NOVEL COMPOUNDS

Field of the Invention

This invention relates to heterocyclic compounds, which are pyrimidinone derivatives having human neutrophil elastase inhibitory properties, and their use in therapy.

Background to the invention

Human neutrophil elastase (HNE) is a 32 kDa serine proteinase found in the azurophilic granules of neutrophils. It has a role in the degradation of a wide range of extracellular matrix proteins, including fibronectin, laminin, proteoglycans, Type III and Type IV collagens as well as elastin (Bieth, G. In *Regulation of Matrix accumulation*, Mecham, R.P. (Eds), Academic Press, NY, USA 1986, 217-306). HNE has long been considered to play an important role in homeostasis through repair and disposal of damaged tissues via degradation of the tissue structural proteins. It is also relevant in the defense against bacterial invasion by means of degradation of the bacterial body. In addition to its effects on matrix tissues, HNE has been implicated in the upregulation of IL-8 gene expression and also induces IL-8 release from the epithelial cells of the lung. In animal models of Chronic Obstructive Pulmonary Disease induced by tobacco smoke exposure both small molecule inhibitors and protein inhibitors of HNE inhibit the inflammatory response and the development of emphysema (Wright, J.L. et al. *Am. J. Respir. Crit. Care Med.* 2002, *166*, 954-960; Churg, A. et al. *Am. J. Respir. Crit. Care Med.* 2003, *168*, 199-207). Thus, HNE may play a role both in matrix destruction and in amplifying inflammatory responses in chronic respiratory diseases where neutrophil influx is a characteristic feature. Indeed, HNE is believed to play a role in several pulmonary diseases, including chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), acute respiratory distress syndrome (ARDS), pulmonary emphysema, pneumonia and lung fibrosis. It is also implicated in several cardiovascular diseases in which tissue remodelling is involved, for example, in heart failure and the generation of

ischaemic tissue injury following acute myocardial infarction.

COPD is an umbrella term encompassing three different pathological conditions, all of which contribute to limitation of airflow: chronic bronchitis, emphysema and small-airway disease. Generally all three will exist to varying extents in patients presenting with COPD, and all three may be due to neutrophil-mediated inflammation, as supported by the increased number of neutrophils observed in bronchoalveolar leakage (BAL) fluids of COPD patients (Thompson, A.B.; Daughton, D.; et al. *Am. Rev. Respir. Dis.* 1989, *140*, 1527-1537). The major pathogenic determinant in COPD has long been considered to be the protease-anti-protease balance (also known as the "elastase:anti-elastase hypothesis"), in which an imbalance of HNE and endogenous antiproteases such as α1-antitrypsin (α_1-AT), secretory leukocyte protease inhibitor (SLPI) and pre-elafin leads to the various inflammatory disorders of COPD. Individuals that have a genetic deficiency of the protease inhibitor α1-antitrypsin develop emphysema that increases in severity over time (Laurrell, C.B.; Erikkson, S *Scand. J. Clin. Invest.* 1963 *15*, 132-140). An excess of HNE is therefore destructive, leading to the breakdown of pulmonary morphology with loss of elasticity and destruction of alveolar attachments of airways in the lung (emphysema) whilst simultaneously increasing microvascular permeability and mucus hypersecretion (chronic bronchitis).

Several human neutrophil inhibitors have need disclosed so far in the art. In particular, International Patent Applications n. WO2011/110858 and n. WO2011/110859 describe some pyrimidine derivatives having human neutrophil elastase inhibitory properties and their use in therapy.

Although several HNE inhibitors have been disclosed so far as above reported, there is still a need for further HNE inhibitors. Particularly, there is still a need for further HNE inhibitors endowed with a high potency for HNE enzyme inhibition. Particularly advantageous would also be the identification of further HNE inhibitors endowed with a high potency for HNE enzyme inhibition and which would show an appropriate developability profile as an inhalation treatment.

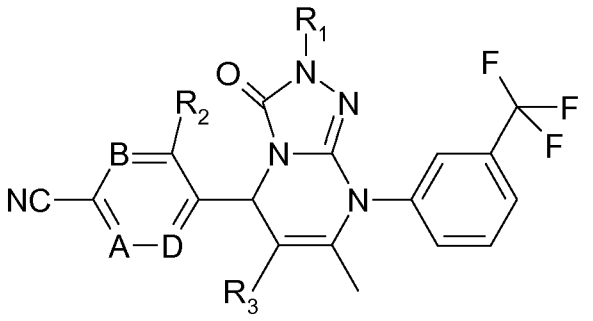
The present invention addresses the above mentioned need by providing the compounds of the invention.

Brief description of the invention

This invention provides novel compounds which are inhibitors of HNE, and are useful in the treatment of diseases or conditions in which HNE activity plays a part.

Detailed Description of the Invention

In one aspect the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

A is CH or N;

B is CH or N;

D is CH or N;

R_1 is selected in the list consisting of:

- hydrogen;
- $(C_1\text{-}C_6)$alkyl;
- $NR_7R_8(C_1\text{-}C_6)$alkyl;
- $(C_1\text{-}C_4)$alkenyl;
- phenyl$(C_1\text{-}C_6)$alkyl wherein such phenyl ring is optionally substituted by a group $NR_{15}R_{16}(C_1\text{-}C_6)$alkyl or by $N^+R_{15}R_{16}R_{17}(C_1\text{-}C_6)$alkyl;
- a group $-CH_2(CH_2)_nOH$;
- a group $-(CH_2)_nCONR_5R_6$;
- a group $-(CH_2)_nSO_2NR_5R_6$;

- a group $-CH_2-(CH_2)_nNR_5SO_2R_6$;

- a group $-(CH_2)_t-(C_6H_4)-SO_2(C_1-C_4)$alkyl;

- a group $-(CH_2)_rSO_2(C_1-C_4)$alkyl wherein such (C_1-C_4)alkyl is optionally substituted by a group $-NR_{15}R_{16}$ or $-N^+R_{15}R_{16}R_{17}$;

- a group $-SO_2$-phenyl wherein such phenyl ring is optionally substituted by $NR_7R_8(C_1-C_6)$alkyl; and

- a group $-(CH_2)_n$-W wherein **W** is a 5-6-membered heteroaryl ring which is optionally substituted by a group $-SO_2(C_1-C_4)$alkyl;

n is 1, 2 or 3;

t is zero, 1, 2 or 3;

r is zero, 1, 2 , 3 or 4;

$\mathbf{R_5}$ is selected in the group consisting of: hydrogen, (C_1-C_6)alkyl, $NR_{16}R_{15}(C_1-C_6)$alkyl and $N^+R_{17}R_{15}R_{16}(C_1-C_6)$alkyl;

$\mathbf{R_6}$ is hydrogen or (C_1-C_6)alkyl;

$\mathbf{R_7}$ is selected in the group consisting of: hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkylcarbonyl, $-SO_2(C_1-C_4)$alkyl and $NR_{16}R_{15}(C_1-C_6)$alkyl;

$\mathbf{R_8}$ is hydrogen or (C_1-C_6)alkyl;

alternatively, $\mathbf{R_7}$ and $\mathbf{R_8}$ together with the nitrogen atom they are linked to may form a (C_5-C_7)heterocycloalkyl ring system which is optionally substituted by one or more groups (C_1-C_6) alkyl and oxo;

$\mathbf{R_{16}}$ is hydrogen or (C_1-C_6)alkyl;

$\mathbf{R_{15}}$ is hydrogen or (C_1-C_6)alkyl;

$\mathbf{R_{17}}$ is hydrogen or (C_1-C_6)alkyl;

$\mathbf{R_3}$ is a group cyano or a group $-C(O)-XR_4$;

X is a divalent group selected from: -O-, $-(CH_2)-$ and -NH-;

$\mathbf{R_4}$ is a group selected in the list consisting of:

- hydrogen;

- (C_1-C_6)alkyl;

- a group of formula -[Alk^1]-Z wherein **Alk^1** represents a (C_1-C_4)alkylene radical and **Z** is:

(i) -NR_9R_{10} wherein R_9 and R_{10} are independently hydrogen, (C_1-C_6)alkyl or (C_3-C_6)cycloalkyl group, wherein such (C_1-C_6)alkyl or (C_3-C_6)cycloalkyl group are optionally substituted by one to four group R_{35} which are at each occurrence independently selected in the group consisting of: (C_1-C_6)alkyl, (C_1-C_6)alkoxyl, hydroxyl, hydroxyl-C_1-C_6-alkyl, halo, trifluoromethyl, trifluoromethoxy; or, taken together with the nitrogen to which they are attached, form a monocyclic (C_5-C_7)heterocyclic ring which may contain a further heteroatom selected from N, O and S and which is optionally substituted by one to four group R_{35} which are at each occurrence independently selected in the group consisting of: (C_1-C_6)alkyl, (C_1-C_6)alkoxyl, hydroxyl, hydroxyl-C_1-C_6-alkyl, halo, trifluoromethyl, trifluoromethoxy;

or

(ii) -$N^+R_{11}R_{12}R_{13}$ wherein R_{11}, R_{12} and R_{13} are each independently (C_1-C_6)alkyl or (C_3-C_6)cycloalkyl group, wherein such (C_1-C_6)alkyl or (C_3-C_6)cycloalkyl group are optionally substituted by one to four group R_{36} which are at each occurrence independently selected in the group consisting of: (C_1-C_6)alkyl, (C_1-C_6)alkoxyl, hydroxyl, hydroxyl-C_1-C_6-alkyl, halo, trifluoromethyl, trifluoromethoxy; or any two of R_{11}, R_{12} and R_{13} taken together with the nitrogen they are linked to form a monocyclic (C_5-C_7)heterocyclic ring which may contain a further heteroatom selected from N, O and S and the other of R_{11}, R_{12} and R_{13} is a (C_1-C_6)alkyl or an optionally substituted (C_3-C_6)cycloalkyl group, wherein such monocyclic(C_5-C_7)heterocyclic, (C_1-C_6)alkyl or (C_3-C_6)cycloalkyl group are optionally substituted by one to four group R_{36} which are at each occurrence independently selected in the group consisting of: (C_1-C_6)alkyl, (C_1-C_6)alkoxyl, hydroxyl, hydroxyl-C_1-C_6-alkyl, halo, trifluoromethyl, trifluoromethoxy;

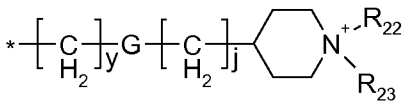
- a radical of formula -$(CH_2)_q$-[Q]–$(CH_2)_p$ Z wherein **Z** is as above defined, q is an integer ranging from zero to 3, p is an integer ranging from zero to 3 and Q represents a divalent group selected from: -O-, phenylene, (C_5-C_7)heterocycloalkylene, (C_3-

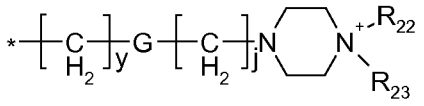
C_6)cycloalkyl and pyridinylene, wherein such phenylene, (C_5-C_7)heterocycloalkylene, (C_3-C_6)cycloalkyl and pyridinylene are optionally substituted by one to four group R_{37} which are at each occurrence independently selected in the group consisting of: (C_1-C_6)alkyl, (C_1-C_6)alkoxyl, hydroxyl, hydroxyl-C_1-C_6-alkyl, halo, trifluoromethyl, trifluoromethoxy;

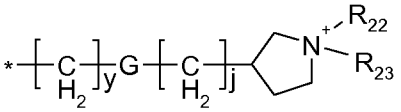
R_2 is selected from a group consisting of:

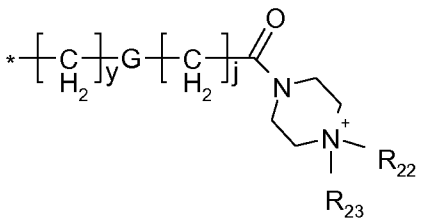
$R_{14}O(C_1$-$C_6)$alkyl; $NR_{18}R_{19}(C_1$-$C_6)$alkyl; -$CONR_{21}R_{20}$; C_2-C_6-alkenyl which C_2-C_6-alkenyl may be optionally substituted by a group –OH or -$NR_{18}R_{19}$; C_2-C_6-alkynyl which C_2-C_6-alkynyl may be optionally substituted by a group –OH or -$NR_{18}R_{19}$; and a group –$[CH_2]_y$-G-$[CH_2]_j$-CH_2-$N^+R_{22}R_{23}R_{24}$

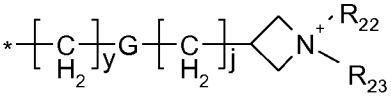
or **R_2** is a group:



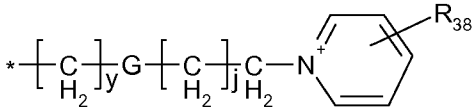








or **R_2** is a group:



R_{14} is hydrogen or (C_1-C_6)alkyl which may be optionally substituted by a group (C_1-C_4)alkoxyl;

R_{18} is hydrogen or (C_1-C_6)alkyl;

R_{19} is hydrogen or (C_1-C_6)alkyl;

R_{20} is selected in the group consisting of: hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkyl$NR_{18}R_{19}$;

R_{21} is hydrogen or (C_1-C_6)alkyl;

j is an integer ranging from zero to 4;

y is an integer ranging from zero to 4;

G is a divalent linker selected from the group consisting of: -O-, -(SO_2)-, NR_{25}, a bond, C_2-C_6-alkenylene, C_2-C_6-alkynylene, (C_3-C_6)cycloalkylene, mono or bicyclic heterocycloalkylene, -[$CONR_{25}$]- and -[$NR_{25}CO$]-;

$\mathbf{R_{25}}$ is hydrogen or (C_1-C_6)alkyl;

$\mathbf{R_{22}}$ is selected in the group consisting of: (C_1-C_6)alkyl, which (C_1-C_6)alkyl is optionally substituted by one or more groups (C_3-C_6)cycloalkyl, phenyl, benzyl, CN, -OR_{26}, -SO_2R_{26}, -CO_2R_{26}, -$CONR_{26}R_{27}$ or -$SO_2NR_{26}R_{27}$; (C_3-C_{10})cycloalkyl which is optionally substituted by one or more groups –OR_{26}, -SO_2R_{26}, -CO_2R_{26}, -$CONR_{26}R_{27}$ or -$SO_2NR_{26}R_{27}$; and (C_4-C_7)heterocycloalkyl which is optionally substituted by one or more groups –OR_{26}, -SO_2R_{26}, -CO_2R_{26}, -$CONR_{26}R_{27}$ or -$SO_2NR_{26}R_{27}$;

$\mathbf{R_{26}}$ is hydrogen or (C_1-C_6)alkyl;

$\mathbf{R_{27}}$ is hydrogen or (C_1-C_6)alkyl;

$\mathbf{R_{23}}$ is hydrogen or (C_1-C_6)alkyl, which (C_1-C_6)alkyl is optionally substituted by one or more groups –OR_{29}, -SO_2R_{29}, -CO_2R_{29}, -$CONR_{29}R_{30}$ or -$SO_2NR_{29}R_{30}$;

$\mathbf{R_{24}}$ is hydrogen or (C_1-C_6)alkyl, which (C_1-C_6)alkyl is optionally substituted by one or more groups –OR_{31}, -SO_2R_{31}, -CO_2R_{31}, -$CONR_{31}R_{32}$ or -$SO_2NR_{31}R_{32}$;

alternatively, $\mathbf{R_{23}}$ and $\mathbf{R_{24}}$ together with the nitrogen atom they are linked to may form a 5-11- membered saturated monocyclic or bicyclic heterocyclic ring system which is optionally substituted by one or more groups –OR_{28}, halo, C_1-C_6 alkyl, -SO_2R_{33}, -CO_2R_{33}, -$CONR_{33}R_{34}$ or -$SO_2NR_{33}R_{34}$; and which 5-11- membered saturated monocyclic or bicyclic ring optionally contains a further heteroatom which is oxygen or nitrogen or a group –SO_2-;

or $\mathbf{R_{22}}$ together with $\mathbf{R_{23}}$, $\mathbf{R_{24}}$ and the nitrogen atom they are linked to, may form a bridged bicyclic heterocyclic ring system;

$\mathbf{R_{28}}$ is hydrogen or (C_1-C_6)alkyl;

$\mathbf{R_{29}}$ is hydrogen or (C_1-C_6)alkyl;

R_{30} is hydrogen or (C_1-C_6)alkyl;

R_{31} is hydrogen or (C_1-C_6)alkyl;

R_{32} is hydrogen or (C_1-C_6)alkyl;

R_{33} is hydrogen or (C_1-C_6)alkyl;

R_{34} is hydrogen or (C_1-C_6)alkyl;

R_{38} represents one or two optional substituents at each occurrence selected in the list consisting of: (C_1-C_6)alkyl, (C_1-C_6)alkoxyl, hydroxyl, hydroxyl-C_1-C_6-alkyl, halo, trifluoromethyl, trifluoromethoxy;

wherein only two of A, B and D may be at the same time a nitrogen atom;

wherein if one or more groups $N^+R_{11}R_{12}R_{13}$- or $N^+R_{15}R_{16}R_{17}$- are present, they form quaternary salts with a pharmaceutically acceptable counter ion;

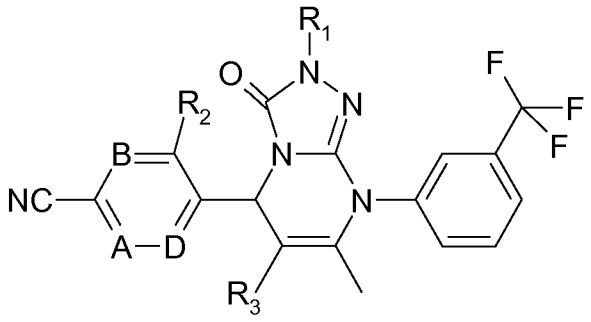
and wherein groups R_5 to R_{38}, and n may have the same or different meanings at each occurrence, if present in more than one group.

Compounds of formula (I) may be prepared in the form of salts, particularly pharmaceutically acceptable salts, N-oxides, hydrates, solvates and polymorphs thereof. Any reference to a compound herein, or reference to "compounds of the invention", "compounds of formula (I)", and the like includes such compounds whether or not in salt, N-oxide, hydrate, solvate or polymorphic form.

Compounds of the invention may be used in the treatment or prevention of diseases in which HNE is implicated, for example chronic obstructive pulmonary disease (COPD), bronchiectasis, chronic bronchitis, lung fibrosis, pneumonia, acute respiratory distress syndrome (ARDS), pulmonary emphysema, smoking-induced emphysema and cystic fibrosis.

Hence other aspects of the invention are (i) a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier or excipient; and (ii) the use of a compound of the invention for the manufacture of a medicament for the treatment or prevention of a disease or condition in which HNE is implicated.

In one embodiment, the invention provides a compound of formula (IB), or a pharmaceutically acceptable salt thereof:



(IB)

wherein

A is CH or N;

B is CH or N;

D is CH or N;

R_1 is selected from the list consisting of:

- hydrogen;
- $(C_1\text{-}C_6)$alkyl;
- $NR_7R_8(C_1\text{-}C_6)$alkyl;
- $(C_1\text{-}C_4)$alkenyl;
- phenyl$(C_1\text{-}C_6)$alkyl wherein such phenyl ring is optionally substituted by a group $NR_{15}R_{16}(C_1\text{-}C_6)$alkyl or by $N^+R_{15}R_{16}R_{17}(C_1\text{-}C_6)$alkyl;
- a group $-CH_2(CH_2)_nOH$;
- a group $-(CH_2)_nCONR_5R_6$;
- a group $-(CH_2)_nSO_2NR_5R_6$;
- a group $-CH_2\text{-}(CH_2)_nNR_5SO_2R_6$;
- a group $-(CH_2)_t\text{-}(C_6H_4)\text{-}SO_2(C_1\text{-}C_4)$alkyl;
- a group $-(CH_2)_rSO_2(C_1\text{-}C_4)$alkyl wherein such $(C_1\text{-}C_4)$alkyl is optionally substituted by a group $-NR_{15}R_{16}$ or $-N^+R_{15}R_{16}R_{17}$;
- a group $-SO_2$-phenyl wherein such phenyl ring is optionally substituted by

$NR_7R_8(C_1\text{-}C_6)$alkyl; and

- a group $-(CH_2)_n$-W wherein **W** is a 5-6-membered heteroaryl ring which is optionally substituted by a group $-SO_2(C_1\text{-}C_4)$alkyl;

n is 1, 2 or 3;

t is zero, 1, 2 or 3;

r is zero, 1, 2 , 3 or 4;

$\mathbf{R_5}$ is selected in the group consisting of: hydrogen, $(C_1\text{-}C_6)$alkyl, $NR_{16}R_{15}(C_1\text{-}C_6)$alkyl and $N^+R_{17}R_{15}R_{16}(C_1\text{-}C_6)$alkyl;

$\mathbf{R_6}$ is hydrogen or $(C_1\text{-}C_6)$alkyl;

$\mathbf{R_7}$ is selected in the group consisting of: hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylcarbonyl, $-SO_2(C_1\text{-}C_4)$alkyl and $NR_{16}R_{15}(C_1\text{-}C_6)$alkyl;

$\mathbf{R_8}$ is hydrogen or $(C_1\text{-}C_6)$alkyl;

alternatively, $\mathbf{R_7}$ and $\mathbf{R_8}$ together with the nitrogen atom they are linked to may form a $(C_5\text{-}C_7)$heterocycloalkyl ring system which is optionally substituted by one or more groups $(C_1\text{-}C_6)$ alkyl and oxo;

$\mathbf{R_{16}}$ is hydrogen or $(C_1\text{-}C_6)$alkyl;

$\mathbf{R_{15}}$ is hydrogen or $(C_1\text{-}C_6)$alkyl;

$\mathbf{R_{17}}$ is hydrogen or $(C_1\text{-}C_6)$alkyl;

$\mathbf{R_3}$ is a group cyano or a group $-C(O)\text{-}XR_4$;

X is a divalent group selected from: -O-, $-(CH_2)$- and -NH-;

$\mathbf{R_4}$ is a group selected in the list consisting of:

- hydrogen;

$-(C_1\text{-}C_6)$alkyl;

-a group of formula $-[Alk^1]$-Z wherein $\mathbf{Alk^1}$ represents a $(C_1\text{-}C_4)$alkylene radical and **Z** is:

(i) $-NR_9R_{10}$ wherein R_9 and R_{10} are independently hydrogen, $(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_6)$cycloalkyl group, wherein such $(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_6)$cycloalkyl group are optionally substituted by one to four group R_{35} which are at each occurrence independently selected

in the group consisting of: (C_1-C_6)alkyl, (C_1-C_6)alkoxyl, hydroxyl, hydroxyl-C_1-C_6-alkyl, halo, trifluoromethyl, trifluoromethoxy; or, taken together with the nitrogen to which they are attached, form a monocyclic (C_5-C_7)heterocyclic ring which may contain a further heteroatom selected from N, O and S and which is optionally substituted by one to four group R_{35} which are at each occurrence independently selected in the group consisting of: (C_1-C_6)alkyl, (C_1-C_6)alkoxyl, hydroxyl, hydroxyl-C_1-C_6-alkyl, halo, trifluoromethyl, trifluoromethoxy;

or

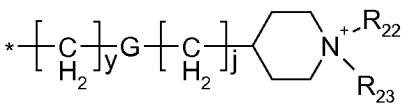
(ii) $-N^+R_{11}R_{12}R_{13}$ wherein R_{11}, R_{12} and R_{13} are each independently (C_1-C_6)alkyl or (C_3-C_6)cycloalkyl group, wherein such (C_1-C_6)alkyl or (C_3-C_6)cycloalkyl group are optionally substituted by one to four group R_{36} which are at each occurrence independently selected in the group consisting of: (C_1-C_6)alkyl, (C_1-C_6)alkoxyl, hydroxyl, hydroxyl-C_1-C_6-alkyl, halo, trifluoromethyl, trifluoromethoxy; or any two of R_{11}, R_{12} and R_{13} taken together with the nitrogen they are linked to form a monocyclic (C_5-C_7)heterocyclic ring which may contain a further heteroatom selected from N, O and S and the other of R_{11}, R_{12} and R_{13} is a (C_1-C_6)alkyl or an optionally substituted (C_3-C_6)cycloalkyl group, wherein such monocyclic (C_5-C_7)heterocyclic, (C_1-C_6)alkyl or (C_3-C_6)cycloalkyl group are optionally substituted by one to four group R_{36} which are at each occurrence independently selected in the group consisting of: (C_1-C_6)alkyl, (C_1-C_6)alkoxyl, hydroxyl, hydroxyl-C_1-C_6-alkyl, halo, trifluoromethyl, trifluoromethoxy;

