of the androgen receptor. Particular compounds of the present invention were obtained through contract synthesis. One skilled in the art will recognize that the compound of Example 56 can be made by the method described above. However, such compound was only obtained through contract synthesis and tested in the assays described below. Androgen receptor mediated activity of the compounds of Examples 1-67 was determined using the following in vitro assays.

The following abbreviations and sources of materials are used:

Fluormone AL Green - a commercially available AR fluoroprobe (PanVera Corp, Product No P3010)

AR-LBD- Purified rat androgen ligand binding domain tagged with Glutathione Transferase (PanVera Corp, Product No P3009)

AR Screening Buffer - pH 7.5 containing protein stabilizing agents and glycerol (PanVera Corp Product No P3011)

DTT – dithiothreitol (PanVera Corp Product No P2325)

Discovery Analyst – is an FP reader

DMSO - dimethylsulphoxide

Androgen Receptor Fluorescence Polarization Assay:

The androgen receptor fluorescence polarization assay is used to investigate the interaction of the compounds with the androgen receptor.

Compounds are added to the 384 well black plates to a final volume of 0.5 µL. Sufficient Fluormone AL Green and AR-LBD are defrosted on ice to give a final concentration of 1 nM and 25 nM, respectively. AR screening buffer is chilled to 4 ^{o}C prior to addition of DTT to give a final concentration of 1 mM. The Fluormone AL Green and AR-LBD in AR Screening Buffer are added to compound plates to give a final volume of 10 µL. The assay is allowed to incubate at 20^{o}C for 5 hours. The plates are counted in a Discovery Analyst with suitable 485 nM excitation and 535 nM emission interference filters. Compounds that interact with the AR result in a lower fluorescence polarization reading. Test compounds are dissolved and diluted in DMSO. Compounds are assayed in singlicate, a four parameter curve fit of the following form being applied

$$y = \frac{a-d}{1+\left(x/c\right)^{b}} + d$$

where a is the minimum, b is the Hill slope, c is the IC_{50} and d is the maximum. Maximum and minimum values are compared to adhesion in the absence of compound and in the presence of 10^{-5}M dihydrotestosterone. Data is presented as the mean pIC_{50} with the standard error of the mean of n experiments. The compounds of Examples 1-67 exhibit a pIC_{50} equal to or greater than 5.0 in representative experiments of the AR fluorescence polarization assay herein described. Compounds with a % max greater than 50 are preferred.

Androgen Receptor Transcription Assay

AR DNA preparation

A plasmid containing an N-terminal truncation of the human AR gene was obtained from ATCC which was missing 154 residues from the N-terminus of the protein. The N-terminal region of the AR gene from a human liver cDNA library generated in-house, was cloned using PCR technique. The N-terminus and C-terminus pieces were PCR-ed together and subcloned in to the pSG5 vector at the BamHI site along with a Kozak sequence. The sequence differs from the published sequence in two regions of high variability within the receptor amongst published sequences. This clone has 1 additional glutamine residue (residue 79) and 3 additional glycine residues (position 475).

MMTV DNA preparation

pGL3-Basic Vector was digested with SmaI and XhoI. pMSG was digested with HindIII blunt ended and then digested with XhoI to excise the pMMTV-LTR. The pMMTV-LTR fragment was then ligated to the SmaI and XhoI sites of pGL3-Basic Vector. The resulting plasmid contains the MMTV promoter from position 26 to the XhoI site, followed by luciferase which is contained between the NcoI and SalI (position 3482) sites.

Assay protocol

Monkey kidney CV-1 cells (ECACC No. 87032605) were transiently transfected with Fugene-6 reagent according to the manufacturer's protocol. Briefly, a T175 flask of CV-1 cells at a density of 80% confluency was transfected with 25g of mix DNA and 75l of Fugene-6. The DNA mix (1.25microg pAR, 2.5microg pMMTV Luciferase and 18.75microg pBluescript (Stratagene)) was incubated with Fugene in 5 ml OptiMEM-1 for 30 min and then diluted up to 20 ml in transfection media (DMEM containing 1% Hyclone, 2mM L-Glutamine and 1% Pen/Strep) prior to addition to the cells. After 24h, cells were washed with PBS, detached from the flask using 0.25% trypsin

and counted using a Sysmex KX-21N. Transfected cells were diluted in assay media (DMEM containing 1% Hyclone, 2mM L-Glutamine and 1% Pen/Strep) at 70 cells/microlitre l. 70microlitres of suspension cells were dispensed to each well of white Nunc 384-well plates, containing compounds at the required concentration. After 24h, 10microlitres of Steady Glo were added to each well of the plates. Plates were incubated in the dark for 10 min before reading them on a Viewlux reader.