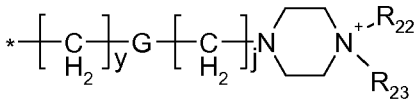
-a radical of formula $-(CH_2)_q$-[Q]–$(CH_2)_p$ Z wherein **Z** is as above defined, q is an integer ranging from zero to 3, p is an integer ranging from zero to 3 and Q represents a divalent group selected from: -O-, phenylene, (C_5-C_7)heterocycloalkylene, (C_3-C_6)cycloalkyl and pyridinylene, wherein such phenylene, (C_5-C_7)heterocycloalkylene, (C_3-C_6)cycloalkyl and pyridinylene are optionally substituted by one to four group R_{37} which are at each occurrence independently selected in the group consisting of: (C_1-C_6)alkyl, (C_1-C_6)alkoxyl, hydroxyl, hydroxyl-C_1-C_6-alkyl, halo, trifluoromethyl, trifluoromethoxy;

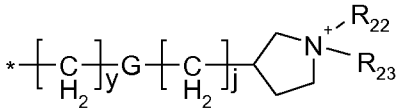
R_2 is selected from a group consisting of:

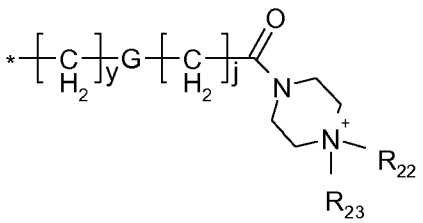
$R_{14}O(C_1\text{-}C_6)$alkyl; $NR_{18}R_{19}(C_1\text{-}C_6)$alkyl; $-CONR_{21}R_{20}$; $C_2\text{-}C_6$-alkenyl which $C_2\text{-}C_6$-alkenyl may be optionally substituted by a group –OH or $-NR_{18}R_{19}$; $C_2\text{-}C_6$-alkynyl which $C_2\text{-}C_6$-alkynyl may be optionally substituted by a group –OH or $-NR_{18}R_{19}$; and a group $-[CH_2]_y\text{-}G\text{-}[CH_2]_j\text{-}CH_2\text{-}N^+R_{22}R_{23}R_{24}$

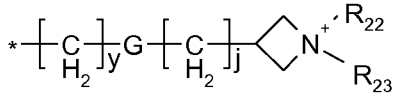
or **R_2** is a group:





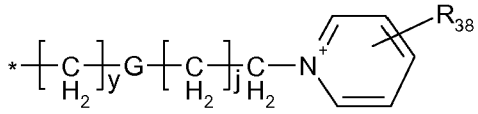






or

or **R_2** is a group:



R_{14} is hydrogen or $(C_1\text{-}C_6)$alkyl which may be optionally substituted by a group $(C_1\text{-}C_4)$alkoxyl;

R_{18} is hydrogen or $(C_1\text{-}C_6)$alkyl;

R_{19} is hydrogen or $(C_1\text{-}C_6)$alkyl;

R_{20} is selected in the group consisting of: hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl$NR_{18}R_{19}$;

R_{21} is hydrogen or $(C_1\text{-}C_6)$alkyl;

j is an integer ranging from zero to 4;

y is an integer ranging from zero to 4;

G is a divalent linker selected from the group consisting of: -O-, $-(SO_2)-$, NR_{25}, a bond, $C_2\text{-}C_6$-alkenylene, $C_2\text{-}C_6$-alkynylene, $(C_3\text{-}C_6)$cycloalkylene, mono or bicyclic heterocycloalkylene, $-[CONR_{25}]-$ and $-[NR_{25}CO]-$;

$\mathbf{R_{25}}$ is hydrogen or (C_1-C_6)alkyl;

$\mathbf{R_{22}}$ is selected from the group consisting of: (C_1-C_6)alkyl, which (C_1-C_6)alkyl is optionally substituted by one or more groups –OR_{26}, -SO_2R_{26}, -CO_2R_{26}, -$CONR_{26}R_{27}$ or -$SO_2NR_{26}R_{27}$;(C_3-C_6)cycloalkyl; and (C_4-C_7)heterocycloalkyl;

$\mathbf{R_{26}}$ is hydrogen or (C_1-C_6)alkyl;

$\mathbf{R_{27}}$ is hydrogen or (C_1-C_6)alkyl;

$\mathbf{R_{23}}$ is hydrogen or (C_1-C_6)alkyl, which (C_1-C_6)alkyl is optionally substituted by one or more groups –OR_{29}, -SO_2R_{29}, -CO_2R_{29}, -$CONR_{29}R_{30}$ or -$SO_2NR_{29}R_{30}$;

$\mathbf{R_{24}}$ is hydrogen or (C_1-C_6)alkyl, which (C_1-C_6)alkyl is optionally substituted by one or more groups –OR_{31}, -SO_2R_{31}, -CO_2R_{31}, -$CONR_{31}R_{32}$ or -$SO_2NR_{31}R_{32}$;

alternatively, $\mathbf{R_{23}}$ and $\mathbf{R_{24}}$ together with the nitrogen atom they are linked to may form a 5-11- membered saturated monocyclic or bicyclic heterocyclic ring system which is optionally substituted by one or more groups –OR_{28}, halo, C_1-C_6 alkyl, -SO_2R_{33}, -CO_2R_{33}, -$CONR_{33}R_{34}$ or -$SO_2NR_{33}R_{34}$; and which 5-11- membered saturated monocyclic or bicyclic ring optionally contains a further heteroatom which is oxygen or nitrogen or a group –SO_2-;

or $\mathbf{R_{22}}$ together with $\mathbf{R_{23}}$, $\mathbf{R_{24}}$ and the nitrogen atom they are linked to, may form a bridged bicyclic heterocyclic ring system;

$\mathbf{R_{28}}$ is hydrogen or (C_1-C_6)alkyl;

$\mathbf{R_{29}}$ is hydrogen or (C_1-C_6)alkyl;

$\mathbf{R_{30}}$ is hydrogen or (C_1-C_6)alkyl;

$\mathbf{R_{31}}$ is hydrogen or (C_1-C_6)alkyl;

$\mathbf{R_{32}}$ is hydrogen or (C_1-C_6)alkyl;

$\mathbf{R_{33}}$ is hydrogen or (C_1-C_6)alkyl;

$\mathbf{R_{34}}$ is hydrogen or (C_1-C_6)alkyl;

$\mathbf{R_{38}}$ represents one or two optional substituents at each occurrence selected in the list consisting of: (C_1-C_6)alkyl, (C_1-C_6)alkoxyl, hydroxyl, hydroxyl-C_1-C_6-alkyl, halo, trifluoromethyl, trifluoromethoxy;

wherein only two of A, B and D may be at the same time a nitrogen atom;

wherein if one or more groups $N^+R_{11}R_{12}R_{13}$- or $N^+R_{15}R_{16}R_{17}$- are present, they form quaternary salts with a pharmaceutically acceptable counter ion;

and wherein groups R_5 to R_{37} and n may have the same or different meanings at each occurrence, if present in more than one group.

Terminology

The term "$(C_a$-$C_b)$alkyl" wherein a and b are integers refers to a straight or branched chain alkyl radical having from a to b carbon atoms. Thus when a is 1 and b is 6, for example, the term includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

The term "$(C_d$-$C_b)$alkenyl" wherein a and b are integers refers to a straight or branched chain alkenyl moiety having from d to b carbon atoms having at least one double bond of either E or Z stereochemistry where applicable. Thus when d is 2 and b is 6, for example, the term includes, for example, vinyl, allyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

By analogy, the expression "$(C_d$-$C_b)$alkenylene" refers to a divalent "$(C_d$-$C_b)$alkenyl" radical as above defined.

The term "$(C_d$-$C_b)$alkynyl" refers to straight or branched carbon chains with one or more triple bonds wherein the number atoms is in the range 2 to 6.

By analogy, the expression "$(C_d$-$C_b)$alkynylene" refers to a divalent "$(C_d$-$C_b)$alkynyl" radical as above defined.

The expressions "$NR_{15}R_{16}(C_a$-$C_b)$alkyl", "$NR_{18}R_{19}(C_a$-$C_b)$alkyl" or "$NR_7R_8(C_a$-$C_b)$alkyl", wherein a and b are as above defined, refer to the above defined "$(C_a$-$C_b)$alkyl" groups wherein one hydrogen atom is replaced by one a group - $NR_{15}R_{16}$, - $NR_{18}R_{19}$ or -NR_7R_8 respectively.

The expression "$N^+R_{15}R_{16}R_{17}(C_a$-$C_b)$alkyl" or "$N^+R_{11}R_{11}R_{13}(C_a$-$C_b)$alkyl" wherein a and b are as above defined, refer to the above defined "$(C_a$-$C_b)$alkyl" groups wherein one hydrogen atom is replaced by one a group - $N^+R_{15}R_{16}$ R_{17} or $N^+R_{11}R_{11}R_{13}$

respectively.

The expressions "mono (C_a-C_b)alkyl" or "di (C_a-C_b)alkyl amino", wherein a and b are integers, refer to an amino group wherein, respectively, one or both hydrogen atoms are replaced by a group (C_a-C_b)alkyl.

The expressions "phenyl(C_a-C_b)alkyl" refer to the above defined "(C_a-C_b)alkyl" radicals wherein one hydrogen atom is replaced by one a phenyl group.

The term "divalent (C_a-C_b)alkylene radical" wherein a and b are integers refers to a saturated hydrocarbon chain having from a to b carbon atoms as above defined and two unsatisfied valences.

The term "(C_a-C_b) cycloalkyl", wherein a and b are integers, refers to saturated monocyclic, bicyclic or tricyclic hydrocarbon groups containing from a to b ring carbon atoms, as appropriate. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, adamantyl.

As used herein, the unqualified term "heterocyclyl" or "heterocyclic" and relates to a saturated mono-, bi- or tri-cyclic non-aromatic radical containing one or more heteroatoms selected from S, N and O. In the case of bicyclic heterocyclic systems, included within the scope of the term are fused, spiro and bridged bicyclic systems, such as for example a quinuclidine ring. In particular, the term "C_a-$C_b$heterocycloalkyl" refers to monocyclic (C_a-C_b)cycloalkyl groups, in which at least one ring carbon atom is replaced by a heteroatom (e.g. N, NH, S or O). Examples of (C_a-C_b)heterocycloalkyl include pyrrolidinyl, thiazolidinyl, piperazinyl, piperidinyl, morpholinyl, thiomorpholinyl.

By analogy, the expression "heterocycloalkylene" refers to a divalent heterocyclic radical as above defined. In particular, the expression "(C_a-C_b)heterocycloalkylene" refers to a divalent (C_a-C_b)heterocycloalkyl radical (such as for example pyrrolidinene) wherein "(C_a-C_b)heterocycloalkyl group is as above defined.

The expression "heteroaryl" refers to mono or bi- cyclic ring systems with 5 to 11 ring atoms, in which at least one ring is aromatic and in which at least one ring atom is a heteroatom (e.g. N, NH, S or O).

Examples of suitable 5,6-membered heteroaryl monocyclic systems include, for instance thiophene, benzene, pyrrole, pyrazole, imidazole, isoxazole, oxazole, isothiazole, thiazole, pyridine, imidazolidine, furan radicals and the like.

The term "(C_a-C_b) alkoxyl" wherein a and b are integers, refers to straight-chained and branched alkoxy groups wherein the number of constituent carbon atoms is in the range from a to b. Particular alkyl groups are methoxyl, ethoxyl, n-propoxyl, isopropoxyl and t-butoxyl.

The symbol "-C_6H_4-" indicates a divalent phenylene ring radical.

The expression "(C_a-C_b)alkylcarbonyl" refers to -CO(C_a-C_b)alkyl groups wherein the group "(C_a-C_b)alkyl" has the meaning above defined.

The expressions "(C_a-C_b)alkylhydroxyl" refer to the above defined "(C_a-C_b)alkyl" radicals wherein one hydrogen atom is replaced by one a group -OH.

Unless otherwise specified, the term "substituted" as applied to any moiety herein means substituted with up to four compatible substituents, each of which independently may be, for example, (C_1-C_6)alkyl, (C_1-C_6)alkoxyl, hydroxyl, hydroxyl-C_1-C_6-alkyl, halo (including fluoro, bromo and chloro), trifluoromethyl, trifluoromethoxy. An "optional substituent" may be one of the foregoing substituent groups.

The term "salt" includes base addition and acid addition salts.

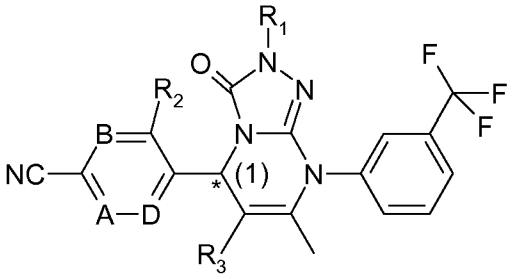
The term "Pharmaceutically acceptable salts" refers to derivatives of compounds of formula (I) wherein the parent compound is suitably modified by converting any of the free acid or basic group, if present, into the corresponding addition salt with any base or acid conventionally intended as being pharmaceutically acceptable.

Compounds of the invention which are acidic can form salts, including pharmaceutically acceptable salts, with bases such as alkali metal hydroxides, e.g. sodium and potassium hydroxides; alkaline earth metal hydroxides e.g. calcium, barium and magnesium hydroxides; with organic bases e.g. N-methyl-D-glucamine, choline tris(hydroxymethyl)amino-methane, L-arginine, L-lysine, N-ethyl piperidine, dibenzylamine and the like. Those compounds which are basic can form salts, including

pharmaceutically acceptable salts with inorganic acids, e.g. with hydrohalic acids such as hydrochloric or hydrobromic acids, sulphuric acid, nitric acid or phosphoric acid and the like, and with organic acids e.g. with acetic, tartaric, succinic, fumaric, maleic, malic, salicylic, citric, methanesulphonic, p-toluenesulphonic, benzoic, benzenesulfonic, glutamic, lactic, and mandelic acids and the like. Those compounds which have quaternary nitrogen can also form quaternary salts with a pharmaceutically acceptable counter-ion such as chloride, bromide, acetate, formate, p-toluenesulfonate, succinate, hemi-succinate, naphthalene-bis sulfonate, methanesulfonate, xinafoate, and the like.

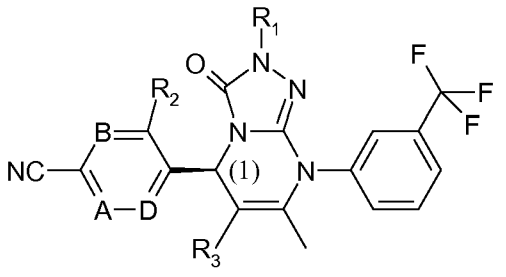
Where the compounds of the invention have at least one stereogenic center, they may exist as enantiomers. When the compounds according to the invention possess two or more stereogenic centers, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

It will be apparent that compounds of general formula (I) at least contain one stereogenic center, namely represented by the carbon atom (1) with an asterisk below, and therefore exist as optical stereoisomers:



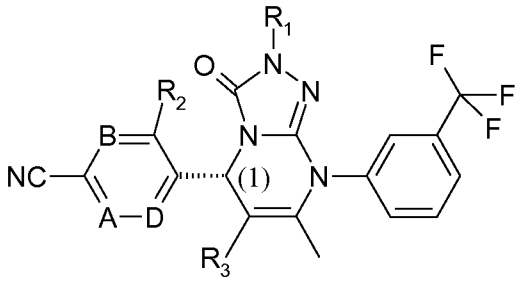
(I)

In one embodiment, the present invention is directed to compounds of formula (I)', which are compounds of formula (I) as above defined where the absolute configuration of carbon (1) is that shown here below:



(I)'

In another embodiment, the present invention is directed to compounds of formula (I)'', which are compounds of formula (I) as above defined where the absolute configuration of carbon (1) is that shown herebelow:



(I)"

The absolute configuration for carbon (1) is assigned on the basis of Cahn-Ingold-Prelog nomenclature based on groups' priorities.

It is to be understood that all preferred groups or embodiments described here below for compounds of formula (I) may be combined among each other and apply as well to compounds of formula (I)', (I)'', (IA) and (IB), *mutatis mutandis*.

In one embodiment, for compounds of formula (I) A is CH, B is CH and D is CH.

In another embodiment, for compounds of formula (I) A is N, B is CH and D is CH.

In a still another embodiment, for compounds of formula (I) A is CH, B is CH and D is N.

In a further another embodiment, for compounds of formula (I) A is CH, B is N and D is CH.

In a still further embodiment, for compounds of formula (I) A is N, B is N and D is CH.

In an additional embodiment, for compounds of formula (I) A is N, B is CH and D is N.

In one embodiment, for compounds of formula (I) when G is $-(SO_2)-$, y is 1.

In one embodiment, R_2 is selected in the group consisting of: $NR_{18}R_{19}(C_1-C_6)$alkyl and C_2-C_6-alkynyl which C_2-C_6-alkynyl is substituted by a group –OH or $-NR_{18}R_{19}$.

In another embodiment, R_2 is $NR_{18}R_{19}(C_1-C_6)$alkyl.

In a further embodiment, R_2 is a group $-[CH_2]_y$-G-$[CH_2]_j$-CH_2-$N^+R_{22}R_{23}R_{24}$.

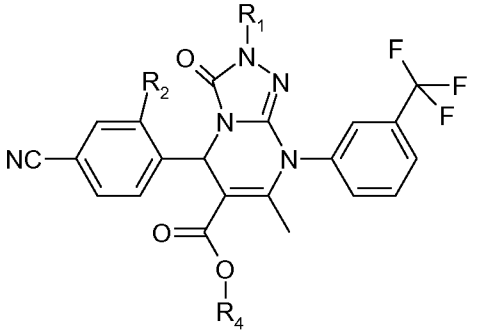
In one embodiment, R_3 is a group cyano or a group $-C(O)-XR_4$. In a another embodiment, R_3 is a group $-C(O)-XR_4$.

In one embodiment, R_4 is optionally substituted (C_1-C_6)alkyl. In another embodiment, R_4 is (C_1-C_6)alkyl.

In one embodiment, X is a divalent group -O- or -NH-. In another embodiment, X is a divalent -O-.

In one embodiment, for compounds of formula (I), R_1 is hydrogen or a group $-(CH_2)_rSO_2(C_1-C_4)$alkyl. In another embodiment, R_1 is hydrogen.

In one embodiment, a compound of formula (IA) is provided



(IA)

wherein R_3 is $-C(O)-XR_4$ and the other groups R_4, R_2 and R_1 are as above defined. In one embodiment, for compounds of formula (IA) R_1 is hydrogen.

In another embodiment, a compound of the invention is selected in the group consisting of:

5-[4-Cyano-2-(4-hydroxy-but-1-ynyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

5-[4-Cyano-2-(3-dimethylamino-prop-1-ynyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

5-[4-Cyano-2-(3-dimethylamino-prop-1-ynyl)-phenyl]-2-(3-methanesulfonyl-propyl)-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

(3-{5-Cyano-2-[2-(3-methanesulfonyl-propyl)-6-methoxycarbonyl-7-methyl-3-oxo-8-m-tolyl-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-prop-2-ynyl)-trimethyl-ammonium formate;

5-[4-Cyano-2-(3-dimethylamino-propyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

5-(4-Cyano-2-dimethylaminomethyl-phenyl)-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

{5-Cyano-2-[6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-trimethyl-ammonium bromide;

(2-{5-Cyano-2-[6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzoylamino}-ethyl)-trimethyl-ammonium chloride;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-trimethyl-ammonium formate;

(R)-5-[4-Cyano-2-(3-dimethylamino-propyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-prop-2-ynyl)-trimethyl-ammonium iodide;

(R)-5-[4-Cyano-2-(3-dimethylamino-prop-1-ynyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3a]pyrimidine-6-carboxylic acid methyl ester;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-

phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-trimethyl-ammonium iodide;

and pharmaceutically acceptable salts thereof.

In a further embodiment, a compound of the invention is selected in the group consisting of:

5-[4-Cyano-2-(4-hydroxy-but-1-ynyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

5-[4-Cyano-2-(3-dimethylamino-prop-1-ynyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

5-[4-Cyano-2-(3-dimethylamino-prop-1-ynyl)-phenyl]-2-(3-methanesulfonyl-propyl)-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

(3-{5-Cyano-2-[2-(3-methanesulfonyl-propyl)-6-methoxycarbonyl-7-methyl-3-oxo-8-m-tolyl-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-prop-2-ynyl)-trimethyl-ammonium formate;

5-[4-Cyano-2-(3-dimethylamino-propyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

5-(4-Cyano-2-dimethylaminomethyl-phenyl)-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

{5-Cyano-2-[6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-trimethyl-ammonium bromide;

(2-{5-Cyano-2-[6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzoylamino}-ethyl)-trimethyl-

ammonium chloride;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-trimethyl-ammonium formate;

(R)-5-[4-Cyano-2-(3-dimethylamino-propyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-prop-2-ynyl)-trimethyl-ammonium iodide;

(R)-5-[4-Cyano-2-(3-dimethylamino-prop-1-ynyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3a]pyrimidine-6-carboxylic acid methyl ester;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-trimethyl-ammonium iodide;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-trimethyl-ammonium iodide;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-(3-methanesulfonyl-propyl)-dimethyl-ammonium formate;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-cyclopropylmethyl-dimethyl-ammonium formate;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-(3-hydroxy-propyl)-dimethyl-ammonium formate;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-(3-methoxy-propyl)-dimethyl-ammonium formate:

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-dimethylcarbamoylmethyl-dimethyl-ammonium formate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-1-azonia-bicyclo[2.2.2]octane formate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-4-aza-1-azonia-bicyclo[2.2.2]octane formate;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-(4-hydroxy-cyclohexyl)-dimethyl-ammonium formate;

4-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-4-methyl-morpholin-4-ium formate;

Adamantan-1-yl-(3-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-ammonium formate;

4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methyl-morpholin-4-ium formate;

{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(3-hydroxy-propyl)-dimethyl-ammonium formate;

{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-

phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-ethyl-dimethyl-ammonium formate;

1-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-pyridinium formate;

1-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-1-azonia-bicyclo[2.2.2]octane formate;

1-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-1,4-dimethyl-piperazin-1-ium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(4-hydroxy-cyclohexyl)-dimethyl-ammonium formate;

1-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-aza-1-azonia-bicyclo[2.2.2]octane formate;

1-{2-[(R)-6-carboxy-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-5-cyano-benzyl}-4-aza-1-azonia-bicyclo[2.2.2]octane formate;

Butyl-{5-cyano-2-[(R)-6-methoxy carbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-ammonium formate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-hydroxy-1-methyl-piperidinium formate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-1-methyl-

pyrrolidinium formate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-1-methyl-piperidinium formate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-1-(2-hydroxy-ethyl)-pyrrolidinium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(3-dimethylcarbamoyl-propyl)-dimethyl-ammonium formate;

Benzyl-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-ammonium formate;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-trimethyl-ammonium bromide;

(S)-5-[4-Cyano-2-(5-hydroxypentyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-trimethyl-ammonium benzenesulfonate;

(5-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-pentyl)-trimethyl-ammonium formate;

(4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-butyl)-trimethyl-ammonium formate;

1-(4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-butyl)-1-azonia-bicyclo[2.2.2]octane formate;

1-(4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-butyl)-1-azonia-bicyclo[2.2.2]octane formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-trimethyl-ammonium bromide;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-trimethyl-ammonium bromide;

1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-pyridinium bromide;

1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-pyridininium formate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-pyridinium bromide;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-pyridinium formate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-pyridinium benzenesulfonate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-

phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-pyridinium chloride;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-pyridinium 2-hydroxy-ethanesulfonate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-pyridinium methanesulfonate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-3-hydroxymethyl-pyridinium tosylate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-3-methyl-pyridinium formate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-2-methyl-pyridinium formate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-3-hydroxymethyl-pyridinium formate;

3-Chloro-1-(3-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-pyridinium formate;

Butyl-(3-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-dimethyl-ammonium formate;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-

cyclohexyl-dimethyl-ammonium formate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-1-methyl-pyrrolidinium formate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-1-methyl-piperidinium formate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-4-hydroxy-1-methyl-piperidinium formate;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-dimethyl-oxetan-3-yl-ammonium formate;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-dimethyl-(tetrahydro-pyran-4-yl)-ammonium formate;

4-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-4-methyl-morpholin-4-ium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-dimethylcarbamoylmethyl-dimethyl-ammonium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-(3-methoxy-propyl)-dimethyl-ammonium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-cyclobutylmethyl-dimethyl-ammonium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-dimethyl-(tetrahydro-pyran-4-ylmethyl)-ammonium formate;

1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-1-(2-hydroxy-ethyl)-pyrrolidinium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-[2-(2-hydroxy-ethoxy)-ethyl]-dimethyl-ammonium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-bis-(2-hydroxy-ethyl)-methyl-ammonium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-(2-hydroxy-ethyl)-dimethyl-ammonium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-ethyl-dimethyl-ammonium formate;

Benzyl-(2-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-dimethyl-ammonium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-cyclohexylmethyl-dimethyl-ammonium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-(3-hydroxy-propyl)-dimethyl-ammonium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-

phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-diethyl-methyl-ammonium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-cyclopropylmethyl-dimethyl-ammonium formate;

1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-1-azonia-bicyclo[2.2.2]octane formate;

1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-3-hydroxymethyl-pyridinium formate;

1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-3-methyl-pyridinium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-cyclobutylmethyl-dimethyl-ammonium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-(tetrahydro-pyran-4-ylmethyl)-ammonium formate;

{{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(2-methoxy-ethyl)-dimethyl-ammonium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-cyclopropylmethyl-dimethyl-ammonium formate;

3-Chloro-1-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-

pyridinium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(2-hydroxy-ethyl)-dimethyl-ammonium formate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methoxy-pyridinium formate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-3-hydroxymethyl-pyridinium formate;

{1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-hydroxymethyl-1-methyl-piperidinium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-ethoxycarbonylmethyl-dimethyl-ammonium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(1,1-dioxo-hexahydro-1lambda*6*-thiopyran-4-ylmethyl)-dimethyl-ammonium formate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-3,4-dihydroxy-1-methyl-pyrrolidinium formate;

4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-ethyl-morpholin-4-ium formate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-dimethylcarbamoyl-1-methyl-piperazin-1-ium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethylcarbamoylmethyl-dimethyl-ammonium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(1-methanesulfonyl-piperidin-4-yl)-dimethyl-ammonium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-oxetan-3-ylmethyl-ammonium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-(3-methylcarbamoyl-propyl)-ammonium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(3-dimethylsulfamoyl-propyl)-dimethyl-ammonium formate

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methanesulfonyl-1-methyl-piperazin-1-ium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-bis-(2-hydroxy-ethyl)-methyl-ammonium formate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4,4-difluoro-1-methyl-piperidinium formate;

4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methyl-[1,4]oxazepan-4-ium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-

phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(3-methoxy-propyl)-dimethyl-ammonium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(3-methanesulfonyl-propyl)-dimethyl-ammonium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-(1-methyl-piperidin-4-yl)-ammonium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-piperidin-4-yl-ammonium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium formate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-pyridinium bromide;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-pyridinium benzenesulphonate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-pyridinium tosylate;

Benzyl-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-ammonium bromide;

Benzyl-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-

ammonium benzenesulfonate;

4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methyl-morpholin-4-ium bromide;

4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methyl-morpholin-4-ium bromide;

4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methyl-morpholin-4-ium bromide;

4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methyl-morpholin-4-ium bromide;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-trimethyl-ammonium benzenesulfonate;

1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-pyridinium 2-hydroxy-ethanesulfonate;

1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-pyridinium methanesulfonate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-pyridinium chloride;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-bis-(2-hydroxy-ethyl)-methyl-ammonium benzenesulfonate;

1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-pyridinium benzenesulfonate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-trimethyl-ammonium 2-hydroxy-ethanesulfonate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-trimethyl-ammonium methanesulfonate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-trimethyl-ammonium chloride;

and pharmaceutically acceptable salts thereof.

The therapeutic utility of the present compounds is pertinent to any disease that is known to be at least partially mediated by the action of human neutrophil elastase. For example, the present compounds may be beneficial in the treatment of chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), bronchiectasis, acute respiratory distress syndrome (ARDS), pulmonary emphysema, pneumonia and lung fibrosis.

Compounds of the invention are useful for treatment of inflammatory respiratory disorders, for example asthma (mild, moderate or severe), steroid resistant asthma, bronchitis, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), pulmonary edema, pulmonary embolism, pneumonia, pulmonary sarcoidosis, pulmonary emphysema, silicosis, pulmonary fibrosis, pulmonary hypertension, respiratory failure, acute respiratory distress syndrome (ARDS), emphysema, chronic bronchitis, tuberculosis, aspergillosis and other fungal infections, hypersensitivity pneumonitis, vasculitic and thrombotic disorders of the lung vasculature, antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, infection due to respiratory syncytial virus, influenza, coronavirus (including

severe acute respiratory syndrome, SARS) and adenovirus, bronchiectasis and lung cancer.

The present invention is also concerned with pharmaceutical formulations comprising, as an active ingredient, a compound of the invention. Other compounds may be combined with compounds of this invention for the prevention and treatment of inflammatory diseases of the lung. Thus the present invention is also concerned with pharmaceutical compositions for preventing and treating inflammatory diseases of the lung comprising a therapeutically effective amount of a compound of the invention and one or more other therapeutic agents.

Suitable therapeutic agents for a combination therapy with compounds of the invention include: (1) a corticosteroid, for example budesonide, beclomethasone, beclomethasone (e.g., as the mono or the dipropionate ester), flunisolide, fluticasone (e.g. as the propionate or furoate ester), Ciclesonide, mometasone (e.g. as the furoate ester), mometasone desonide, rofleponide, hydrocortisone, prednisone, prednisolone, methyl prednisolone, naflocort, deflazacort, halopredone acetate, fluocinolone acetonide, fluocinonide, clocortolone, tipredane, prednicarbate, alclometasone dipropionate, halometasone, rimexolone, deprodone propionate, triamcinolone, betamethasone, fludrocoritisone, desoxycorticosterone, rofleponide, etiprednol dicloacetate and the like. Steroid drugs can additionally include steroids in clinical or pre-clinical development for respiratory diseases such as GW-685698, GW-799943, GSK 870086, QAE397, NCX-1010, NCX-1020, NO-dexamethasone, PL-2146, NS-126 (formerly ST-126). Steroid drugs can also additionally include next generation molecules in development with reduced side effect profiles such as selective glucocorticoid receptor agonists (SEGRAs), including ZK-216348 and AZD5423; (2) a β2-adrenoreceptor agonist, such as albuterol, bambuterol, terbutaline, fenoterol, formoterol, formoterol fumarate, salmeterol, salmeterol xinafoate, arformoterol, arfomoterol tartrate, indacaterol (QAB-149), carmoterol, BI 1744 CL, GSK159797 (milveterol), GSK59790, GSK159802, GSK642444 (vilanterol), GSK678007, GSK96108, clenbuterol, procaterol, bitolterol, LAS100977 (abediterol),

BI1744CL (olodaterol) and brodxaterol; (3) a leukotriene modulator, for example montelukast, zafirlukast or pranlukast; (4) anticholinergic agents, for example selective muscarinic-3 (M3) receptor antagonists such as ipratropium bromide, tiotropium, tiotropium bromide (Spiriva®), glycopyrronium bromide, aclidinium bromide, LAS34273, GSK656398, GSK233705, GSK 573719 (umeclidinium), LAS35201, QAT370 and oxytropium bromide; (5) phosphodiesterase-IV (PDE-IV) inhibitors, for example roflumilast, cilomilast or theophylline; (6) an antitussive agent, such as codeine or dextramorphan; and (7) a non-steroidal anti-inflammatory agent (NSAID), for example ibuprofen or ketoprofen; (8) a mucolytic, for example N acetyl cysteine or fudostein; (9) a expectorant/mucokinetic modulator, for example ambroxol, hypertonic solutions (e.g. saline or mannitol) or surfactant; (10) a peptide mucolytic, for example recombinant human deoxyribonoclease I (dornase-alfa and rhDNase) or helicidin; (11) antibiotics, for example azithromycin, tobramycin and aztreonam; and (12) p38 Mitogen Activated Protein (MAP) kinase inhibitors, such as GSK 856553 and GSK 681323; (12) inhibitors of Janus Kinases (JAK) such as CP-690550 or GLPG0634; (13) Spleen Tyrosine Kinase (SYK) inhibitors such as R406, R343 or PRT062607; (14) inhibitors of delta and/or gamma isoforms of Phosphatidylinositol 3-kinase (PI3K).; (15) anti-retroviral agents such as ribavirin, zanamivir or laninamivir; (16) PPAR-γ agonists such as pioglitazone and rosiglitazone.

In one aspect, the invention provides for the use of inhaled administration of compounds of the invention in combination with other anti-inflammatory drugs and bronchodilator drug combinations (i.e. triple combination product), including but not limited to salmeterol xinafoate/fluticasone propionate (Advair/Seretide®), vilanterol/fluticasone furoate (BREO ELLIPTA^{TM}), formoterol fumarate/budesonide (Symbicort®), formoterol fumarate/mometasone furoate, formoterol fumarate/beclometasone dipropionate (Foster®), formoterol fumarate/fluticasone propionate (FlutiForm®), Indacaterol/mometasone furoate, Indacaterol/QAE-397,

GSK159797/GSK 685698, GSK159802/GSK 685698, GSK642444/GSK 685698, formoterol fumarate/ciclesonide, arformoterol tartrate/ciclesonide.

In another aspect, the invention provides for the use of inhaled administration of compounds of the invention in combination with other bronchodilator drug combinations, particularly β_2 agonist/M_3 antagonist combinations (i.e. triple combination product), including but not limited to salmeterol xinafoate/tiotropium bromide, formoterol fumarate/tiotropium bromide, formoterol fumarate/ glycopyrrolate (PT003), BI 1744 CL/tiotropium bromide, indacaterol/NVA237, indacterol/QAT-370, formoterol/ LAS34273, umeclidinium/vilanterol (Anoro™), GSK159797/GSK 573719, GSK159802/GSK 573719, GSK642444/GSK 573719, GSK159797/GSK 233705, GSK159802/GSK 233705, GSK642444/GSK 233705.

The weight ratio of the first and second active ingredients may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used.

The magnitude of prophylactic or therapeutic dose of a compound of the invention will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound and its route of administration, and will generally be determined by clinical trial as required in the pharmaceutical art. It will also vary according to the age, weight and response of the individual patient. In general, the daily dose range will lie within the range of from about 0.001 mg to about 100 mg per kg body weight of a mammal, preferably 0.01 mg to about 50 mg per kg, and most preferably 0.1 to 10 mg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

Another aspect of the present invention provides pharmaceutical compositions which comprise a compound of the invention and a pharmaceutically acceptable carrier. The term “composition”, as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results,

directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the invention encompass any composition made by admixing a compound of the invention, additional active ingredient(s), and pharmaceutically acceptable excipients.

The pharmaceutical compositions of the invention comprise a compound of the invention as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dosage of a compound of the present invention. In therapeutic use, the active compound may be administered by any convenient, suitable or effective route. Suitable routes of administration are known, and include oral, intravenous, rectal, parenteral, topical, ocular, nasal, buccal and pulmonary (by inhalation).

Compositions suitable for administration by inhalation are known, and may include carriers and/or diluents that are known for use in such compositions. The composition may contain 0.01-99% by weight of active compound. Preferably, a unit dose comprises the active compound in an amount of 1 μg to 10 mg.

The most suitable dosage level may be determined by any known suitable method. It will be understood, however, that the specific amount for any particular patient will depend upon a variety of factors, including the activity of the specific compound that is used, the age, body weight, diet, general health and sex of the patient, time of administration, the route of administration, the rate of excretion, the use of any other drugs, and the severity of the disease to be treated.

For delivery by inhalation, the active compound is preferably in the form of microparticles. They may be prepared by a variety of techniques, including spray-drying, freeze-drying and micronisation.

By way of example, a composition of the invention may be prepared as a suspension for delivery from a nebuliser or as an aerosol in a liquid propellant, for example for use in a pressurised metered dose inhaler (PMDI). Propellants suitable for use in a PMDI are known to the skilled person, and include CFC-12, HFA-134a, HFA-227, HCFC-22 (CCl2F2) and HFA-152 (CH4F2 and isobutane).

In a preferred embodiment of the invention, a composition of the invention is in dry powder form, for delivery using a dry powder inhaler (DPI). Many types of DPI are known.

Microparticles for delivery by administration may be formulated with excipients that aid delivery and release. For example, in a dry powder formulation, microparticles may be formulated with large carrier particles that aid flow from the DPI into the lung. Suitable carrier particles are known, and include lactose particles; they may have a mass median aerodynamic diameter of greater than 90 μm.

In the case of an aerosol-based formulation, a preferred composition is:

Compound of the invention	24 mg / canister
Lecithin, NF Liq. Conc.	1.2 mg / canister
Trichlorofluoromethane, NF	4.025 g / canister
Dichlorodifluoromethane, NF	12.15 g / canister.

Compounds of the invention may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which present compounds are useful. Such other drugs may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound of the invention. When a compound of the invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the invention is preferred.

Accordingly, the pharmaceutical compositions of the invention include those that also contain one or more other active ingredients, in addition to a compound of the invention.

The agents of the invention may be administered in inhaled form. Aerosol generation can be carried out using, for example, pressure-driven jet atomizers or ultrasonic atomizers, preferably using propellant-driven metered aerosols or propellant-free administration of micronised active compounds from, for example, inhalation capsules or other "dry powder" delivery systems.

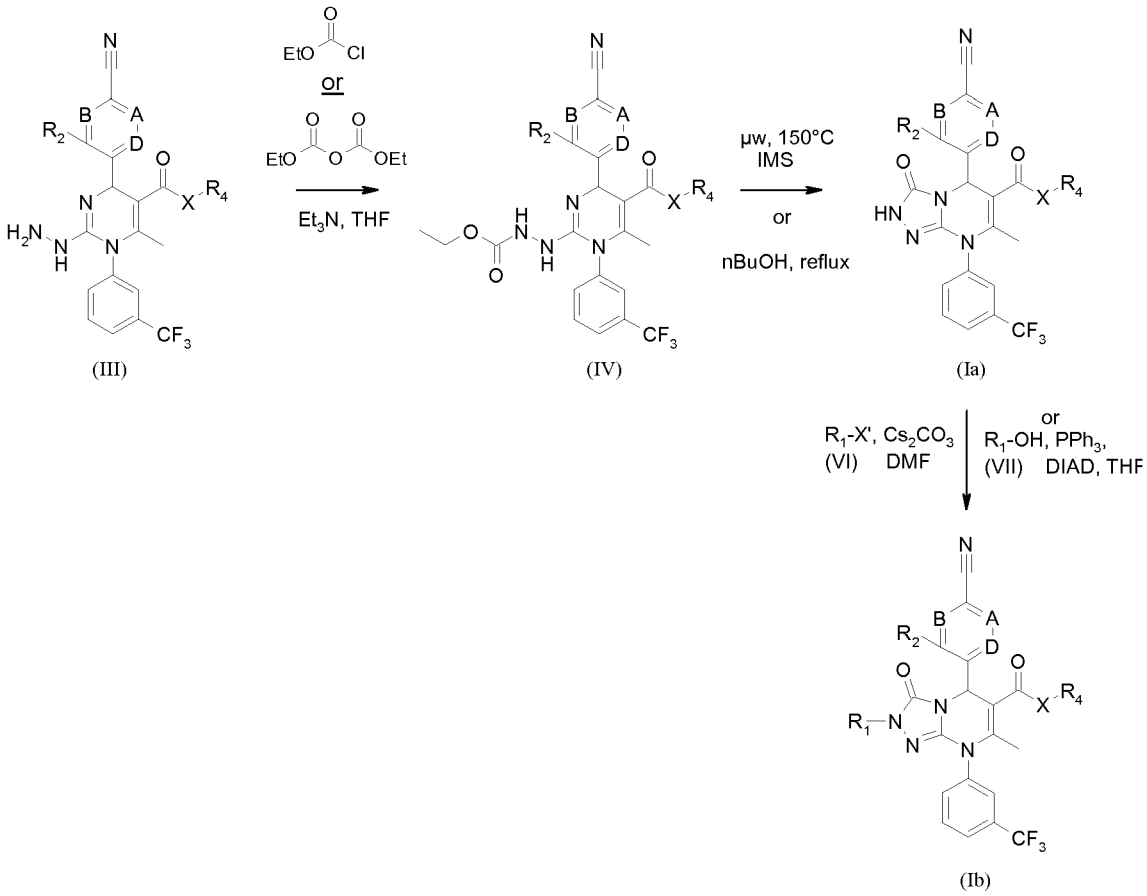
The active compounds may be dosed as described depending on the inhaler system used. In addition to the active compounds, the administration forms may additionally contain excipients, such as, for example, propellants (e.g. Frigen in the case of metered aerosols), surface-active substances, emulsifiers, stabilizers, preservatives, flavorings, fillers (e.g. lactose in the case of powder inhalers) or, if appropriate, further active compounds.

For the purposes of inhalation, a large number of systems are available with which aerosols of optimum particle size can be generated and administered, using an inhalation technique which is appropriate for the patient. In addition to the use of adaptors (spacers, expanders) and pear-shaped containers (e.g. Nebulator®, Volumatic®), and automatic devices emitting a puffer spray (Autohaler®), for metered aerosols, in particular in the case of powder inhalers, a number of technical solutions are available (e.g. Diskhaler®, Rotadisk®, Turbohaler® or the inhalers for example as described EP-A-0505321).

Methods of Synthesis

In one aspect of the invention, a process for the preparation of compounds of the invention (Ia), i.e. compounds of formula (I) wherein R_1 is hydrogen and R_3 is $-COXR_4$, and of compounds of the invention of formula (Ib), i.e. compounds of formula (I) wherein R_1 is not hydrogen and R_3 is $-COXR_4$, is provided, according to general synthetic routes reported in Scheme A here below.

Scheme A

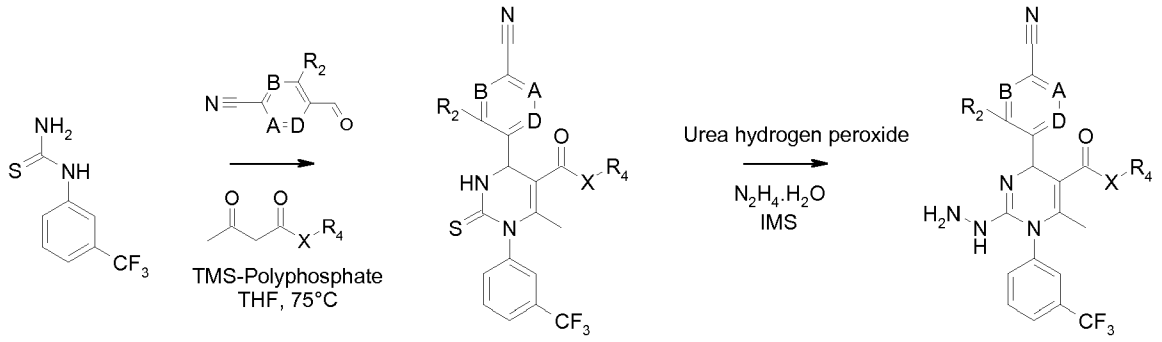


Compounds of formula (IV) may be prepared from compounds of formula (III) by reaction with ethyl chloroformate (or ethyl pyrocarbonate) in the presence of a base such as triethylamine in a solvent such as THF at a temperature of from 0°C to reflux. Compounds of formula (IV) may be transformed into compounds of formula (Ia) by heating in an appropriate solvent. Suitable conditions include the use of a solvent such as IMS and heating using microwave irradiation at a temperature of up to 150°C or conventional heating in a solvent such as n-butanol at reflux. Compounds of formula (Ia), as above defined, may be converted into compounds of formula (Ib), as above defined, by reaction with an alkyl halide (VI) of formula R_1-X' wherein X' is an appropriate leaving group (X' = Cl, Br, I, Tosylate etc.) in a solvent such as DMF in the presence of a base such as cesium carbonate at a temperature of from room temperature to 100°C. Alternatively, the transformation may be achieved by Mitsunobu reaction with an alcohol

(VII) of formula R_1OH. Typical reagents employed are triphenyl phosphine and DIAD in a solvent such as THF.

Compounds of formula (III) wherein R_4 is $(C_1\text{-}C_6)$alkyl, may be prepared according to Scheme B below:

Scheme B

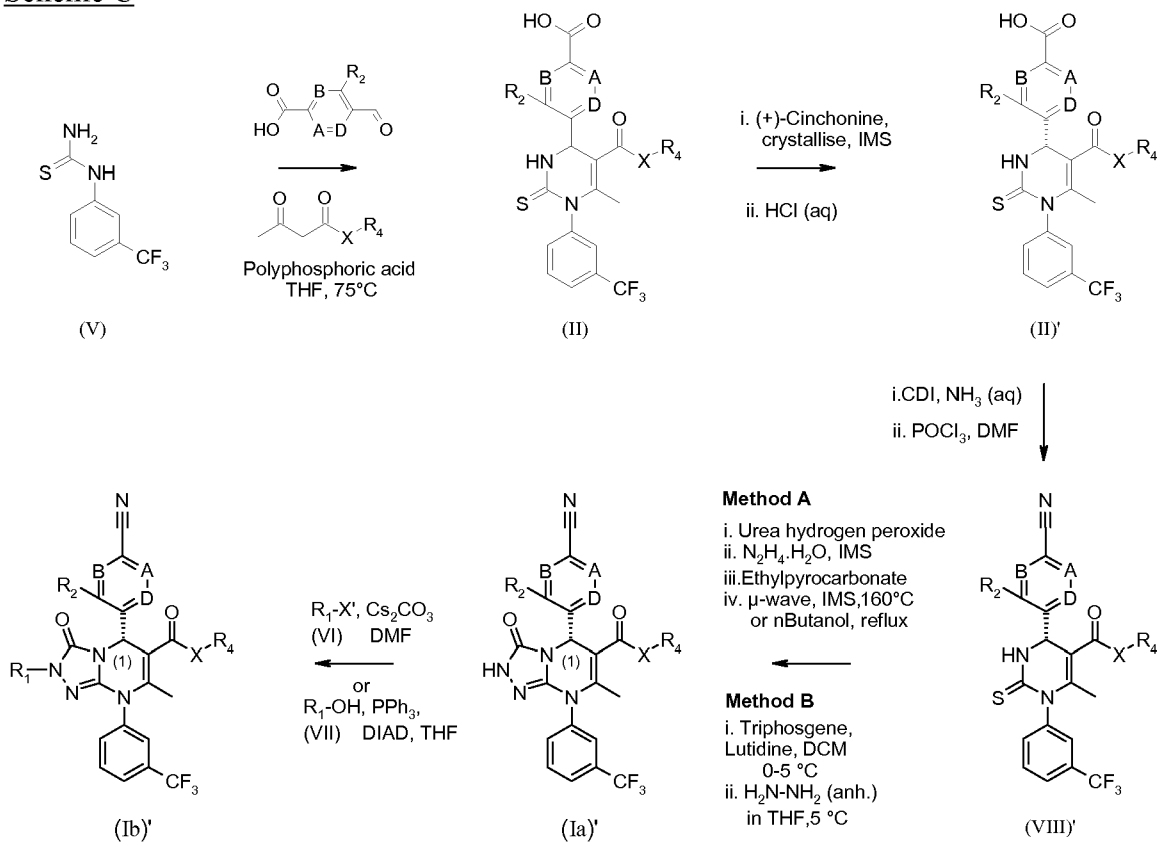


(V) (VIII) (III)

Compounds of formula (V) may be reacted with a benzaldehyde such as 3-bromo-4-formyl-benzonitrile and an acetoacetate such as ethyl acetoacetate in the presence of an acid such as TMS-polyphosphate in a solvent such as THF at a temperature of from room temperature to reflux to give compounds of formula (VIII), wherein R_4 is $(C_1\text{-}C_6)$alkyl and the other groups are as define for compounds of formula (I). Compounds of formula (III) may be prepared from compounds of formula (VIII) by reaction with an oxidizing agent such as urea hydrogen peroxide followed by *in-situ* treatment with hydrazine hydrate in IMS.