Analysis

All data was normalized to the mean of 16 high and 16 low control wells on each plate. A four parameter curve fit of the following form was then applied

$$y = \frac{a-d}{1+\left(x/c\right)^{b}} + d$$

Where a is the minimum, b is the Hill slope, c is the XC50 and d is the maximum. Data is presented as the mean pXC50 with the standard deviation of the mean of n experiments. Compounds with a pEC50 equal to or greater than 5.0 are preferred.

Castrated Male Rat Model (ORX Rat)

The activity of representative compounds of the present invention as modulators of the androgen receptor was investigated using a castrated male rat model (ORX) as described in C.D. Kockakian, *Pharmac. Therap.* **B 1**(2), 149-177 (1975); C. Tobin and Y. Joubert, *Developmental Biology* **146**,131-138 (1991); J. Antonio, J.D. Wilson and F.W. George, *J Appl. Physiol.* **87**(6) 2016-2019 (1999)) the disclosures of which herein are incorporated by reference to the extent that they describe the ORX model.

Androgens have been identified as playing important roles in the maintenance and growth of many tissues in both animals and humans. Muscles, like the levator ani and bulbocavernosus, and sexual accessory organs, such as the prostate glands and seminal vesicles have high expression levels of the androgen receptor and are known to respond quickly to exogenous androgen addition or androgen deprivation through testicular ablation. Castration produces dramatic atrophy of muscle and sexual accessory organs; whereas the administration of exogenous androgens to the castrated animal results in effective hypertrophy of these muscles and sexual accessory organs. Although the levator ani muscle, also known as the dorsal bulbocavernosus, is not 'true skeletal muscle' and definitely

sex-linked, it is reasonable to use this muscle to screen muscle anabolic activities of test compounds because of its androgen responsiveness and simplicity of removal.

Male Sprague-Dawley rats weighing 160-180 grams were used in the study. The rats were singly caged upon receiving and throughout the study. Bilateral orchidectomies were performed in sterilized surgical conditions under isoflurane anesthesia. An anteroposterior incision was made in the scrotum. The testicles were exteriorized and the spermatic artery and vas deferens were ligated with 4.0 silk 0.5 cm proximal to the ligation site. The testicles then were removed by a surgical scissors distal to the ligation sites. The tissue stumps were returned to the scrotum, the scrotum and overlying skin were closed by a surgical stapler. The Sham-ORX rats underwent all procedures except ligation and scissors cutting. The rats were assigned randomly into study groups 7-10 days post surgery based on the body weight.

Dihydrotestosterone (DHT) was used as a positive control (1-10 mg/kg s.c.). The compound of Example 10 was administered 20mg/kg orally for 7 days. The rats were weighed daily and doses were adjusted accordingly. The general well being of the animal was monitored throughout the course of the study.

At the end of the study, the rats were euthanized in a CO_2 chamber. The ventral prostate glands (VP), seminal vesicles (SV), levator ani muscle (LA) and bulbocavernosus (BC) were carefully dissected. The tissues were blotted dry, the weights were recorded, and then saved for histological and molecular analysis. The VP and SV weights serve as androgenic indicators and LA and BC as anabolic indicators. The ratio of anabolic to androgenic activities was used to evaluate the test compounds. Serum luteinizing hormone (LH), follicle stimulating hormone (FSH) and other potential serum markers of anabolic activities were also analyzed.

The compounds of Examples 1 and 10 were tested in this animal model. Animals treated with the compound of Example 10 showed levator ani hypertrophy and very little if any detectable prostate stimulation.

All research complied with the principles of laboratory animal care (NIH Publication No. 85-23, revised 1985) and GlaxoSmithKline policy on animal use.

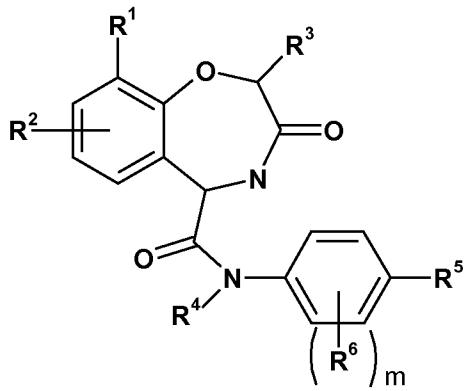
Although specific embodiments of the present invention are herein illustrated and described in detail, the invention is not limited thereto. The above detailed descriptions are provided as exemplary of the present invention and should not be construed as constituting any limitation of the invention. Modifications will be obvious to those skilled in the art, and all modifications that do not depart from the

spirit of the invention are intended to be included within the scope of the appended claims.