Furthermore compounds of formula (I)', which are compounds of formula (I) as above defined where the absolute configuration of carbon (1) is that shown herebelow can be prepared according to Scheme C.

Scheme C



Compounds of formula (II) may be obtained from compounds of formula (V) by reacting with 3-bromo-4-formyl-benzoic acid using a similar method described for the transformation of compounds of formula (V) to compounds of formula (VIII) in Scheme B. Compounds of formula (II)', which are compounds of formula (II) wherein the absolute configuration at stereogenic center (1) is as reported in Scheme C, may be obtained from compounds of formula (II) by forming a chiral diastereomeric salt with a suitable chiral amine such as (+)-Cinchonine in a suitable solvent such as dioxane, followed by treatment of the salt with an acid such as hydrochloric acid to give the enantiomerically pure compounds of formula (II)'. Compounds of formula (VIII)', which are compounds of formula (VIII) wherein the absolute configuration at stereogenic center (1) is as reported in Scheme C, may be prepared from compounds of formula (II)' by reaction with aqueous ammonia in the presence of a coupling agent such as carbonyl diimidazole in a solvent such as THF at a temperature of from 0°C to room temperature to give the intermediate primary amide. Conversion of the amide to compounds of formula

(VIII)' may be carried out using a dehydrating agent. Suitable conditions include the use of a solvent such as DMF and a dehydrating agent such as phosphorus oxychloride at a temperature of from 0°C to room temperature.

Compounds of formula (Ia)' and (Ib)', which are compounds of formula (Ib) and (Ia) as above defined and wherein the absolute configuration of carbon (1) is that shown in Scheme C (Method A), may be obtained from compounds of formula (VIII)' using similar methods described for the transformation of compounds of formula (VIII) to compounds of formula of formula (Ia) and (Ib) in Schemes B and A. Alternatively, compounds of formula (Ia)' and (Ib)', which are compounds of formula (Ib) and (Ia) as above defined and wherein the absolute configuration of carbon (1) is that shown in Scheme C may be also be obtained from compounds of formula (VIII)' using method B; wherein compounds of formula (VIII)' may be reacted with a chlorocarbonyl-containing/releasing compound such as phosgene or triphosgene and anhydrous hydrazine in the presence of a base such as 2,6-lutadine in a solvent such as dichloromethane at a temperature of from -5-5°C to give compounds of formula (Ia)' wherein R_4 is (C_1-C_6)alkyl and the other groups are as define for compounds of formula (I).

The skilled person would understand that by selecting of the appropriate chiral amine and its absolute configuration, derivatives of formula (II)'', (VIII)'', (Ib)'' and (Ia)'' [which are compounds of formula (II), (VIII), (Ib) and (Ia) respectively wherein the absolute configuration at stereogenic center (1) is opposite to that reported in Scheme C] may be obtained.

The skilled person may introduce, where appropriate, suitable variations to the conditions specifically described in the experimentals in order to adapt the synthetic routes to the provision of further compounds of the invention. Such variations may include, but are not limited to, use of appropriate starting materials to generate different compounds, changes in the solvent and temperature of reactions, replacement of reactives with analogous chemical role, introduction or removal of protection/de-protection stages of functional groups sensitive to reaction conditions and reagents, as well as introduction

or removal of specific synthetic steps oriented to further functionalisation of the chemical scaffold.

Processes which can be used and are described and reported in Examples should not be viewed as limiting the scope of the synthetic methods available for the preparation of the compounds of the invention.

Compounds used as starting materials or intermediates may be commercially available, their preparation may be specifically described in the literature or they may be prepared according to methods available in the literature and well known to the person skilled in the art.

The process described is particularly advantageous as it is susceptible of being properly modulated, through any proper variant known to the skilled person, so as to obtain any of the desired compounds of the invention. Such variants are comprised within the scope of the present invention.

From all of the above, it should be clear to the skilled person that any of the described groups may be present as such or in any properly protected form. In particular, functional groups present in the Intermediates and Examples and which could generate unwanted side reaction and by-products, need to be properly protected before the alkylation, acylation, coupling or sulfonylation takes place. Likewise, subsequent deprotection of those same protected groups may follow upon completion of the said reactions.

In the present invention, unless otherwise indicated, the term "protecting group" designates a protective group adapted to preserve the function of the group it is bound to. Typically, protective groups are used to preserve amino, hydroxyl, or carboxyl functions. Appropriate protecting groups may thus include, for example, benzyl, benzyloxycarbonyl, t-butoxycarbonyl, alkyl or benzyl esters or the like, which are well known to those skilled in the art [see, for a general reference, T.W. Green; Protective Groups in Organic Synthesis (Wiley, N.Y. 1981)].

Likewise, selective protection and de-protection of any of the said groups, for

instance including carbonyl, hydroxyl or amino groups, may be accomplished according to very well known methods commonly employed in organic synthetic chemistry.

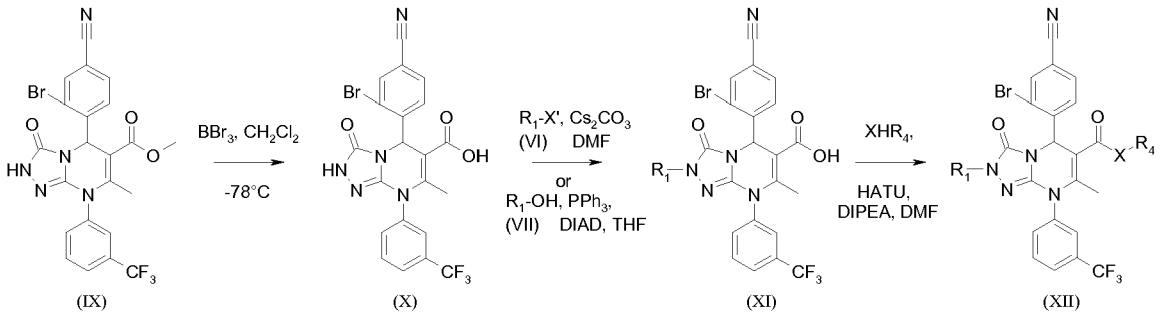
Optional salt formation of the compounds of formula (I) may be carried out by properly converting any of the free acidic or amino groups into the corresponding pharmaceutically acceptable salts. In this case too, the operative conditions being employed for the optional salification of the compounds of the invention are all within the ordinary knowledge of the skilled person.

The diastereoisomers of compounds of formula (I), where available, may be obtained according to methods well known in the art, such as for example by preparative HPLC or by chromatographic purifications. A racemic mixture of compounds of formula (I) may as well be separated using preparative HPLC and a column with a chiral stationary phase, or resolved to yield individual enantiomers using methods well known in the art. Furthermore, chiral intermediates may be resolved and used to prepare chiral compounds of the invention.

From all of the above, it should be clear to the skilled person that the above process, comprehensive of any variant thereof for the preparation of suitable compounds of the invention, may be conveniently modified so as to adapt the reaction conditions to the specific needs, for instance by choosing appropriate condensing agents, solvents and protective groups, as the case may be.

Compounds of formula (XII), wherein R_3 is a group $-COXR_4$, R_1 is as defined above, A, B and D are CH and R_2 is bromine or other suitable activating group taken from the group, but not exclusively, Cl, I, OTf, may be prepared from compounds of formula (IX) according to Scheme D here below reported:

Scheme D



Treatment of a compound of formula (IX) with a strong Lewis acid such as boron tribromide in a solvent such as DCM at a temperature of from -78°C to room temperature followed by quench with water or methanol can provide compounds of formula (X).

It should be clear to the skilled person that other appropriate protecting group strategies may be contemplated and that the acid (X) represents a versatile intermediate for further functionalisation as well as for preparation of compounds of formula (XII).

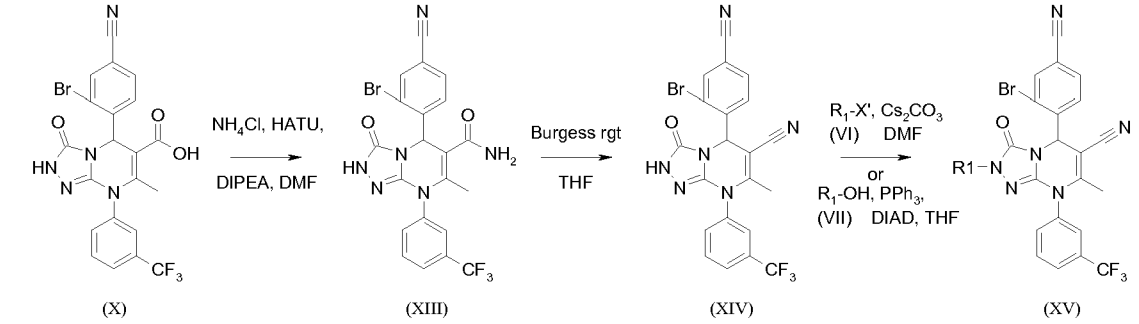
It is in fact to be underlined that many of the synthetic routes herebelow described starting from compounds of formula (IX) (i.e. in Schemes F, G and H) may be applicable, as the skilled person would understand, to compounds of formula (X) and (XII) also, to get to additional compounds of formula (I), (Ia) and (Ib).

By way of example, by appropriate derivatization of a compound of formula (X), as above defined, into a compound of formula (XI) wherein R_1 is not hydrogen, corresponding compounds of formula (XII) wherein R_1 is not hydrogen may be obtained. Compounds of formula (XI) may be obtained from compounds of formula (X) using the methods described for the transformation of compounds of formula (Ia) to compounds of formula (Ib) in Scheme A.

Compounds of formula (XII) may be prepared from compounds of formula (XI) by reaction with an alcohol or amine XHR_4 such as ammonia or 2-methoxy-ethanol in the presence of a coupling agent such as HATU in a solvent such as DMF in the presence of a base such as triethylamine at a temperature of from room temperature to 80°C. The synthetic route shown in Scheme D would be of benefit in introducing $-XR_4$ substituents

at a late stage.

Scheme E



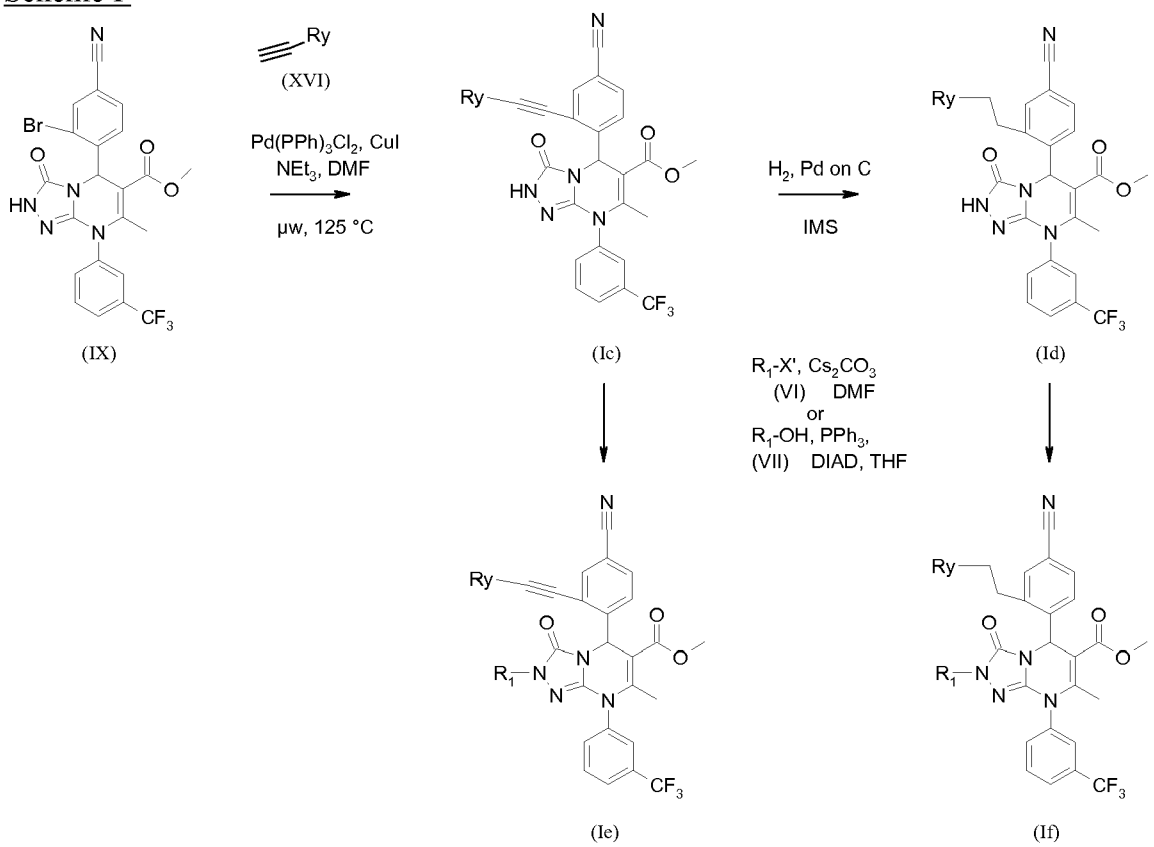
Compounds of formula (XIV) and (XV), i.e. compounds of formula (XII) wherein R_3 is a group –CN, may be prepared according to Scheme E from compounds of formula (X). Compounds of formula (XIII), which are compounds of formula (XII) wherein R_1 is H and XR_4 is NH_2, may be prepared by reaction with ammonia in the presence of a coupling agent such as HATU in a solvent such as DMF in the presence of a base such as triethylamine at a temperature of from room temperature to 80°C.

Compounds of formula (XIV) may be prepared from compounds of formula (XIII) by reaction with a dehydrating agent such as Burgess reagent in a solvent such as THF at a temperature of from room temperature to reflux. Compounds of formula (XV) may be obtained from compounds of formula (XIV) using the methods described for the transformation of compounds of formula (Ia) to compounds of formula (Ib) in Scheme A.

It will then be apparent to the skilled person that by adaptation of synthetic routes herebelow described in schemes F or G and starting from compounds of formula (XIV) or (XV), compounds of formula (Im), i.e. compounds of formula (I) wherein R_3 is a group cyano, may be prepared.

Compounds of formula (Ic), (Id), (Ie) and (If) i.e. compounds of formula (I) wherein R_3 is a group $–COXR_4$, X is oxygen, R_4 is a methyl group, R_1 is as defined above, A, B and D are CH and R_2 is respectively a group as reported in Scheme F where R_y may have different meanings according to those described for compounds of formula (I), may be prepared from compounds of formula (IX) according to Scheme F here below reported:

Scheme F

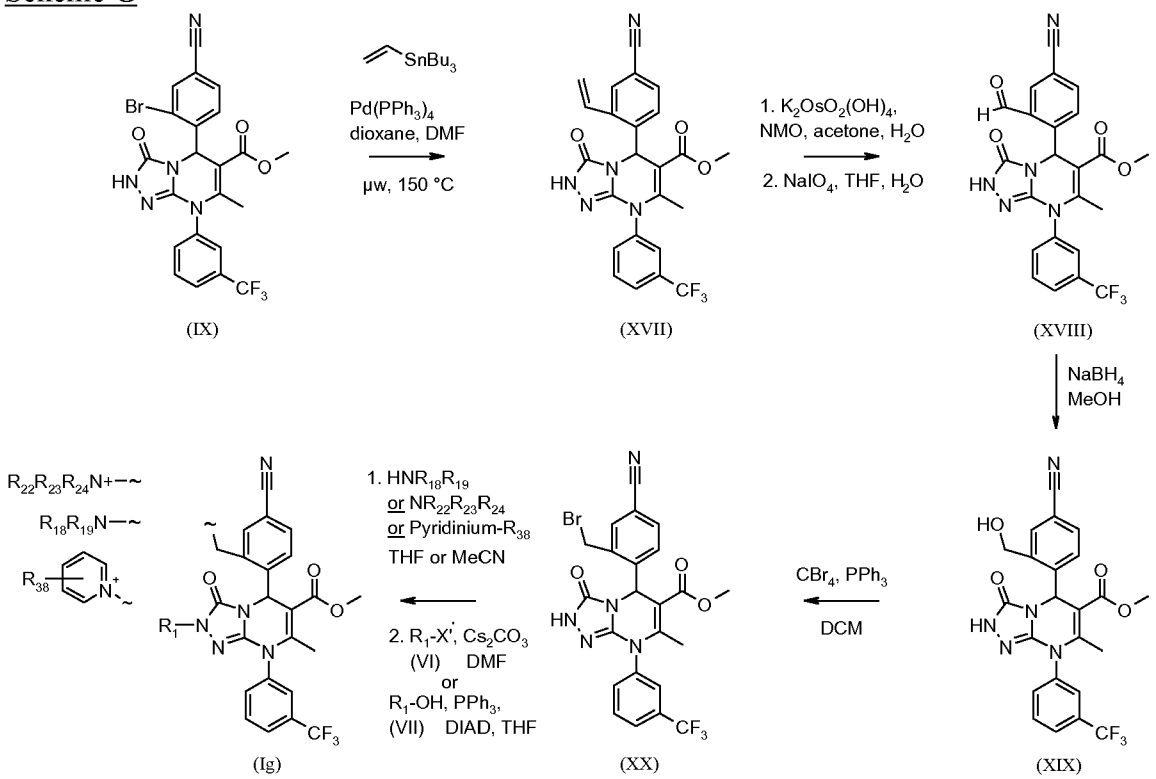


The transformation of compounds of formula (IX) into compounds of formula (Ic) may be achieved by reaction with a suitably unsubstituted acetylic compound (XVI) in the presence of a catalytic mixture such as *bis*(triphenylphosphine) palladium(II) dichloride and copper (l) iodide with a base such as triethylamine in a solvent such as DMF at a temperature of up to 120°C, typically using microwave irradiation. Compounds of formula (Id) may be prepared from compounds of formula (Ic) by hydrogenation using a catalyst such as Pd/C in a solvent such as IMS.

Furthermore, compounds of the formula (Ie) and (If) may be obtained from compounds of formula (Ic) and (Id), respectively, using the methods described for the transformation of compounds of formula (Ia) to compounds of formula (Ib) in Scheme A.

Compounds of formula (Ig) i.e. compounds of formula (I) wherein R_3 is a group $-COXR_4$, R_1 is as defined above, X is oxygen, R_4 is a methyl group, A, B and D are CH and R_2 is a methylene linked tertiary amine $NR_{18}R_{19}$ or quaternary amine $NR_{22}R_{23}R_{24}$ may be prepared from compounds of formula (IX) according to Scheme G below:

Scheme G



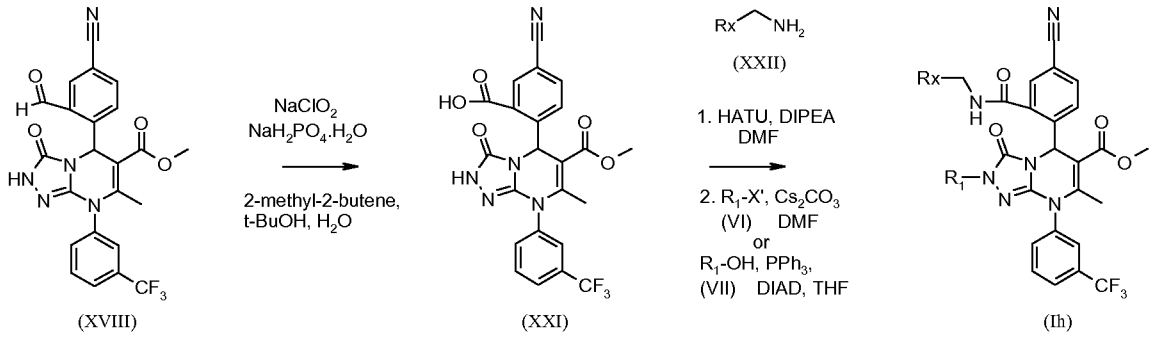
The transformation of compounds of formula (IX) into compounds of formula (XVII) may be achieved by reaction with a suitable nucleophile such as vinyltributyl stannane in the presence of a catalyst such *tetrakis*(triphenylphosphine) palladium(0) in a solvent such as dioxane or DMF at a temperature of up to 150°C, typically using microwave irradiation. Compounds of formula (XVIII) may be prepared from compounds of formula (XVII) following a 2 step procedure starting with oxidation using a catalyst such as potassium osmate dihydrate with a co-oxidant such as *N*-methylmopholine-*N*-oxide in a solvent mixture such as acetone/water at room temperature. Compounds of formula (XVIII) are thus obtained following cleavage of the intermediate diol using a suitable reagent such as sodium periodate in an appropriate solvent mixture such as THF/water. Compounds of formula (XIX) may be obtained from compounds of formula (XVIII) by reduction, typically using a reducing agent such as sodium borohydride in a solvent such as MeOH. Compounds of formula (XX) may be obtained from compounds of formula (XIX) by bromination. Suitable conditions involve reaction with an appropriate brominating agent such as carbon tetrabromide with triphenyl phosphine in a

solvent such as dichloromethane at a temperature of from 0°C to room temperature. Conversion of compounds of formula (XX) to either tertiary or quaternary amines of formula (Ig) can be achieved by reaction with a suitable secondary amine of formula $NHR_{18}R_{19}$ or tertiary amine of formula $NR_{22}R_{23}R_{24}$, respectively, in a suitable solvent such as THF or MeCN. Alternatively, quaternary amines of the formula (Ig) may be obtained sequentially from tertiary amines of formula (Ig) followed by reaction with a suitable electrophile such as methyl bromide in a suitable solvent such as MeCN at room temperature. Furthermore, conversion of compounds of formula (XX) to pyridinium compounds of formula (Ig) can be achieved by reaction with a suitably substituted pyridine-containing compound, pyridine(R38).

It should be clear to the skilled person that the aldehyde (XVIII) represents a versatile intermediate for further functionalisation as well as for preparation of compounds of formula (Ig).

Compounds of formula (Ih), i.e. compounds of formula (I) wherein R_3 is a group –$COXR_4$, R_1 is as defined above, A, B and D are CH, X is oxygen, R_4 is a methyl group, and R_2 is an amide-linked group as reported in Scheme H where R_x may have different meanings according to those described for compounds of formula (I), may be prepared from compounds of formula (XVIII) according to Scheme H below:

Scheme H



(XVIII) (XXI) (Ih)

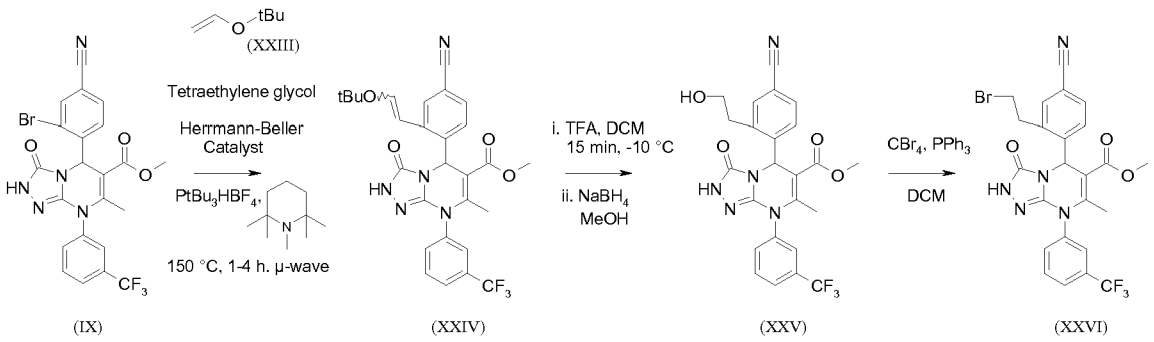
Compounds of formula (XXI) may be prepared from compounds of formula (XVIII) using suitable oxidizing reagent agent such as sodium chlorite and an appropriate co-reductant such as 2-methyl-2-butene in a suitable solvent mixture such as *tert*-

butanol/water and using an appropriate base such as sodium dihydrogenphosphate at room temperature. Typically, compounds of formula (Ih) where R_1 = H may be obtained from compounds of formula (XXI) by reaction with an amine (XXII) in the presence of a coupling agent such as HATU in a solvent such as DMF in the presence of a base such as triethylamine at a temperature of from room temperature to 80°C.

Furthermore, compounds of the formula (Ig) and (Ih) where $R_1 \neq H$ may be obtained from compounds of formula (Ig) and (Ih) where R_1 = H, using the methods described for the transformation of compounds of formula (Ia) to compounds of formula (Ib) in Scheme A. It should be clear to the skilled person that other appropriate protecting group strategies may be contemplated at R1 and that the incorporation of R1 (where $R_1 \neq$ H) can be possible at any intervening step in the synthesis of compounds of the invention, (Ig) and (Ih).

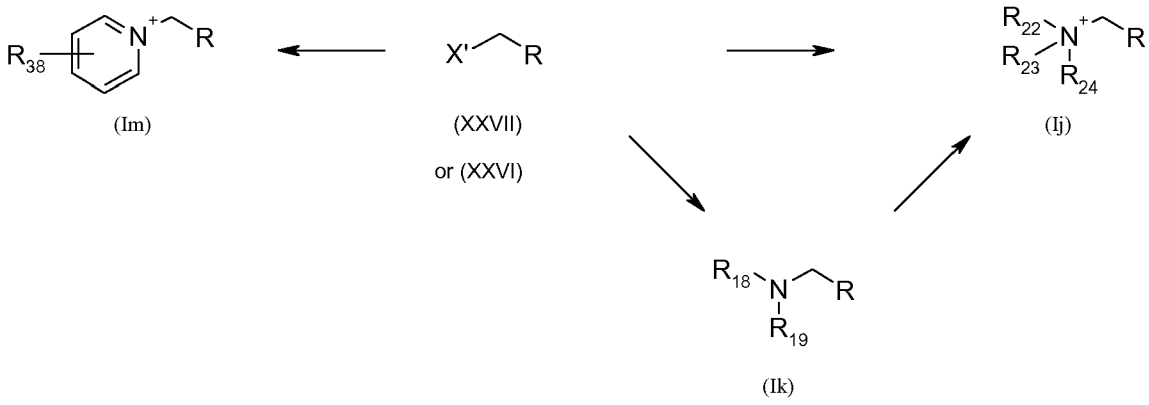
A compound of formula (XXVI) may be prepared according to Scheme J from a compound of formula (IX). A compound of formula (XXIV) may be prepared using Heck coupling chemistry by reaction with an appropriately substituted vinyl compound (XXIII) in the presence of an appropriate catalyst/ligand system such as Herrmann-Beller catalyst/tributylphosphine tetrafluoroborate in a solvent such as tetraethylene glycol or dimethoxyethane in the presence of a base such as pentamethylpiperidine at a temperature of from room temperature to 160°C. A compound of formula (XXV) may be prepared from compounds of formula (XXIV) following hydrolysis and reduction steps using an acid such as trifluoroacetic acid in a solvent such as DCM at -10°C to give the intermediate aldehyde, and a reducing agent such as sodium borohydride in a solvent such as MeOH at a temperature of from 0°C to room temperature to give a compound of formula (XXV). A compound of formula (XXVI) can be prepared from a compound of formula (XXV) using a mixture of carbon tetrabromide/triphenyl phosphine in a solvent such as DCM at a temperature of from 0°C to 50°C.

Scheme J



Compounds of formula (Ij), (Ik) or (Im), i.e. compounds of formula (I) where R_2 is defined as $(C_1\text{-}C_4)$alkylene$N^+R_{22}R_{23}R_{24}$, a group $(C_1\text{-}C_4)$alkylene$NR_{18}R_{19}$, a group $[CH_2]_yG[CH_2]_jCH_2\text{-}N^+$pyridinium(R38), respectively as substituents, may be prepared according to Scheme K. Similarly, compounds of formula (Ij), (Ik) or (Im), i.e. compounds of formula (I) where R_2 is defined as a group alkyne-Ry or $C(O)NHCH_2Rx$ may be prepared according to Scheme K. Compounds of formula (Ij), (Ik) or (Im) may also be prepared similarly from compounds of formula (XXVII).

Scheme K



Compounds of formula (Ij) can be obtained directly by alkylation reaction of an appropriate tertiary amine $R_{22}R_{23}R_{24}N$, such as trimethylamine or dimethylpiperazine, with compounds of formula (XXVII) wherein X' is an appropriate leaving group (X' = Cl, Br, I, Tosylate etc.) and group $-CH_2R$ represents the portion of a compound of formula (Ij) remaining out of its substitution by a group $(C_1\text{-}C_4)$alkyleneN^+R_{22} R_{23} R_{24}. Typical

conditions could involve heating a tertiary amine in a solvent such as ethanol or THF at elevated temperatures of between 60°C and 150°C, using microwave irradiation.

Alternatively, the transformation of compounds of formula (XXVII) to compounds of formula (Ij) may be achieved *via* the tertiary amine (Ik) where R_{18} and R_{19} ≠ H. Tertiary amine compounds of formula (Ik) may be prepared from compounds of formula (XXVII) by reaction with a secondary amine $R_{19}R_{18}NH$. Typical reaction conditions include the use of a base such as cesium carbonate or potassium carbonate in a solvent such as DMF at RT. The conversion of compounds of formula (Ik), where R_{18} and R_{19} ≠ H, to compounds of formula (Ij) can be obtained using methylating agents such as methyl bromide, methyl iodide or methyl benzenesulfonate. Typical reaction conditions consist of the use of a solvent such as MeCN or acetone at a temperature of between RT to 60°C under conventional or microwave heating.

Furthermore, primary and secondary amine compounds of formula (Ik) may also be prepared from compounds of formula (XXVII) by reaction with ammonia or a suitable primary amine $R_{18}NH_2$, respectively to give a primary amine or secondary amine.

Compounds of formula (Im) can be obtained directly by alkylation reaction of an appropriate pyridine-containing compound such as pyridine with compounds of formula (XXVII), wherein X' is an appropriate leaving group (X' = Cl, Br, I, Tosylate etc.) and group $-CH_2R$ represents the portion of a compounds of formula (Im) remaining out of its substitution by a group $[CH_2]_yG[CH_2]_jCH_2$-N^+pyridinium(R38). Typical conditions could involve heating compounds of formula (XXVII), with pyridine in a solvent such as MeCN or THF at elevated temperatures of between 50°C and 100°C, using microwave irradiation.

Compounds of formula (Ij), (Ik) or (Im), i.e. compounds of formula (I) which incorporate a group R_y or R_x (see Scheme F/H) defined as $(C_1$-$C_4)$alkylene$N^+R_{22}R_{23}R_{24}$, a group $(C_1$-$C_4)$alkylene$NR_{18}R_{19}$, or a group $[CH_2]_yG[CH_2]_jCH_2$-N^+pyridinium(R38), respectively as substituents, may be also be prepared according to Scheme K from compounds of formula (XXVI).

General Experimental Details

Reactions were not carried out under an inert atmosphere unless specified and all solvents and commercial reagents were used as received.

Purification by chromatography refers to purification using the CombiFlash ® Companion purification system or the Biotage SP1 purification system. Where products were purified using an Isolute® SPE Si II cartridge, 'Isolute SPE Si cartridge' refers to a pre-packed polypropylene column containing unbonded activated silica with irregular particles with average size of 50 μm and nominal 60Å porosity. Fractions containing the required product (identified by TLC and/or LCMS analysis) were pooled, the organic fraction removed by evaporation, and the remaining aqueous fraction lyophilised, to give the final product. Where thin layer chromatography (TLC) has been used, it refers to silica gel TLC using plates, typically 3 × 6 cm silica gel on aluminium foil plates with a fluorescent indicator (254 nm), (e.g. Fluka 60778). Microwave experiments were carried out using a Biotage Initiator 60™ which uses a single-mode resonator and dynamic field tuning. Temperature from 40-250°C can be achieved, and pressures of up to 30 bar can be reached.

NMR spectra were obtained on a Varian Unity Inova 400 spectrometer with a 5 mm inverse detection triple resonance probe operating at 400 MHz or on a Bruker Avance DRX 400 spectrometer with a 5 mm inverse detection triple resonance TXI probe operating at 400 MHz or on a Bruker Avance DPX 300 spectrometer with a standard 5mm dual frequency probe operating at 300 MHz. Shifts are given in ppm relative to tetramethylsilane.

Compound names were generated using the Autonom 2000 feature in MDL ISIS™/Draw 2.5 SP2 software.

Preparative HPLC Conditions

HPLC System 1

C18-reverse-phase end-capped column (250 × 21.2 mm Gemini column with 5 μm particle size), eluting with a gradient of A: water; B: MeCN (0.1% formic acid added)

with a flow rate typically 18 mL/min and gradient of 1%/min increasing in B. UV detection at 254 nm.

HPLC System 2

C18-reverse-phase end-capped column (250 × 21.2 mm Gemini column with 5 μm particle size), eluting with a gradient of A: water; B: methanol (0.1% formic acid added) with a flow rate typically 13 mL/min and gradient of 1%/min increasing in B. UV detection at 254 nm.

Analytical LC-MS Conditions

LC-MS Method 1

The Waters ZQ quadrupole mass spectrometer with a C18-reverse-phase column (30 × 4.6 mm Phenomenex Luna 3 μm particle size), elution with A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid. Gradient:

Gradient – Time	flow (mL/min)	%A	%B
0.00	2.0	95	5
0.30	2.0	95	5
4.30	2.0	5	95
5.30	2.0	5	95
5.80	2.0	95	5
6.00	2.0	95	5

Detection - MS, ELS, UV (200 μl/min split to the ESI source with in-line HP1100 PDA detector)

MS ionisation method - Electrospray (positive and negative ion)

LC-MS Method 2

Waters Micromass ZMD quadrupole mass spectrometer with a C18-reverse-phase column (30 × 4.6 mm Phenomenex Luna 3 μm particle size), elution with A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid. Gradient:

Gradient – Time	flow(mL/min)	%A	%B
0.00	2.0	95	5
0.50	2.0	95	5
4.50	2.0	5	95
5.50	2.0	5	95
6.00	2.0	95	5

Detection - MS, ELS, UV (100 µl split to MS with in-line UV detector)

MS ionisation method - Electrospray (positive and negative ion)

LC-MS Method 3

Waters Micromass ZQ2000 mass spectrometer with a C18-reverse-phase column (100 × 2.1 mm Acquity BEH with 1.7 µm particle size) maintained at 40°C, elution with A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid. Alternatively, where specified, a C18-reverse-phase (100 × 2.1 mm Acquity UPLC BEH Shield 1.7 µm particle size) column was used.

Gradient:

Gradient – Time	flow (mL/min)	%A	%B
0.00	0.4	95	5
0.40	0.4	95	5
6.00	0.4	5	95
6.80	0.4	5	95
7.00	0.4	95	5
8.00	0.4	95	5

Detection - MS, UV PDA

MS ionisation method - Electrospray (positive/negative ion).

LC-MS Method 4

Waters Platform LC quadrupole mass spectrometer with a C18-reverse-phase column (30 × 4.6 mm Phenomenex Luna 3 µm particle size), elution with A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid. Gradient:

Gradient – Time	flow (mL/min)	%A	%B
0.00	2.0	95	5
0.50	2.0	95	5
4.50	2.0	5	95
5.50	2.0	5	95
6.00	2.0	95	5

Detection - MS, ELS, UV (Split - 200µl/min split to the ESI source with in-line HP1100 DAD detection)

MS ionisation method - Electrospray (positive and negative ion).

LC-MS Method 5

Waters VG Platform II quadrupole spectrometer with a C18-reverse-phase column (30 × 4.6 mm Luna 3 µm particle size), elution with A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid.

Gradient:

Gradient - Time	flow	%A	%B
0.00	2.0	95	5
0.30	2.0	95	5
4.30	2.0	5	95
5.30	2.0	5	95
5.80	2.0	95	5
6.00	2.0	95	5

Detection - MS, ELS, UV (Split – 200 µl/min split to the ESI source with in-line HP1050 DAD detection)

MS ionisation method - Electrospray (positive and negative ion)

MDAP System:

Instrumentation: Agilent 1260 infinity purifications system. Agilent 6100 series single Quadrupole LC/MS

Column: XSELECT CSH Prep C18 5 µm OBD, 30X150 mm, RT

Mobile Phase A: 0.1% aqueous formic acid

Mobile Phase B: 0.1% formic acid in acetonitrile

Flow: 60 ml/min

Gradient Program: 10%-95%, 22 min, centred around a specific focused gradient

Sample Injection of a 20-60mg/ml solution in DMSO (+ optional formic acid and water).

Abbreviations used in the experimental section:

9-BBN 9-Borabicyclo[3.3.1]nonane

dba Dibenzylideneacetone

DCE Dichloroethane

DCM Dichloromethane

DIPEA Di-isopropylethylamine

DMF *N*,*N*-dimethylformamide

DMSO Dimethylsulphoxide

Dppf 1,1′-Bis(diphenylphosphino)ferrocene

Et_2O Diethyl ether

EtOAc Ethyl acetate

HPLC High performance liquid chromatography

IMS Industrial methylated spirits

LC-MS Liquid chromatography-mass spectrometry

MeCN Acetonitrile

MDAP Mass Directed Automatic Purification

NBS *N*-Bromosuccinimide

NMO *N*-Methylmorpholine-*N*-Oxide

Rt Retention time

RT Room temperature

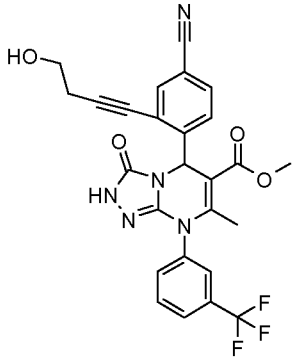
THF Tetrahydrofuran

In the procedures that follow, some of the starting materials are identified through an "Intermediate" or "Example" number. This is provided merely for assistance

to the skilled chemist. The starting material may not necessarily have been prepared from the batch referred to.

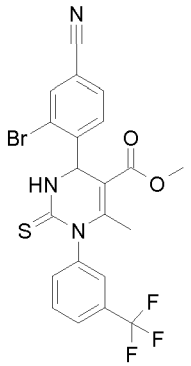
When reference is made to the use of a "similar" or "analogous" procedure, as will be appreciated by those skilled in the art, such a procedure may involve minor variations, for example reaction temperature, reagent/solvent amount, reaction time, work-up conditions or chromatographic purification conditions.

Example 1



5-[4-Cyano-2-(4-hydroxy-but-1-ynyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

Intermediate 1



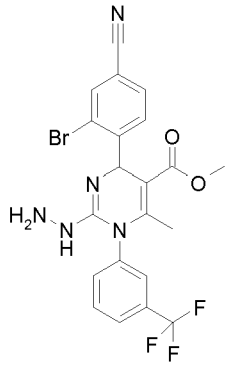
4-(2-Bromo-4-cyanophenyl)-6-methyl-2-thioxo-1-(3-trifluoromethylphenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester

3-Trifluoromethylphenylthiourea (12.8 g, 87 mmol), 2-bromo-4-cyanobenzaldehyde (18.3 g, 87 mmol) and methyl acetoacetate (10.4 mL, 96 mmol) were dissolved in THF (300 mL) under an atmosphere of N_2 and then trimethylsilylphosphate (18 g) in THF (50 mL) was added and the mixture heated at 75°C. After 17 hours the

reaction mixture was allowed to cool, poured onto 0.5 M HCl (600 mL) and stirred for 30 mins. The mixture was extracted into EtOAc. The organic phase was washed with water, then brine and dried (Na_2SO_4) before being concentrated *in vacuo*. The resulting solid was triturated with Et_2O (50 mL), filtered and the solid collected to yield the title compound as a white solid (22.2 g).

LC-MS (Method 2): Rt = 4.03 min, m/z = 432 $[M(79Br)+H]^+$

Intermediate 2

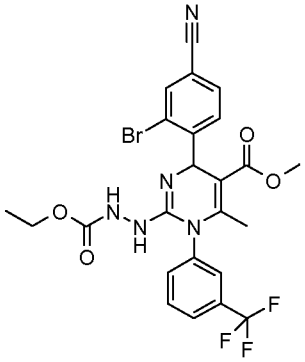


4-(2-Bromo-4-cyanophenyl)-2-hydrazino-6-methyl-1-(3-trifluoromethylphenyl)-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester

Intermediate 1 (4.6 g, 9 mmol) was dissolved in IMS (350 mL), urea hydrogen peroxide (3.4 g, 36.2 mmol) was added and the mixture stirred for 2 hours at RT before addition of hydrazine hydrate (4.1 mL, 54.4 mmol). The mixture was stirred for a further 2 hours at RT, filtered, the filtrate collected and then the solvent reduced to a low volume *in vacuo*. The resultant residue was partitioned between EtOAc and brine. The organic layer was separated, washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. The resulting residue was used directly in the next step.

LC-MS (Method 2): Rt = 2.49 min, m/z = 508 $[M(^{79}Br)+H]^+$

Intermediate 3

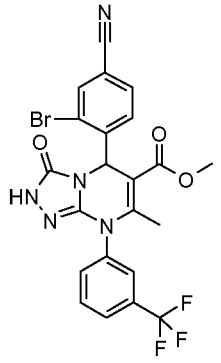


4-(2-Bromo-4-cyanophenyl)-2-(*N*'-ethoxycarbonyl-hydrazino)-6-methyl-1-(3-trifluoro methylphenyl)-1,4-dihydro-pyrimidine-5-carboxylic acid methyl ester

Intermediate 2 (approximately 9 mmol) was dissolved in DCM (40 mL) under an atmosphere of N_2 and cooled to -78°C before addition of triethylamine (1.7 mL, 12 mmol) and ethyl chloroformate (765 µL, 8 mmol). The reaction mixture was stirred at -78°C and allowed to warm slowly to RT over 16 hours and then partitioned between EtOAc and water. The organic layer was separated, washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. The resulting residue was purified by silica gel chromatography eluting with a gradient of 0-50% EtOAc in cyclohexane to give the title compound as a yellow solid (2 g over 2 steps).

LC-MS (Method 2): Rt = 3.55 min, m/z = 580 $[M(^{79}Br)+H]^+$

Intermediate 4



5-(2-Bromo-4-cyanophenyl)-7-methyl-3-oxo-8-(3-trifluoromethylphenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

Route A

Intermediate 3 (2 g, 3.5 mmol) was dissolved in IMS (20 mL) and heated at 160°C

for 1 hour using microwave irradiation. The solvent was removed *in vacuo* and the resulting residue triturated with Et_2O, filtered and the solid collected to yield the title compound as a white solid (1.5 g).

LC-MS (Method 3): Rt = 4.65 min, m/z = 534 $[M(^{79}Br)+H]^+$

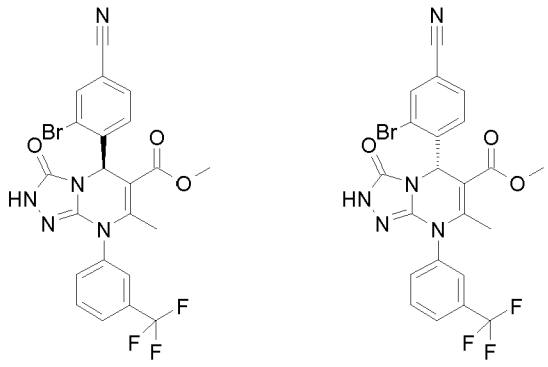
^1H NMR (400 MHz, DMSO) δ 11.20 (1H, s), 8.18 (1H, d, J = 1.6 Hz), 8.09 (1H, br s), 7.93-7.75 (5H, m), 6.23 (1H, d, J = 1.2 Hz), 3.49 (3H, s), 2.13 (3H, s).

Route B

To Intermediate 1 (75 g, 147 mmol) dissolved in dry DCM (1350 mL) and 2,6-lutidine (51.3 mL) at 0°C under nitrogen was added portion-wise triphosgene (13.82 g) with stirring. After 5 min the reaction was warmed to 20°C and stirred for 25 mins. The reaction mixture was cooled to 10°C and added *via* a cannula to a stirred solution of anhydrous hydrazine (0.419 moles) in THF (400 mL) and MeCN (380 mL) cooled in an ice bath. After a further 5 mins the reaction was warmed to 20°C and stirred at RT for 2 ¼ h. Water (800 mL) degassed with nitrogen was added to the reaction and the organic layer washed with further water (800 mL) and then brine (500 mL). The organic layer was dried (Na_2SO_4) and evaporated in *vacuo* and the residue was re-dissolved in toluene (300 mL) and again evaporated in *vacuo*. The residue was dissolved in toluene (500 mL) a final time and concentrated to a weight ~200 g. The resultant solution was diluted with Et_2O (500 mL) and left to crystallise. The title compound was collected by filtration to give yellow solid (32.1g). The mother liquors were concentrated in *vacuo* and the resultant residue was dissolved in DCM and left to crystallise. The solid was collected to give further title product as a yellow solid (2.56 g).

LC-MS (710016978): Rt = 3.39 min, m/z = 533.9 $[M(^{79}Br)+H]^+$

Intermediate 4a/4b



(4a) (4b)

(R) and (S) 5-(2-Bromo-4-cyano-phenyl)-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

The enantiomers of Intermediate 4 (155 mg, 0.290 mmol) were separated by preparative HPLC chromatography on a chiral phase [Daicel Chiralpak IC column (5 µm, 250 mm x 10 mm, 1% MeOH/DCM eluent, 5 mL/min flow rate, 220 nm detection)] to give 69 mg of the (R) enantiomer (first eluting and assigned as 4a) and 71 mg of the (S) enantiomer (second eluting and assigned as 4b).

5-[4-Cyano-2-(4-hydroxy-but-1-ynyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester (Example 1)

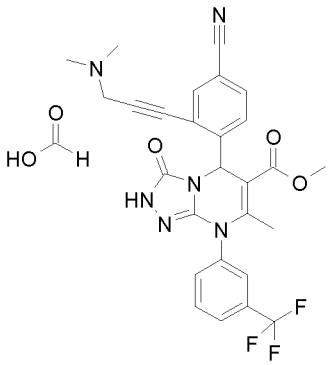
Intermediate 4 (150 mg, 0.28 mmol), 3-butyn-1-ol (42 mL, 0.57 mmol), *bis*(triphenylphosphine) palladium(II) dichloride (15 mg, 0.021 mmol) and copper (I) iodide (6 mg, 0.024 mmol) were dissolved in DMF (1.5 mL) and triethylamine (1.5 mL) and then purged with N_2 for 5 mins. The reaction mixture was then heated at 120°C for 1 hour using microwave irradiation. The reaction mixture was then filtered through a plug of silica and the resulting residue was purified by reverse phase HPLC (Method 1) using a gradient of 10-60% (+0.1% formic acid) MeCN in water to yield the title compound as an off-white solid (32 mg).