CLAIMS

What is claimed:

1. A compound of formula (I)



(I)

or a salt or solvate thereof,

wherein:

R^1 is C_{1-2}alkyl, halogen, or CF_3;

R^2 is H, Cl, F, or methyl;

R^3 is H or methyl;

R^4 is H, C_{1-6}alkyl, or benzyl optionally substituted with CF_3;

R^5 is methyl, nitro, halogen, CN, CF_3, or $-C(O)OCH_2CH_3$;

R^6 is Cl, F, or CF_3;

m is 0 or 1;

wherein:

when R^1 is ethyl or CF_3,

R^2 is H;

when R^1 is methyl, R^2 is H, and m is 0,

R^5 is nitro, halogen, CN, CF_3, or $-C(O)OCH_2CH_3$;

when R^1 is methyl, R^2 is H, and m is 1,

R^5 and R^6 are both Cl, or

R^5 is Br and R^6 is Cl or F, or

R^5 is CN and R^6 is CF_3;

when R^1 and R^2 are both methyl,

m is 0 and R^5 is CF_3, Br, nitro, or CN;

when R^1 is methyl, R^2 is F, and m is 0,

R^5 is CN, CF_3, or Br;

when R^1 is methyl, R^2 is F, and m is 1,

R^5 and R^6 are both Cl;

when R^1 is ethyl, R^2 is H, and m is 0,

R^5 is methyl, CF_3, nitro, CN, Br, or $C(O)OCH_2CH_3$;

when R^1 is ethyl, R^2 is H, and m is 1,

R^5 and R^6 are both Cl, or

R^5 is CN and R^6 is CF_3; and

when R^1 and R^2 are both Cl and m is 1,

R^5 and R^6 are both Cl, or

R^5 is CN and R^6 is CF_3.

2. A compound as claimed in claim 1, wherein R^1 and R^2 are both Cl.

3. A compound as claimed in any of claims 1 to 2, wherein m is 0.

4. A compound as claimed in any of claims 1 to 2, wherein m is 1.

5. A compound as claimed in any of claims 1 to 3 wherein R^5 is CF_3.

6. A compound as claimed in claim 1, wherein R^1 is $C_{1\text{-}2}$alkyl, Cl, or CF_3.

7. A compound as claimed in any of claims 1, and 3 to 6 wherein R^2 is H.

8. A compound as claimed in any of claims 1, and 3 to 7 wherein R^1 is methyl.

9. A compound as claimed in any of claims 1 to 8 wherein R^3 is H.

10. A compound as claimed in any of claims 1 to 9 wherein R^4 is H.

11. A compound as claimed in any of claims 1 to 4, and 6 to 10 wherein R^5 is nitro, CF3, Br, Cl, or CN.

12. A compound as claimed in any of claims 1 to 4, and 6 to 11 wherein R^5 is nitro.

13. A compound as claimed in any of claims 1 to 2, and 4 to 12 wherein m is 1 and the R^6 substituent is ortho to the R5 substituent.

14. A compound as claimed in claim 1, selected from the group consisting of

9-methyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

7,9-dichloro-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-chloro-*N*-(3,4-dichlorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-chloro-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

7,9-dichloro-*N*-(4-cyanophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-chloro-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-ethyl-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-nitrophenyl)-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(3,4-dichlorophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

7,9-dichloro-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-bromophenyl)-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-ethyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

7,9-dichloro-*N*-(3,4-dichlorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(3,4-dichlorophenyl)-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-bromophenyl)-2,9-dimethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

7,9-dichloro-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-bromophenyl)-9-chloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-methyl-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-bromophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(3,4-dichlorophenyl)-9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-cyanophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

8,9-dichloro-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-chloro-*N*-(4-cyanophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-cyanophenyl)-9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

8,9-dichloro-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-bromophenyl)-8,9-dichloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

ethyl 4-{[(7,9-dichloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)carbonyl]amino}benzoate;

8,9-dichloro-*N*-(3,4-dichlorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

6-fluoro-9-methyl-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-bromophenyl)-6-fluoro-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-bromophenyl)-9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(3,4-dichlorophenyl)-6-fluoro-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-[4-cyano-3-(trifluoromethyl)phenyl]-9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

8,9-dichloro-*N*-(4-cyanophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-bromophenyl)-6,9-dimethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

7,9-dichloro-*N*-(4-fluorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

6,9-dimethyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

6,9-dichloro-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-cyanophenyl)-6-fluoro-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-[4-cyano-3-(trifluoromethyl)phenyl]-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-[4-cyano-3-(trifluoromethyl)phenyl]-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