LC-MS (Method 3): Rt = 4.30 min, m/z = 524 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (1H, s), 7.79 (1H, d, J = 8 Hz), 7.72-7.67 (2H, m),

7.60 (1H, s), 7.54 (2H, dd, J = 8, 2 Hz), 7.37 (1H, d, J = 8 Hz), 6.64 (1H, s), 3.87-3.77 (2H, m), 3.58 (3H, s), 2.76-2.63 (2H, m), 2.58 (1H, s), 2.24 (3H, s).

Example 2



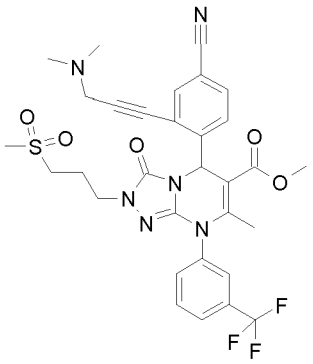
5-[4-Cyano-2-(3-dimethylamino-prop-1-ynyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester formate salt

Intermediate 4 (400 mg, 0.75 mmol), 1-dimethylamino-2-propyne (160 µL, 1.5 mmol), *bis*(triphenylphosphine)palladium(II) dichloride (79 mg, 0.11 mmol) and copper (I) iodide (43 mg, 0.23 mmol) were dissolved in DMF (2.5 mL) and triethylamine (2.5 mL) and purged with N_2 for 5 mins. The reaction was then heated at 125°C for 50 mins using microwave irradiation. The reaction mixture was filtered through a plug of celite and then diluted with EtOAc. The resultant solution was washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. A portion of the resulting residue (25 mg) was purified by reverse phase HPLC (Method 1) using a gradient of 10-40% MeCN in water (+0.1% formic acid) and gave the title compound as an off-white solid (11 mg).

LC-MS (Method 3): Rt = 3.38 min, m/z = 537 $[M+H]^+$

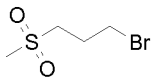
^1H NMR (400 MHz, $CDCl_3$) δ 9.30 (1H, br s), 8.28 (1H, s), 7.82-7.71 (3H, m), 7.64-7.58 (3H, m), 7.42 (1H, d, J = 8 Hz), 6.50 (1H, s), 3.84 (1H, d, J = 17 Hz), 3.76 (1H, d, J = 17 Hz), 3.60 (3H, s), 2.60 (6H, s), 2.26 (3H, s).

Example 3



5-[4-Cyano-2-(3-dimethylamino-prop-1-ynyl)-phenyl]-2-(3-methanesulfonyl-propyl)-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

Intermediate 5



1-Bromo-3-methanesulfonyl-propane

3-(Methylsulfonyl)-1-propanol (276 mg, 2 mmol) was dissolved in DCM (10 mL) and then CBr_4 (730 mg, 2.2 mmol) was added followed by PPh_3 (580 mg, 2.2 mmol) portionwise under an atmosphere of N_2. The resulting solution was stirred at RT for 17 hours. The mixture was partitioned between DCM and water. The organic layer was separated, washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. The resulting residue was purified by silica gel chromatography eluting with 50% EtOAc in cyclohexane to yield the title compound as a colourless oil (297 mg).

^{1}H NMR (400 MHz, DMSO) δ 3.63 (2H, t, J = 7 Hz), 3.25-3.20 (2H, m), 3.01 (3H, s), 2.27-2.19 (2H, m).

5-[4-Cyano-2-(3-dimethylamino-prop-1-ynyl)-phenyl]-2-(3-methanesulfonyl-propyl)-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

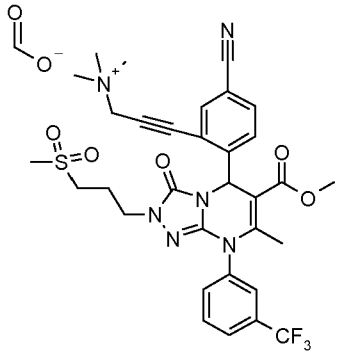
Example 2 (34.5 mg, 0.06 mmol) was dissolved in DMF (1 mL) and then cesium carbonate (25 mg, 0.08 mmol) and intermediate 4 (13 mg, 0.06 mmol) were added. The

mixture was stirred at RT for 16 hours. The mixture was partitioned between EtOAc and water. The organic layer was separated, and the aqueous layer extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. The resulting residue was purified by silica gel chromatography eluting from 0-10% (2 M NH_3 in MeOH) in DCM to yield the title compound as a white solid (4 mg).

LC-MS (Method 3): Rt = 3.45 min, m/z = 657 $[M+H]^+$

^1H NMR (400 MHz, $CDCl_3$) δ 7.82-7.69 (3H, m), 7.63-7.58 (3H, m), 7.43 (1H, d, J = 8 Hz), 6.50 (1H, s), 3.74-3.59 (2H, m), 3.61 (3H, s), 3.55 (2H, s), 2.95-2.90 (2H, m), 2.80 (3H, s), 2.40 (6H, s), 2.24 (3H, s), 2.12-2.04 (2H, m).

Example 4



(3-{5-Cyano-2-[2-(3-methanesulfonyl-propyl)-6-methoxycarbonyl-7-methyl-3-oxo-8-m-tolyl-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-prop-2-ynyl)-trimethyl-ammonium formate

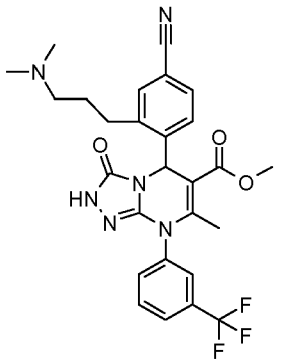
Example 3 (16 mg, 0.02 mmol) was dissolved in a 30% methyl bromide in MeCN solution (1 mL) and then K_2CO_3 (10 mg) was added. The mixture was stirred at RT for 24 hours. The reaction mixture was filtered and then evaporated *in vacuo*. The resulting residue was purified by reverse phase HPLC (Method 1) eluting from 10-40% MeCN in water (+0.1% formic acid) and gave the title compound as a white solid (11 mg).

LC-MS (Method 3): Rt = 3.45 min, m/z = 671 [M+H]+

1H NMR (400 MHz, DMSO) δ 8.46 (2H, s), 8.16-8.15 (1H, m), 7.96-7.92 (2H, m), 7.89-7.82 (2H, m), 6.34 (1H, s), 4.78 (1H, d, J = 16 Hz), 4.72 (1H, d, J = 16 Hz), 3.64-3.56 (2H, m), 3.53 (3H, s), 3.27 (9H, s), 3.05-2.92 (2H, m), 2.88 (3H, s), 2.17 (3H, s), 1.86-

1.77 (2H, m).

Example 5



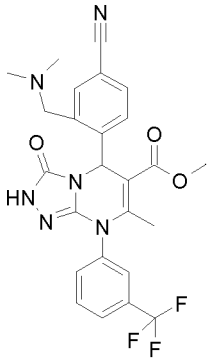
5-[4-Cyano-2-(3-dimethylamino-propyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

Example 2 (35 mg, 0.06 mmol) was dissolved in IMS (0.5 mL) and then added to a suspension of 10% palladium on carbon (approx. 30 mg) in IMS (0.5 mL). The mixture was stirred under a H_2 atmosphere (balloon) for 2 hours and then filtered through Celite© and the filtrate evaporated *in vacuo*. The resulting residue was purified by silica gel chromatography eluting from 0-10% (2 M NH_3 in MeOH) in DCM to give the title compound as a white solid (6 mg).

LC-MS (Method 3): Rt = 3.43 min, m/z = 541 $[M+H]^+$

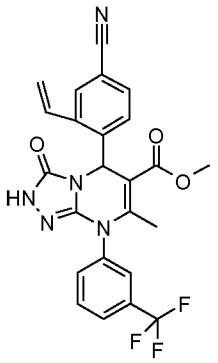
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (1H, d, J = 9 Hz), 7.72 (1H, t, J = 8 Hz), 7.64 (1H, s), 7.59 (1H, d, J = 8 Hz), 7.54 (1H, s), 7.50 (1H, dd, J = 8, 1 Hz), 7.37 (1H, d, J = 8 Hz), 6.28 (1H, s), 3.59 (3H, s), 3.28-3.20 (1H, m), 3.07-2.99 (1H, m), 2.48 (2H, t, J = 7 Hz), 2.28 (6H, s), 2.24 (3H, s), 2.07-1.99 (1H, m), 1.94-1.85 (1H, m).

Example 6



5-(4-Cyano-2-dimethylaminomethyl-phenyl)-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

Intermediate 6

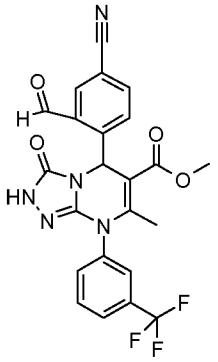


5-(4-Cyano-2-vinyl-phenyl)-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

Intermediate 4 (1.42 g, 2.66 mmol), tributyl vinyl stannane and palladium-*tetrakis*(triphenylphosphine) were dissolved in dioxane (18 mL) and a few drops of DMF and the resulting solution was purged with N_2 for 5 minutes. The reaction mixture was then heated at 150°C for 1 hour using microwave irradiation. The reaction mixture was purified by silica gel chromatography eluting with a gradient of 0-70% EtOAc in cyclohexane followed by trituration with Et_2O to yield the title compound as an off-white solid (1.02 g).

LC-MS (Method 2): Rt = 3.52 min, m/z = 482 $[M+H]^+$

Intermediate 7

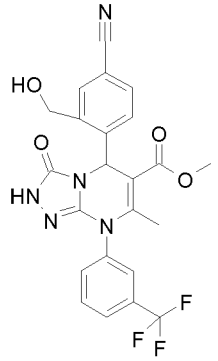


5-(4-Cyano-2-formyl-phenyl)-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

Intermediate 6 (0.8 g, 1.66 mmol) was suspended in acetone (4.5 mL) and water (0.5 mL). Potassium osmate dihydrate (31 mg, 0.08 mmol) was added, followed by NMO (0.39 g, 3.32 mmol) and the reaction mixture stirred vigorously at RT for 18 hours. $Na_2S_2O_5$ (4 g, 21.06 mmol) was then added and the reaction diluted with DCM and stirred for a further 20 minutes. The resultant mixture was filtered through celite and then evaporated *in vacuo*. The resultant residue was taken up in THF (8 mL) and water (8 mL) and then cooled to 0°C before sodium periodate (0.71 g, 3.32 mmol) was added. The reaction mixture was allowed to warm to RT and then stirred for 3 hours before being diluted with saturated aqueous $NaHCO_3$ and then extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$ then brine, dried (Na_2SO_4) and evaporated *in vacuo*. The resulting residue was purified by silica gel chromatography eluting with a gradient of 50-70% EtOAc in cyclohexane to yield the title compound as a pink solid (0.56 g).

LC-MS (Method 1): Rt = 2.98 min, m/z = 484 $[M+H]^+$

Intermediate 8



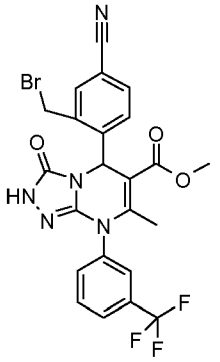
5-(4-Cyano-2-hydroxymethyl-phenyl)-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

Intermediate 7 (273 mg, 0.57 mmol) was dissolved in MeOH (5 mL) and sodium borohydride (26 mg, 0.68 mmol) was added and the reaction stirred at RT for 2 hours.

The mixture was evaporated *in vacuo* and the residue partitioned between EtOAc and water and the phases separated. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. The resulting residue was triturated with Et_2O, filtered and the solid collected to yield the title compound as an off-white solid (184 mg).

LC-MS (Method 2): Rt = 3.24 min, m/z = 486 [M+H]+

Intermediate 9



5-(2-Bromomethyl-4-cyano-phenyl)-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

Intermediate 8 (approximately 0.1 mmol) was dissolved in DCM (1 mL) and the solution cooled to 0°C. Carbon tetrabromide (40 mg, 0.12 mmol) was added, followed by triphenylphosphine (29 mg, 0.11 mmol) and the reaction stirred at RT. After 5 hours, further portions of carbon tetrabromide (53 mg, 0.16 mmol) and triphenylphosphine (42 mg, 0.16 mmol) were added and stirring continued at RT for 16 hours. The reaction mixture was diluted with DCM and washed with water followed by brine, dried (Na_2SO_4) and evaporated *in vacuo*. The resulting residue was purified by silica gel chromatography eluting with a gradient of 50-80% EtOAc in cyclohexane to give the title compound as a white solid (19 mg).

LC-MS (Method 1): Rt = 3.12 min, m/z = 548 $[M+H]^+$

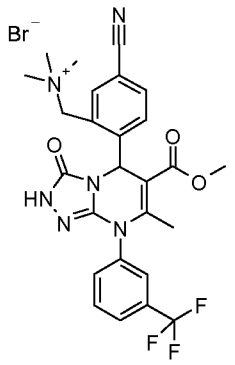
5-(4-Cyano-2-dimethylaminomethyl-phenyl)-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester (Example 6)

Intermediate 9 (23 mg, 0.04 mmol) was dissolved in THF (0.5 mL), 2 M dimethylamine in MeOH (0.5 mL) was added and the reaction stirred at RT. After 2 hours the reaction mixture was evaporated to dryness and the resulting residue was purified by silica gel chromatography eluting with a gradient of 0-5% (2 M NH_3 in MeOH) in DCM to yield the title compound as a white solid (13 mg).

LC-MS (Method 3): Rt = 3.38 min, m/z = 513 $[M+H]^+$

^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (1H, s), 7.82-7.81 (2H, m), 7.74 (1H, t, J = 8 Hz), 7.65 (1H, s), 7.60 (1H, d, J = 7 Hz), 7.55-7.52 (1H, m), 7.38 (1H, d, J = 8 Hz), 6.31 (1H, s), 4.16 (1H, d, J = 16 Hz), 3.86 (1H, d, J = 16 Hz), 3.61 (3H, s), 2.38 (6H, s), 2.26 (3H, s).

Example 7



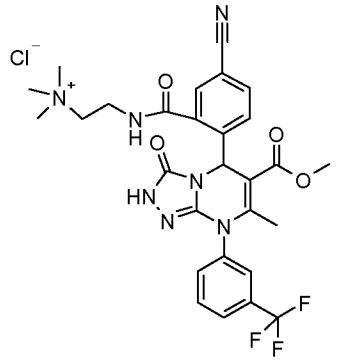
{5-Cyano-2-[6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-trimethyl-ammonium bromide

Intermediate 9 (17 mg, 0.03 mmol) was dissolved in THF (2 mL) and 31% trimethylamine in EtOH (2 mL) and the mixture stirred at RT for 72 hours. The solvent was removed *in vacuo* and the resulting residue was purified by reverse phase HPLC using a gradient of 10-90% MeCN in water to give the title compound as a white solid (6 mg).

LC-MS (Method 3): Rt = 3.28 min, m/z = 527 $[M]^+$

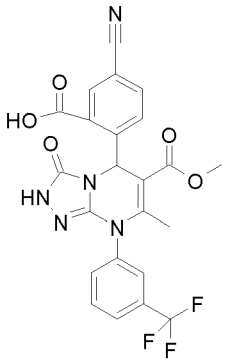
^{1}H NMR (400 MHz, DMSO) δ 11.34 (1H, s), 8.11 (2H, s), 8.03 (1H, dd, J = 2 and 8 Hz), 7.95-7.79 (4H, m), 6.48 (1H, s), 5.13 (1H, d, J = 14 Hz), 4.98 (1H, d, J = 14 Hz), 3.52 (3H, s), 3.26 (9H, s), 2.07 (3H, s).

Example 8



(2-{5-Cyano-2-[6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzoylamino}-ethyl)-trimethyl-ammonium chloride

Intermediate 10



5-(2-Carboxy-4-cyano-phenyl)-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

Intermediate 7 (50 mg, 0.1 mmol) was dissolved in *tert*-butanol (700 µL) and water (170 µL), then sodium dihydrogenphosphate (14 mg, 0.1 mmol) and 2-methyl-2-butene (2 M in THF, 220 µL, 0.44 mmol) were added, followed by sodium chlorite (40 mg, 0.35 mmol) and the mixture was stirred at RT for 4 hours. The mixture was acidified to pH 1 with aqueous 1 M HCl and then extracted with EtOAc and the combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated *in vacuo* to yield the title

compound as a cream foam.

LC-MS (Method 1): Rt = 2.77 min, m/z = 500 $[M+H]^+$

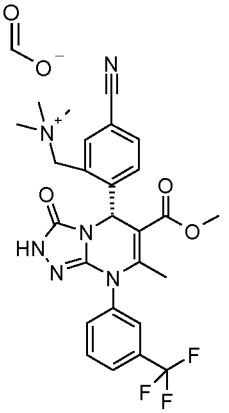
(2-{5-Cyano-2-[6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzoylamino}-ethyl)-trimethyl-ammonium chloride (Example 8)

Intermediate 10 (0.1 mmol) was dissolved in DMF (2 mL) and diisopropylethylamine (68 µL, 0.4 mmol) was added followed by HATU (57 mg, 0.15 mmol). (2-Aminoethyl)trimethylammonium chloride hydrochloride (22 mg, 0.12 mmol) was added and the mixture stirred at RT for 16 hours. The mixture was partitioned between EtOAc and water. The organic layer was separated, and the aqueous layer extracted with EtOAc and the combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. The resulting residue was purified by reverse phase HPLC using a gradient of 10-90% MeCN in water (+0.1% formic acid) to give the formate of the title compound as a white solid. Following elution through Amberlite IRA458 chloride resin, the title compound was obtained as a white solid (14 mg).

LC-MS (Method 3): Rt = 3.28 min, m/z = 584 $[M]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.63 (1H, s), 9.48 (1H, s), 7.98-7.92 (3H, m), 7.88-7.80 (4H, m), 6.40 (1H, m), 3.87-3.71 (2H, m), 3.57 (2H, t, J = 7 Hz), 3.41 (3H, s), 3.17 (9H, s), 2.16 (3H, s).

Example 9



{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-

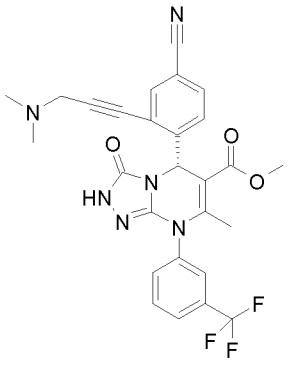
phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-trimethyl-ammonium formate

The title compound was prepared from Intermediate 4b (2.05 g, 3.81 mmol) using an analogous method to Example 7. Following MDAP purification the title compound was obtained as a white solid (107 mg).

LC-MS (Method 3): Rt = 3.28 min, m/z = 527 $[M]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.59 (1H, s), 8.42 (1.6H, s, formate) 8.11 (2H, m), 8.04 (1H, dd, J = 1.7 and 8.3 Hz), 7.95-7.79 (4H, m), 6.49 (1H, s), 5.13 (1H, d, J = 14 Hz), 4.98 (1H, d, J = 14 Hz), 3.52 (3H, s), 3.26 (9H, s), 2.07 (3H, s).

Example 10



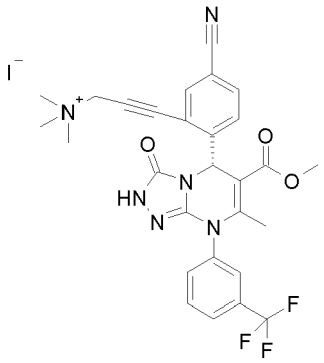
(R)-5-[4-Cyano-2-(3-dimethylamino-prop-1-ynyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3a]pyrimidine-6-carboxylic acid methyl ester

Intermediate 4b (500 mg, 0.94 mmol), 1-dimethylamino-2-propyne (305 µl, 3.76 mmol), *bis*(triphenylphosphine)palladium(II) dichloride (65 mg, 0.093 mmol) and copper (I) iodide (43 mg, 0.096 mmol) were dissolved in dioxane (4 mL) and triethylamine (0.48 mL) and purged with Argon for 5 mins. The reaction was then heated at 120°C for 30 mins using microwave irradiation. The reaction mixture was diluted with ethyl acetate and washed with water and the organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified by chromatography eluting from 0-5% (2 M NH_3 in MeOH) in DCM to yield the title compound as a brown gum (159 mg).

LC-MS (Method 1): Rt = 2.48 min, m/z = 537 $[M+H]^+$

1H NMR (400 MHz, DMSO) δ 8.75 (1H, br s), 7.80 (1H, d, J = 7.8 Hz), 7.76 (1H, d, J = 1.6 Hx), 7.72 (1H, t, J = 7.8 Hz), 7.64 (1H, bs), 7.62-7.54 (2H, m), 7.42 (1h, d, J = 8.1 Hz), 6.48 (1H, m), 3.52 (2H, m), 3.60 (3H, s), 2.38 (6H, s), 2.24 (3H, s).

Example 11



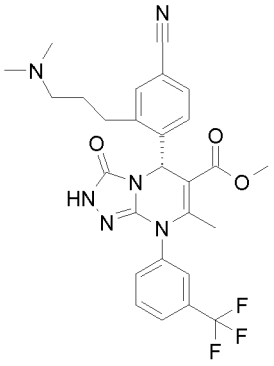
(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-prop-2-ynyl)-trimethyl-ammonium iodide

Example 10 (41 mg, 0.076 mmol) in MeCN (1 mL) was treated with iodomethane (24 µL, 0.385 mmol). After 20 min the reaction was concentrated *in vacuo* and the residue sonicated with diethyl ether and the solid residue collected by filtration to give the title compound as a pale brown solid (36 mg).

LC-MS (Method 3): Rt = 3.47 min, m/z = 555.4 $[M]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.24 (1H, s), 8.12 (1H, s), 7.95-7.89 (2H, m), 7.85-7.79 (2H, m), 7.71 (1H, dd, J = 1.5, 8.1 Hz), 7.66 (1H, bd, J = 8.1Hz), 6.17 (1H, s), 3.52 (3H, s), 3.48 (2H, t, J = 8.5 Hz), 3.27 (1H, m) 3.13 (9H, s),) 2.97 (1H, m) 2.40 (1H, m), 2.20 (1H, m) and 2.15 (3H, s).

Example 12



Route A

(R)-5-[4-Cyano-2-(3-dimethylamino-propyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

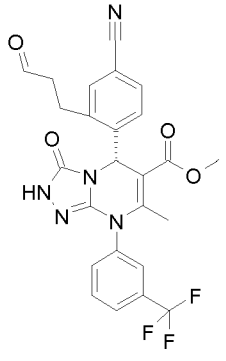
The title compound was prepared from Example 10 (120 mg, 0.223 mmol) using an analogous method to Example 5 except that the reaction required warming to 50°C to progress satisfactorily. The resulting residue was purified by chromatography eluting from 3-8% (2 M NH_3 in MeOH) in DCM to yield the title compound as a brown gum (45 mg).

LC-MS (Method 3): Rt = 2.55 min, m/z = 541 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (1H, d, J = 9 Hz), 7.72 (1H, t, J = 8 Hz), 7.64 (1H, s), 7.59 (1H, d, J = 8 Hz), 7.54 (1H, s), 7.50 (1H, dd, J = 8, 1 Hz), 7.37 (1H, d, J = 8 Hz), 6.28 (1H, s), 3.59 (3H, s), 3.28-3.20 (1H, m), 3.07-2.99 (1H, m), 2.48 (2H, t, J = 7 Hz), 2.28 (6H, s), 2.24 (3H, s), 2.07-1.99 (1H, m), 1.94-1.85 (1H, m).

Route B to Example 12

Intermediate 11



(R)-5-[4-Cyano-2-(3-oxo-propyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

A suspension of tri-*tert*-butylphosphonium tetrafluoroborate (163 mg, 0.56 mmol) and tris(dibenzylideneacetone)dipalladium(0) in dry dioxane (20 mL) was degassed with argon for 10 mins. To this was added a solution of Intermediate 4b (5.0 g, 9.36 mmol) in dry dioxane (30 mL), followed by allyl alcohol (2.55 mL, 37.43 mmol) and *N,N*-dicyclohexylmethylamine (4.01 mL, 18.72 mmol). The resulting mixture was stirred at 60°C for 30 mins then cooled, filtered through Celite and concentrated *in vacuo* to yield the title compound as a dark yellow foam which was used without further purification (287 mg).