7,9-dichloro-*N*-(4-methylphenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

6,9-dimethyl-3-oxo-*N*-[4-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

2,9-dimethyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

8,9-dichloro-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-fluorophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

ethyl 4-{[(9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)carbonyl]amino}benzoate;

9-chloro-*N*-(4-methylphenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

8,9-dichloro-*N*-(4-fluorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-fluorophenyl)-3-oxo-9-(trifluoromethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-chloro-*N*-(4-fluorophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

ethyl 4-{[(9-ethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)carbonyl]amino}benzoate;

9-ethyl-*N*-(4-methylphenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

ethyl 4-{[(8,9-dichloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepin-5-yl)carbonyl]amino}benzoate;

8,9-dichloro-*N*-(4-methylphenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-bromophenyl)-7,9-dichloro-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-bromo-3-chlorophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-bromo-3-fluorophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-chlorophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-bromo-2-fluorophenyl)-9-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-(4-bromophenyl)-*N*,9-dimethyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-methyl-*N*-(3-methylbutyl)-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-methyl-*N*-(4-nitrophenyl)-3-oxo-*N*-{[4-(trifluoromethyl)phenyl]methyl}-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

N-ethyl-9-methyl-*N*-(4-nitrophenyl)-3-oxo-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-methyl-*N*-(4-nitrophenyl)-3-oxo-*N*-(phenylmethyl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-methyl-*N*-(4-nitrophenyl)-3-oxo-*N*-propyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide;

9-methyl-*N*-(4-nitrophenyl)-3-oxo-*N*-pentyl-2,3,4,5-tetrahydro-1,4-benzoxazepine-5-carboxamide; or a salt or solvate thereof.

15. A pharmaceutical composition comprising a compound according to any one of claims 1 to 14, and a pharmaceutically acceptable carrier.

16. A compound as claimed in any one of claims 1 to 14 for use as an active therapeutic substance.

17. A method for the treatment of hypogonadism, sarcopenia, osteoporosis, muscle wasting, wasting diseases, cancer cachexia, frailty, prostatic hyperplasia, prostate cancer, breast cancer, menopausal and andropausal vasomotor conditions, urinary incontinence, sexual dysfunction, erectile dysfunction, depression, uterine fibroid disease, endometriosis, acne, hirsutism, male contraception, impotence, and a method of male and female hormone replacement therapy, stimulation of hematopoiesis, and anabolism, comprising the administration of a compound according to any one of claims 1 to 14.

18. A compound according to any one of claims 1 to 14 for use in the treatment of hypogonadism, sarcopenia, osteoporosis, muscle wasting, wasting diseases, cancer cachexia, frailty, prostatic hyperplasia, prostate cancer, breast cancer, menopausal and andropausal vasomotor conditions, urinary incontinence, sexual dysfunction, erectile dysfunction, depression, uterine fibroid disease, endometriosis, acne, hirsutism, male contraception, impotence, and in the use as male and female hormone replacement therapy, as a stimulant of hematopoiesis, and as an anabolic agents.

19. Use of a compound according to any one of claims 1 to 14 in the manufacture of a medicament for use in the treatment of hypogonadism, sarcopenia, osteoporosis, muscle wasting, wasting diseases, cancer cachexia, frailty, prostatic hyperplasia, prostate cancer, breast cancer, menopausal and andropausal vasomotor conditions, urinary incontinence, sexual dysfunction, erectile dysfunction, depression, uterine fibroid disease, endometriosis, acne, hirsutism, male contraception, impotence, and in the use as male and female

hormone replacement therapy, as a stimulant of hematopoiesis, and as an anabolic agent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/58091

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/00; A61K 31/00, 31/553 (2008.04)
USPC - 514/211.05
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/211.05

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/211.09; 540/490, 546, 552 (text search-see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); DialogWeb; Google Scholar
Search Terms Used: benzoxazepine, carboxamide, non-steroidal, androgen receptor.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 3,676,460 A (Hirohashi et al.) 11 July 1972 (11.07.1972) col 1, ln 19-45; col 2, ln 60-65	1-4, 6 and 14
Y	US 3,953,469 A (Krapcho) 27 April 1976 (27.04.1976) col 1, ln 12-30	1-4, 6 and 14
Y	US 5,770,594 A (Hamanaka et al.) 23 June 1998 (23.06.1998) col 2, ln 20-45	2 and 4

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 June 2008 (20.06.2008)	09 JUL 2008
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/58091

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5, 7-13 and 15-19
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.