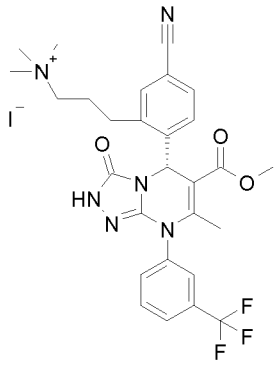
LC-MS (Method 4): Rt = 3.32/3.49 min, m/z = 512 $[M+H]^+$

(R)-5-[4-Cyano-2-(3-dimethylamino-propyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester (Example 12)

To a solution of crude intermediate 11 (4.79 g, 9.36 mmol) in MeOH (80 mL) at 5°C was added dimethylamine solution (2 M in methanol, 37.44 mL, 74.88 mmol) followed by sodium cyanoborohydride (647 mg, 10.30 mmol), zinc chloride (647 mg, 4.74 mmol) and 1 M HCl (56 mL, 56.0 mmol). The mixture was stirred for 30 mins and allowed to warm to RT. The resultant mixture was then partitioned between DCM and water and the aqueous layer extracted with DCM (x 2) and the combined organic layers dried (Na_2SO_4), and concentrated *in vacuo*. The resulting residue was purified by chromatography using an Isolute® SPE Si NH_2 cartridge eluting with a gradient from 2-9% (2 M NH_3 in MeOH) in DCM. The crude product was further purified by NH_2 cartridge, eluting with 0-10% MeOH in EtOAc to afford the title compound as a cream foam (3.9 g)

LC-MS (Method 4): Rt = 2.50 min, m/z = 541 $[M+H]^+$

Example 13



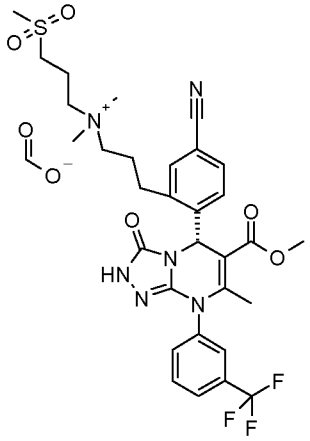
(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-trimethyl-ammonium iodide

The title compound was prepared from Example 12 (41 mg, 0.076 mmol) using an analogous method to Example 11 to give the title compound as a pale brown solid (38 mg).

LC-MS (Method 3): Rt = 3.47 min, m/z = 555.4 $[M]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.24 (1H, s), 8.12 (1H, s), 7.95-7.89 (2H, m), 7.85-7.79 (2H, m), 7.71 (1H, dd, J = 1.5, 8.1 Hz), 7.66 (1H, bd, J = 8.1Hz), 6.17 (1H, s), 3.52 (3H, s), 3.48 (2H, t, J = 8.4 Hz), 3.27 (1H, m) 3.13 (9H, s), 2.97 (1H, m) 2.40 (1H, m), 2.20 (1H, m) and 2.15 (3H, s).

Example 14



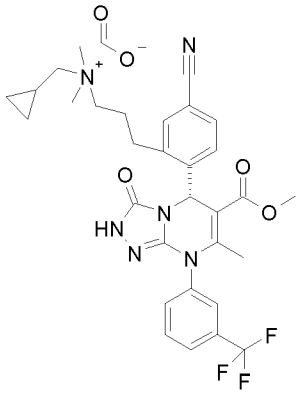
(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-(3-methanesulfonyl-propyl)-dimethyl-ammonium formate

To a solution of Example 12 (150 mg, 0.28 mmol) in MeCN (2 mL) was added 1-bromo-3-methanesulfonyl-propane (225 mg, 1.12 mmol). The resulting mixture was heated at 90°C for 40 mins using microwave irradiation. The solvent was removed *in vacuo* and the resultant residue was purified by reverse phase chromatography (MDAP), giving the title compound as an off-white solid (65 mg)

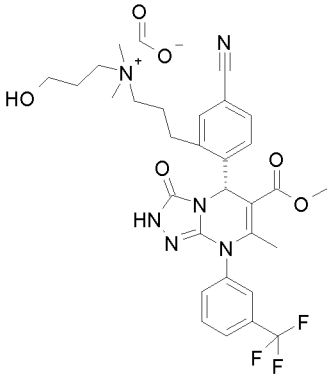
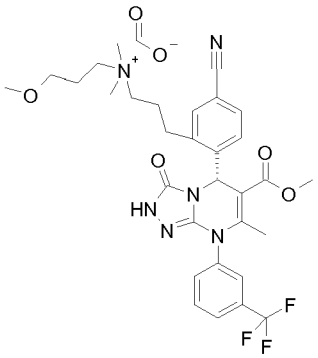
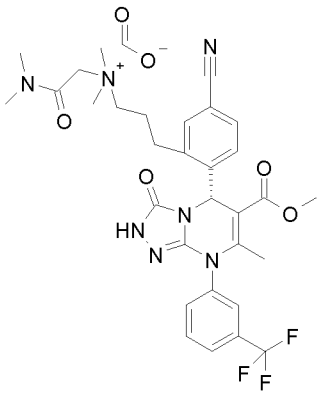
LC-MS (Method 3): Rt = 3.53 min, m/z = 661.2 $[M]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.44 (1H, bs), 8.46 (1H, s), 8.14 (1H, s), 7.97-7.91 (2H, m), 7.91-7.87 (2H, m), 7.73 (1H, dd, J = 1.6, 8.2 Hz), 7.67 (1H, bd, J = 8.2Hz), 6.20 (1H, s), 3.54 (3H, s), 3.52 (2H, t, J = 8.3 Hz), 3.45 (2H, t, J = 8.3 Hz), 3.36-3.20 (4H, m), 3.14 (6H, s), 3.07 (3H, s), 2.98 (1H, m), 2.42 (1H, m), 2.26-2.14 (2H, m), 2.17 (3H, s)

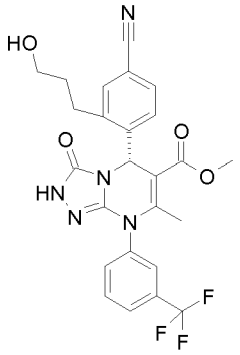
The following examples were prepared from Example 12 and the appropriately substituted alkyl halide using an analogous method to Example 14:

Ex	Structure	Name	LC-MS (Method 3)	NMR
15		(3-{5-Cyano-2-[(R)-6-methoxy-carbonyl-7-methyl-3-oxo-8-(3-trifluoro-methyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-cyclopropylmethyl-dimethyl-ammonium formate	Rt = 3.68 min, m/z = 595.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.44 (1H, bs), 8.44 (1H, s), 8.14 (1H, s), 7.98-7.91 (2H, m), 7.88-7.83 (2H, m), 7.73 (1H, dd, J = 1.5, 8.0 Hz), 7.67 (1H, bd, J = 8.2Hz), 6.20 (1H, s), 3.54 (3H, s), 3.52 (2H, t, J = 8.3 Hz), 3.34-3.24 (3H, m), 3.13 (6H, s), 2.99 (1H, m), 2.41 (1H, m), 2.21 (1H, m), 2.17 (3H, s), 1.22 (1H, m), 0.77-0.71 (2H, m), 0.48-0.41 (2H, m)

(continued)

16		(3-{5-Cyano-2-[(R)-6-methoxy-carbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-(3-hydroxy-propyl)-dimethyl-ammonium formate	Rt = 3.60 min, m/z = 599.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.44 (1H, bs), 8.47 (1H, s), 8.14 (1H, s), 7.97-7.89 (2H, m), 7.87-7.80 (2H, m), 7.73 (1H, dd, J = 1.5, 8.0 Hz), 7.67 (1H, bd, J = 8.2Hz), 6.20 (1H, s), 3.54 (3H, s), 3.53-3.38 (7H, m), 3.27 (1H, m), 3.11 (6H, s), 2.99 (1H, m), 2.38 (1H, m), 2.18 (1H, m) 2.17 (3H, s) 1.94-1.85 (2H, m)
17		(3-{5-Cyano-2-[(R)-6-methoxy-carbonyl-7-methyl-3-oxo-8-(3-trifluoro-methyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-(3-methoxy-propyl)-dimethyl-ammonium formate	Rt = 3.79 min, m/z = 613.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.46 (1H, bs), 8.45 (1H, s), 8.14 (1H, s), 7.97-7.90 (2H, m), 7.87-7.81 (2H, m), 7.73 (1H, dd, J = 1.5, 8.0 Hz), 7.67 (1H, bd, J = 8.2Hz), 6.20 (1H, s), 3.54 (3H, s), 3.51-3.37 (6H, m), 3.28 (3H, s), 3.26 (1H, m) 3.11 (6H, s), 2.98 (1H, m), 2.40 (1H, m), 2.18 (1H, m) 2.17 (3H, s) 2.04-1.95 (2H, m)
18		(3-{5-Cyano-2-[(R)-6-methoxy-carbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-dimethyl-carbamoyl-methyl-dimethyl-ammonium formate	Rt = 3.73 min, m/z = 626.3$[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.46 (1H, bs), 8.48 (1H, s), 8.14 (1H, s), 7.97-7.91 (2H, m), 7.87-7.81 (2H, m), 7.73 (1H, dd, J = 1.5, 8.0 Hz), 7.67 (1H, bd, J = 8.2Hz), 6.17 (1H, s), 4.50 (2H, s) 3.77 (2H, t, J = 8.5 Hz) 3.54 (3H, s), 3.30 (6H, s), 3.29 (1H, m), 2.99 (3H, s), 2.97 (1H, m), 2.90 (3H, s) 2.44 (1H, m), 2.20 (1H, m) 2.17 (3H, s)

Intermediate 12

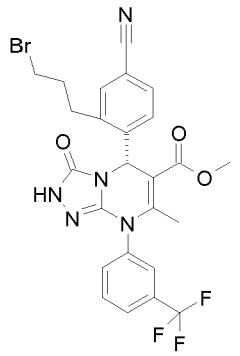


(R)-5-[4-Cyano-2-(3-hydroxy-propyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

To a solution of intermediate 11 (4.30 mmol) in MeOH (40 mL) at 5°C was added sodium borohydride (163 mg, 4.30 mmol) portion-wise. The mixture was stirred for 30 mins and allowed to warm to RT. The solvent was removed *in vacuo* and the residue was partitioned between 1 N HCl and EtOAc. The aqueous layer was extracted with EtOAc (x 2) and the combined organic extracts dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified by chromatography eluting with a gradient of 0-10% MeOH in DCM to give the title compound as a yellow foam (990 mg).

LC-MS (Method 4): Rt = 3.29 min, m/z = 514 $[M+H]^+$

Intermediate 13



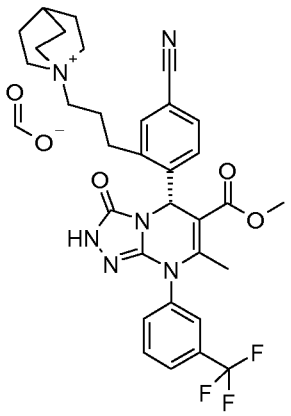
(R)-5-[2-(3-Bromo-propyl)-4-cyano-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

To a solution of intermediate 12 (780 mg, 1.52 mmol) in DCM (20 mL) at 5°C

was added carbon tetrabromide (756 mg, 2.28 mmol) followed by triphenylphosphine (598 mg, 2.28 mmol). The resulting mixture was stirred for 1.5 h and allowed to warm to RT. The solution was diluted with DCM and washed with water and the organic layer dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was purified by chromatography eluting from 0-50% EtOAc in cyclohexane to give the title compound as a yellow foam (620 mg).

LC-MS (Method 4): Rt = 3.90 min, m/z = 576/578 $[M+H]^+$ (Br isotopic pattern)

Example 19



1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-1-azonia-bicyclo[2.2.2]octane formate

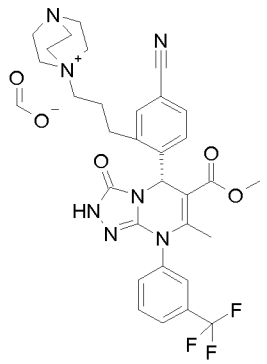
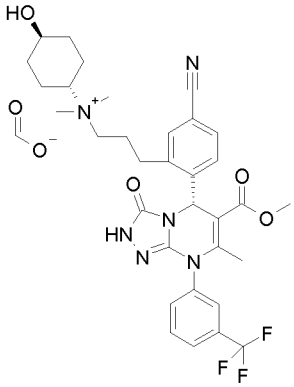
To a solution of Intermediate 13 (100 mg, 0.17 mmol) in MeCN (2 mL) was added quinuclidine (77 mg, 0.69 mmol). The mixture was heated at 90°C for 30 mins using microwave irradiation. The solvent was removed *in vacuo* and the residue was purified by reverse phase chromatography (MDAP), giving the title compound as an off-white solid (98 mg).

LC-MS (Method 3): Rt = 3.80 min, m/z = 607.3 $[M]^+$

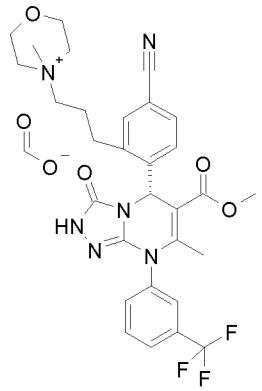
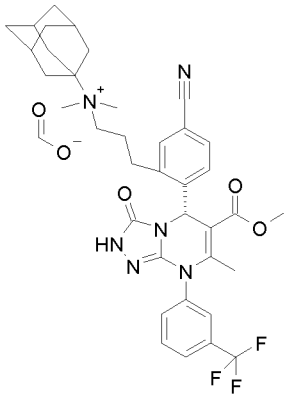
^{1}H NMR (400 MHz, DMSO) δ 11.52 (1H, bs), 8.45 (1H, s), 8.14 (1H, s), 7.97-7.91 (2H, m), 7.87-7.81 (2H, m), 7.73 (1H, dd, J = 1.6, 8.2 Hz), 7.67 (1H, bd, J = 8.2Hz), 6.19 (1H, s), 3.54 (3H, s), 3.51-3.43 (6H, m), 3.34-3.22 (3H, m), 2.95 (1H, m), 2.36 (1H, m) 2.17

(3H, s), 2.17 (1H, m) 2.10 (1H, m), 1.93-1.85 (6H, m)

The following examples were prepared from Intermediate 13 and the appropriately substituted tertiary amine using an analogous method to Example 19:

Ex	Structure	Name	LC-MS (Method 3)	NMR
20		1-(3-{5-Cyano-2-[(R)-6-methoxy-carbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-4-aza-1-azonia-bicyclo-[2.2.2]octane formate	Rt = 3.52 min, m/z = 608.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.46 (1H, bs), 8.49 (1H, s), 8.14 (1H, s), 7.97-7.91 (2H, m), 7.87-7.81 (2H, m), 7.73 (1H, dd, J = 1.5, 8.0 Hz), 7.67 (1H, bd, J = 8.2Hz), 6.20 (1H, s), 3.56-3.30 (8H, m), 3.54 (3H, s), 3.29 (1H, m) 3.10-3.03 (6H, m), 2.97 (1H, m), 2.40 (1H, m), 2.18 (1H, m) 2.17 (3H, s)
21*		(3-{5-Cyano-2-[(R)-6-methoxy-carbonyl-7-methyl-3-oxo-8-(3-trifluoro-methyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-(4-hydroxy-cyclohexyl)-dimethyl-ammonium formate	Rt = 2.93 min, m/z = 639.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.42 (1H, bs), 8.47 (1H, s), 8.12 (1H, s), 7.97-7.99 (2H, m), 7.87-7.79 (2H, m), 7.73-7.62 (2H, m), 6.19 (1H, s), 3.65-3.38 (3H, m, partially obscured by water peak), 3.54 (3H, s), 3.22 (1H, m), 3.03 (3H, s), 3.01 (3H, s), 2.93 (1H, m), 2.40 (1H, m), 2.17 (1H, m) 2.15 (3H, s), 2.07 (2H, m), 1.93 (2H, m), 1.59 (2H, m) 1.28 (2H, m)

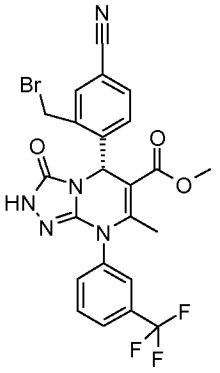
(continued)

22		4-(3-{5-Cyano-2-[(R)-6-methoxy-carbonyl-7-methyl-3-oxo-8-(3-trifluoro-methyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-4-methyl-morpholin-4-ium formate	Rt = 3.63 min, m/z = 597.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.52 (1H, bs), 8.50 (1H, s), 8.12 (1H, bs), 7.95-7.90 (2H, m), 7.85-7.80 (2H, m), 7.71 (1H, dd, J = 1.6, 8.1 Hz), 7.65 (1H, bd, J = 8.1Hz), 6.20 (1H, s), 3.96 (4H, m), 3.65 (2H, m, partially obscured by water peak), 3.54 (3H, s), 3.49 (4H, m), 3.29 (1H, m), 3.14 (3H, s), 2.98 (1H, m), 2.41 (1H, m), 2.20 (1H, m) 2.17 (3H, s)
23*		Adamantan-1-yl-(3-{5-cyano-2-[(R)-6-methoxy-carbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-ammonium formate	Rt = 3.33 min, m/z = 675.4 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.43 (1H, bs), 8.47 (1H, s), 8.12 (1H, bs), 7.96-7.87 (2H, m), 7.87-7.78 (2H, m), 7.72-7.62 (2H, m), 6.21 (1H, s), 3.52 (3H, s), 3.36 (2H, m, partially obscured by water peak), 3.22 (1H, m), 2.90 (1H, m), 2.90 (3H, s), 2.88 (3H, s) 2.43 (1H, m), 2.25 (3H, bs), 2.13 (3H, s), 2.08 (7H, m) 1.66 (6H, m)

* = Alternative Acquity UPLC BEH Shield RP18 1.7 micron 100 mm x 2.1 mm used in LCMS method

5

Intermediate 14

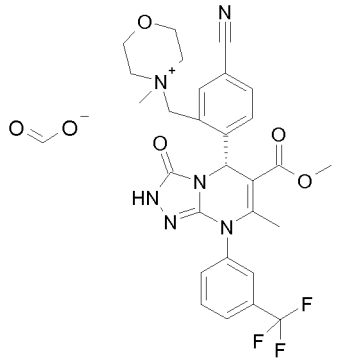


(R)-5-(2-Bromomethyl-4-cyano-phenyl)-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

The title compound was prepared from Intermediate 4b (0.5 g, 1.03 mmol) using analogous methods to those employed to make Intermediate 9 and gave the title compound as a colourless gum (1.26 g).

LC-MS (Method 4); Rt = 3.70 min, m/z = 548.0 $[M(^{79}Br)+H]^+$

Example 24



4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methyl-morpholin-4-ium formate

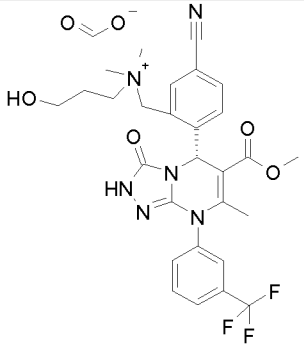
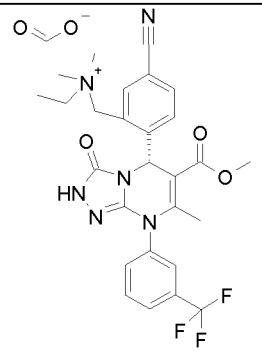
Intermediate 14 (110 mg, 0.2 mmol) was heated in *N*-methylmorpholine (6 mL) under argon for 11 h at 50°C. The resultant material was partitioned between EtOAc and water, and the aqueous layer was separated and subjected to purification by HPLC (System 1). The crude product fractions were concentrated to remove MeCN and treated

with concentrated aqueous ammonia (10% by volume) for 15 min at room temperature. The solution was further purified by chromatography using a C_{18} Isolute cartridge and eluting from 0-30% MeCN (+0.1% HCO_2H) to give, following freeze drying, the title product as a white solid (34 mg).

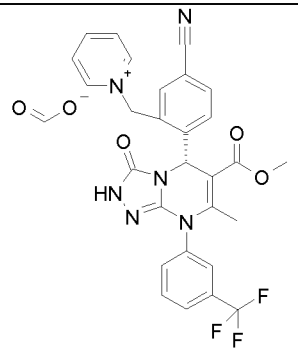
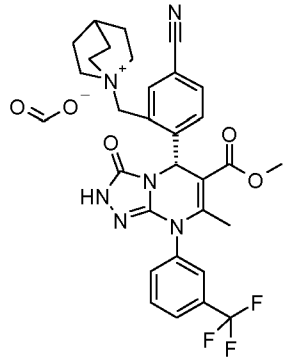
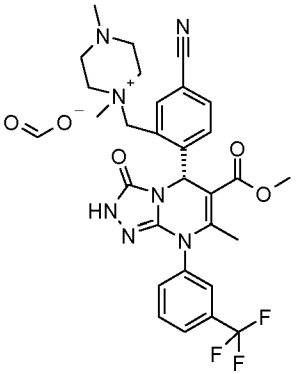
LC-MS (Method 3): Rt = 3.37 min, m/z = 569.2 [M]+

1H NMR (400 MHz, DMSO-D_6) δ 8.43 (1.H, s), 8.10 (2H, m), 8.03 (1H, dd, J = 8.0, 1.5 Hz), 7.95-7.79 (4H, m), 6.54 (1H, s), 5.22 (1H, d, J = 13.8 Hz), 5.10 (1H, d, J = 13.8 Hz), 4.09-3.53 (8H, m), 3.54 (3H, s), 3.28 (3H, s) and 2.07 (3H, s).

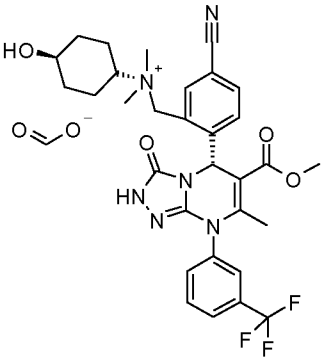
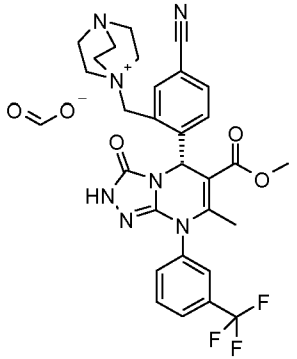
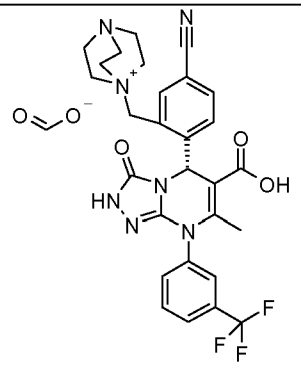
The following examples were prepared from Intermediate 14 using an analogous method to Example 24:

Ex	Structure	Name	LC-MS (Method 3)	NMR
25		{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(3-hydroxy-propyl)-dimethyl-ammonium formate	Rt = 3.27 min, m/z = 571.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.5 (1H, bs), 8.45 (1H, s), 8.13 (1H, d, J = 1.5 Hz), 8.1 (1H, bs), 8.02 (1H, dd, J = 8, 1.5 Hz). 7.95-7.79 (4H, m), 6.48 (1H, s), 5.11 (1H, d, J = 14.0 Hz), 4.96 (1H, d, J = 14.0 Hz), 3.64, (2H, m), 3.56 (2H, m), 3.53 (3H, s), 3.21 (3H, s), 3.16 (3H, s), 2.07 (3H, s) and 2.02 (2H, m)
26		{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-ethyl-dimethyl-ammonium formate	Rt = 3.39 min, m/z = 541.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.41 (1H, bs), 8.41 (1 H, s), 8.12-8.08 (m, 2H), 8.02 (1H, dd, J = 8.0, 1.5 Hz). 7.95-7.79 (4H, m), 6.47 (1H, s), 5.10 (1H, d, J = 14.0 Hz), 4.94 (1H, d, J = 14.1 Hz), 3.65-3.56 (2H, m), 3.5 (3H, s), 3.18 (3H, s), 3.14 (3H, s), 2.07 (3H, s) and 1.39 (3H, t, J = 7.2 Hz)

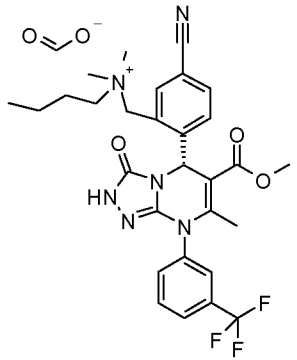
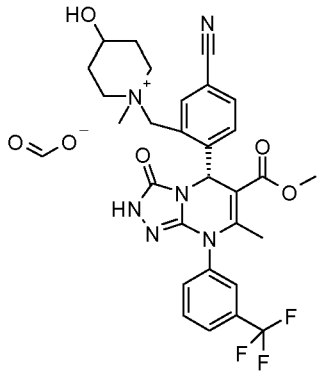
(continued)

27		1-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-pyridinium formate	Rt = 3.40 min, m/z = 547.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 9.36 (2H, d, J = 5.9 Hz), 8.69 (1H, t, J = 7.6 Hz), 8.39 (1.9 H, s), 8.24 (2H, m), 8.16 (1H, bs), 7.96-7.90 (3H, m), 7.86-7.81 (3H, m), 7.77 (1H, m), 6.56 (1H, d, J = 15.1 Hz), 6.14 (1H, d, J = 15.1 Hz), 6.42 (1H, s), 3.55 (3H, s) and 2.18 (3H, s)
28		1-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-1-azonia-bicyclo[2.2.2]octane formate	Rt = 3.48 min, m/z = 579.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.49 (1H, bs), 8.37 (1H, s), 8.10 (1H, bs), 8.08 (1H, d, J = 1.6 Hz), 8.01 (1H, dd, J = 8.3, 1.6 Hz). 7.95-7.79 (4H, m), 6.43 (1H, s), (1H, d, J = 14.4 Hz), 4.86 (1H, d, J = 14.4 Hz), 3.78-3.68 (3H, m), 3.65-3.55 (3H, m), 3.53 (3H, s), 2.11-2.06 (1H, m), 2.07 (3H, s) and 1.95-1.85 (6H, m)
29		1-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-1,4-dimethyl-piperazin-1-ium formate	Rt = 2.99 min, m/z = 582.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.48 (1H, bs), 8.42 (1H, s), 8.12-8.08 (m, 2H), 8.02 (1H, dd, J = 8.1, 1.6 Hz). 7.95-7.79 (4H, m), 6.51 (1H, s), 5.18 (1H, d, J = 14.1 Hz), 5.05 (1H, d, J = 14.1 Hz), 3.84-3.74 (2H, m), 3.63-3.53 (2H, m), 3.54 (3H, s), 3.15 (3H, s), 2.88-2.79 (2H, m), 2.72-2.61 (2H, m), 2.31 (3H, s) and 2.07 (3H, s))

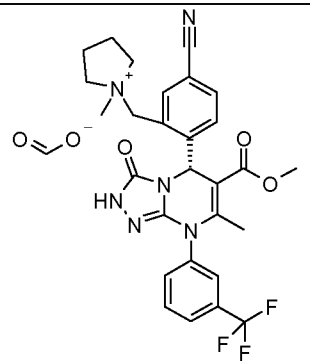
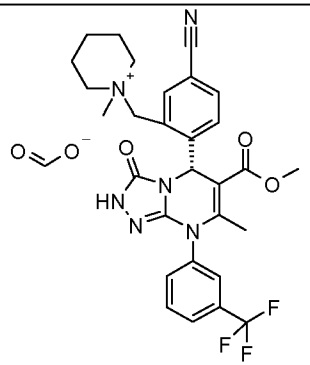
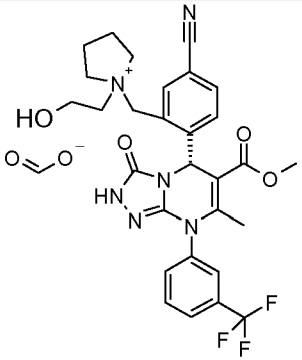
(continued)

30		{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]-pyrimidin-5-yl]-benzyl}-(4-hydroxy-cyclohexyl)-dimethyl-ammonium formate	Rt = 3.33 min, m/z = 611.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.4 (1H, bs), 8.45 (1H, s), 8.12-8.07 (m, 2H), 8.02 (1H, dd, J = 8.1, 1.6 Hz). 7.95-7.79 (4H, m), 6.35 (1H, s), 5.17 (1H, d, J = 13.8 Hz), 4.86 (1H, d, J = 13.8 Hz), 3.77-3.68 (1H, m), 3.53 (3H, s), 3.54-3.45 (1H, m), 3.17 (3H, s), 3.04 (3H, s), 2.36-2.27 (2H, m), 2.10-2.00 (2H, m), 2.09 (3H, s), 1.84-1.68 (2H, m) and 1.38-1.23 (2H, m)
31		1-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-aza-1-azonia-bicyclo[2.2.2]octane formate	Rt = 3.23 min, m/z = 580.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.48 (1H, bs), 8.44 (1H, s), 8.10 (1H, bs), 8.08 (1H, d, J = 1.7 Hz), 8.02 (1H, dd, J = 8.2, 1.7 Hz). 7.95-7.79 (4H, m), 6.45 (1H, s), 5.10 (1H, d, J = 14.4 Hz), 4.95 (1H, d, J = 14.4 Hz), 3.67-3.58 (3H, m), 3.55-3.46 (3H, m), 3.53 (3H, s), 3.10-3.02 (6H, m) and 2.08 (3H, s)
32**		1-{2-[(R)-6-carboxy-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-5-cyano-benzyl}-4-aza-1-azonia-bicyclo[2.2.2]octane formate	Rt = 3.00 min, m/z = 566.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.04 (1H, bs), 8.27 (1 H, s), 8.02 (1H, d, J = 1.7 Hz), 7.92 (1H, bs), 7.95 (1H, dd, J = 8.3, 1.7 Hz). 7.95-7.72 (3H, m), 7.62 (1H, d, J = 8.3 Hz), 6.37 (1H, s), 5.44 (1H, d, J = 14.3 Hz) , 4.87 (1H, d, J = 14.3 Hz), 3.67-3.47 (6H, m), 3.08-2.99 (6H, m) and 2.04 (3H, s)

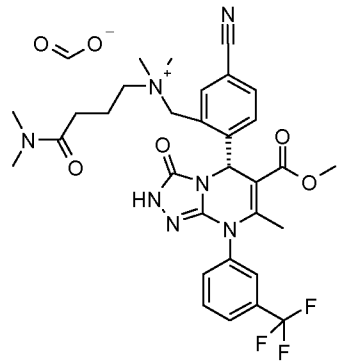
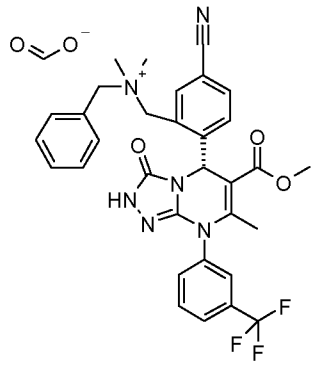
(continued)

33		Butyl-{5-cyano-2-[(R)-6-methoxy carbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-ammonium formate	Rt = 3.64 min, m/z = 569.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.51 (1H, bs), 8.42 (1H, s), 8.12-8.09 (m, 2H), 8.02 (1H, dd, J = 8.2, 1.7 Hz). 7.95-7.79 (4H, m), 6.46 (1H, s), 5.11 (1H, d, J = 14.2 Hz), 4.95 (1H, d, J = 14.2 Hz), 3.61-3.47 (2H, m, partially obscured by water peak), 3.53 (3H, s), 3.20 (3H, s), 3.15 (3H, s), 2.07 (3H, s) 1.87-1.77 (2H, m), 1.44-1.34 (2H, m) and 0.98 (3H, t, J = 7.3 Hz)
34		1-{5-Cyano-2-[(R)-6-methoxycarbonyl -7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-hydroxy-1-methyl-piperidinium formate	Rt = 3.39 min, m/z = 583.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.40 (1H, bs), 8.42 (1H, s), 8.15-8.06 (m, 2H), 8.02 (1H, bd, J = 8.2). 7.95-7.79 (4H, m), 6.48, 6.50 (1H, 2s), 5.2-4.97 (2H, m), 3.92-3.2 (5H, m, partially obscured by water peak), 3.53 (3H, s), 3.16, 3.13 (3H, 2s), 2.18-1.98 (2H, m), 2.07 (3H, s), 1.91-1.75 (2H, m)

(continued)

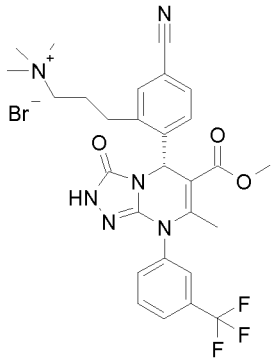
35		1-{5-Cyano-2-[(R)-6-methoxycarbonyl -7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-1-methyl-pyrrolidinium formate	Rt = 3.53 min, m/z = 553.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.3 (1H, bs), 8.43 (1H, s), 8.14-8.09 (m, 2H), 8.00 (1H, dd, J = 8.2, 1.6 Hz). 7.95-7.79 (4H, m), 6.48 (1H, s), 5.18 (1H, d, J = 14.2 Hz), 5.09 (1H, d, J = 14.2 Hz), 3.88-3.71 (4H, m), 3.53 (3H, s), 3.05 (3H, s), 2.22-2.1 (4H, m) and 2.09 (3H, s)
36		1-{5-Cyano-2-[(R)-6-methoxycarbonyl -7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-1-methyl-piperidinium formate	Rt = 3.57 min, m/z = 567.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 8.41 (1H, s), 8.13-8.06 (m, 2H), 8.02 (1H, dd, J = 8.2, 1.5 Hz). 7.95-7.79 (4H, m), 6.49 (1H, s), 5.13 (1H, d, J = 14.2 Hz), 5.00 (1H, d, J = 14.2 Hz), 3.73-3.48 (4H, m), 3.54 (3H, s), 3.15 (3H, s), 2.07 (3H, s) 2.01-1.78 (4H, m) 1.74-1.65 (1H, m) and 1.55-1.41 (1H, m)
37		1-{5-Cyano-2-[(R)-6-methoxycarbonyl -7-methyl-3-oxo-8-(3-trifluoromethy l-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-1-(2-hydroxy-ethyl)-pyrrolidinium formate	Rt = 3.50 min, m/z = 583.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 8.42 (1H, s), 8.16 (1H, d, J=1.5Hz), 8.11 (1H, bs), 7.98 (1H, dd, J = 1.5, 8.2 Hz), 7.95-7.79 (4H, m), 6.41 (1H, s), 5.30 (1H, d, J = 14.8 Hz), 5.19 (1H, d, J = 14.8 Hz), 4.03-3.92 (2H, m), 3.90-3.82 (4H, m), 3.75-3.48 (2H, m), 3.54 (3H, s), 2.15-2.04 (4H, m) and 2.08 (3H, s)

(continued)

38		{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(3-dimethylcarbamoyl-propyl)-dimethyl-ammonium formate	Rt = 3.50 min, m/z = 626.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 8.43 (1H, s), 8.16 (1H, d, J=1.6Hz), 8.10 (1H, bs), 8.01 (1H, dd, J = 1.6, 8.2 Hz), 7.95-7.79 (4H, m), 6.48 (1H, s), 5.10 (1H, d, J = 14.1 Hz), 4.98 (1H, d, J = 14.1 Hz), 3.57-3.51 (2H, m), 3.54 (3H, s), 3.22 (3H, s), 3.18 (3H, s) 2.97 (3H, s), 2.85 (3H, s) 2.46 (2H, t, J = 6.7 Hz), 2.14-2.02 (2H, m), 2.07 (3H, s)
39		Benzyl-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-ammonium formate	Rt = 3.80 min, m/z = 603.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.48 (1H, bs), 8.40 (1.7H, s), 8.17 (1H, d, J=1.6Hz), 8.10 (1H, bs), 8.03 (1H, dd, J = 1.6, 8.3 Hz), 7.95-7.79 (4H, m), 7.66-7.51 (5H, m), 6.49 (1H, s), 5.26 (1H, d, J = 14.1 Hz), 5.03 (1H, d, J = 14.1 Hz), 4.87 (1H, d, J = 12.4 Hz), 4.74 (1H, d, J = 12.4 Hz), 3.50 (3H, s) 3.13 (3H, s), 3.11 (3H, s) and 2.08 (3H, s)

** Example 32 was formed as a by-product during the preparation of Example 31 and was isolated during HPLC purification.

Example 40



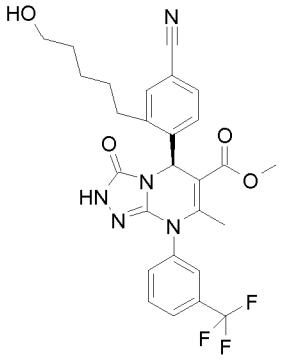
(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-trimethyl-ammonium bromide

To a solution of Example 12 (2.0 g, 3.70 mmol) in MeCN (10 mL) at 5°C was added a 26% solution of methyl bromide in acetonitrile (10 mL) drop-wise. The mixture was allowed to warm to room temperature and stirred for 2 h. The solvent was evaporated *in vacuo*. The resulting residue was taken up in 30% MeCN in water (30 mL) and freeze dried to yield a white solid (2.05 g).

LC-MS (Method 3): Rt = 3.48 min, m/z = 555.2 $[M]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.26 (1H, s), 8.14 (1H, s), 7.96-7.92 (2H, m), 7.87-7.82 (2H, m), 7.73 (1H, dd, J = 1.5, 8.1 Hz), 7.68 (1H, bd, J = 8.1Hz), 6.19 (1H, s), 3.54 (3H, s), 3.51 (2H, t, J = 8.4 Hz), 3.30 (1H, m) 3.15 (9H, s), 2.99 (1H, m) 2.42 (1H, m), 2.22 (1H, m) and 2.17 (3H, s).

Example 41



(S)-5-[4-Cyano-2-(5-hydroxypentyl)-phenyl]-7-methyl-3-oxo-8-(3-

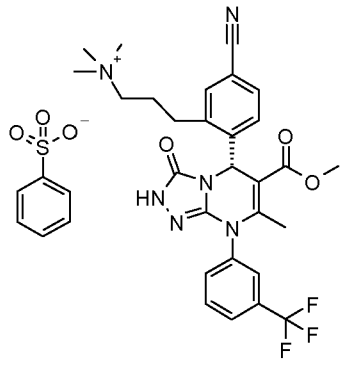
trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

To pent-4-en-1-ol (51 mg) under argon at 0°C was added a solution of 9-BBN (0.5 M in THF, 2.24 ml). The solution was then stirred at rt for 2h. Cesium carbonate (241 mg, 0.74 mmol), Intermediate 4a (200 mg, 0.37 mmol), $PdCl_2$(dppf).DCM (30 mg, 0.037 mmol) and water (0.2 mL) were then added. The mixture was heated at reflux for 6 h then DMF (1 mL) was added and the THF distilled off under a stream of argon. The reaction was heated at 115°C under argon for a further 1.5 h. The mixture was cooled and diluted with EtOAc and water and the organic extract was dried (Na_2SO_4) and concentrated *in vacuo*. The resultant residue was purified by chromatography, eluting with 0-10% methanol in DCM, and then by HPLC (System 1) eluting from 20-80% MeCN in water (+ 0.1% HCO_2H) to give the title compound as a colourless gum, (25 mg).

C-MS (Method 1): Rt = 3.24 min, m/z = 542.1 $[M+H]^+$

1H NMR (400 MHz, $CDCl_3$) δ 9.69 (1H, s), 7.80 (1H, d, J = 7.8 Hz), 7.72 (1H, t, J = 7.8 Hz), 7.63 (1H, s), 7.58 (1H, d, J = 7.8 Hz), 7.5 (1H, bs), 7.48 (1H, bd, J = 7.4 Hz), 7.33 (1H, d, J = 7.4 Hz), 6.29 (1H, s), 3.59 (3H, s), 3.55 (2H, t, J = 6.16 Hz), 3.33-3.24 (1H, m), 2.95-2.85 (1H, m), 2.24 (3H, s), 1.90-1.68 (2H, m), 1.68-1.47 (4H, m).

Example 42



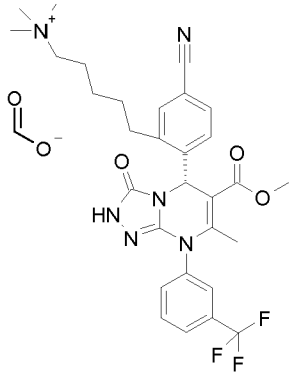
(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-trimethyl-ammonium benzenesulfonate

Amberlite IRA 458 'chloride' resin (40 g, wet) was converted to the besylate equivalent by passing a solution of benzene sulphonic acid (400 mL, 10% aqueous solution) through the resin in a glass column at a slow rate of 5-10 mL/minute. Following this, the resin was washed with water until the filtrate had a pH of ~ 5/6. The resin was stored "damp" prior to use. A solution of Example 40 (1 g, 1.57 mmol) in a round-bottom flask (250 mL) was treated with 30% MeCN/water (60 mL) and then mixed with the besylate resin (40 g, wet). The resulting mixture was gently agitated by slowly rotating the flask on a Buchi evaporator for 50 min. at atmospheric pressure. The contents were placed in a resin tube, then filtered and washed with 30% MeCN/water and the filtrate was freeze dried to give the title compound as a white electrostatic solid (1.01 g).

LC-MS (Method 3):Rt = 3.47 min, m/z = 555.4 $[M]^+$

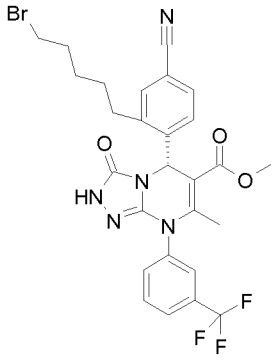
^{1}H NMR (400 MHz, DMSO) δ 11.24 (1H, s), 8.12 (1H, s), 7.96-7.89 (2H, m), 7.86-7.80 (2H, m), 7.74-7.63 (2H, m), 7.63-7.55 (2H, m, besylate), 7.35-7.27 (3H, m, besylate), 6.17 (1H, s), 3.52 (3H, s), 3.51-3.43 (2H, m), 3.32-3.21 (1H, m) 3.13 (9H, s), 3.03-2.91 (1H, m) 2.40 (1H, m), 2.20 (1H, m), 2.15 (3H, s).

Example 43



(5-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-pentyl)-trimethyl-ammonium formate

Intermediate 15



(R)-5-[2-(5-Bromo-pentyl)-4-cyano-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

The title compound was prepared from Intermediate 4b (240 mg, 0.45 mmol) using analogous methods to those used for Example 41 and Intermediate 13 and gave the desired compound as a yellow gum (90 mg).

LC-MS (Method 3): Rt = 4.12 min, m/z = 604 $[M(^{79}Br)+H]^+$

(5-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-pentyl)-trimethyl-ammonium formate (Example 43)

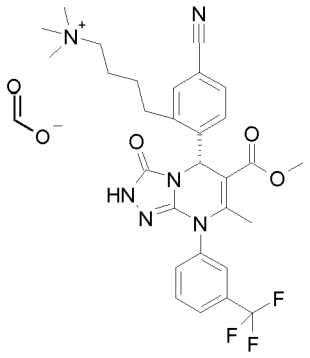
The title compound was prepared from Intermediate 15 (89 mg, 0.15 mmol) using an analogous method to that used for Example 7 and gave the desired compound as a yellow gum (10 mg) following chromatographic purification (HPLC system 1).

LC-MS (Method 3):Rt = 3.66 min, m/z = 583.3 $[M]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.28 (1H, bs), 8.42 (1.6H, s, formate), 8.09 (1H, s), 7.95-7.86 (2H, m), 7.84-7.77 (1H, m), 7.69-7.58 (3H, m), 6.18 (1H, s), 3.51 (3H, s), 3.37-3.28 (2H, m) 3.26-3.14 (1H, m), 3.06 (9H, s), 3.07-2.95 (1H, m), 2.14 (3H, s), 1.93-1.70 (4H,

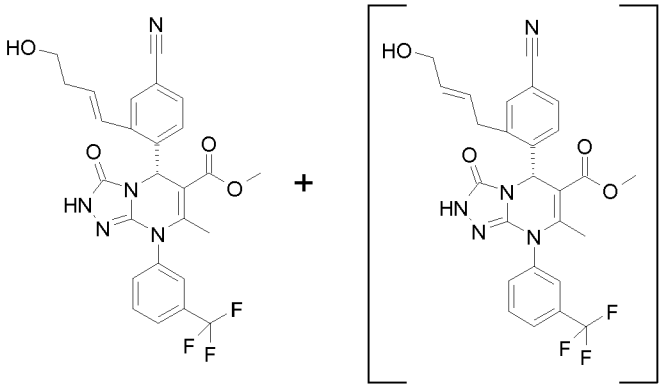
m), 1.51-1.39 (2H, m).

Example 44



(4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-butyl)-trimethyl-ammonium formate

Intermediate 16



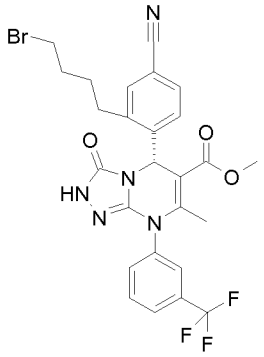
(R)-5-[2-(5-Bromo-pentyl)-4-cyano-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

To a mixture of Intermediate 4b (1.0 g, 1.87 mmol), but-3-en-1-ol (270 mg, 3.74 mmol), tri-tertiary-butyl phosphonium tetrafluoroborate (100 mg, 0.34 mmol), $Pd_2(dba)_3$ (90 mg, 0.10 mmol) and dicyclohexyl-methyl-amine (1.80 mL, 8.42 mmol) was added DMF (10 mL) and the resulting solution degassed under Argon. The mixture was then heated at 95°C for 18 h. The mixture was cooled, diluted with EtOAc and aqueous 10% citric acid and the organic extract was washed with brine, then dried (Na_2SO_4) and concentrated *in vacuo*. The resultant residue was purified by chromatography, eluting

with 0-5% MeOH in DCM to give the title compound as a yellow solid (816 mg), which was contaminated with over 50% of an isomeric by-product (shown above). This material was used without further purification.

LC-MS (Method 4):Rt = 3.35 min, m/z = 526.2 $[M+H]^+$

Intermediate 17



(R)-5-[2-(4-Bromo-butyl)-4-cyano-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

The title compound was prepared from Intermediate 16 (270 mg, 0.51 mmol) using analogous methods to those used for Example 5 and Intermediate 13 and gave the desired compound as a white solid (260 mg).

LC-MS (Method 4):Rt = 3.99 min, m/z = 589.9$[M(^{79}Br)+H]^+$

(4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-butyl)-trimethyl-ammonium formate (Example 44)

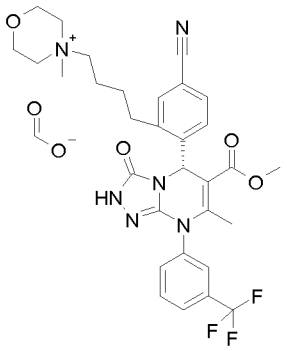
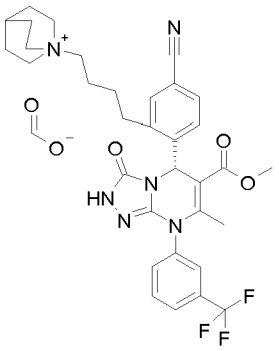
The title compound was prepared from Intermediate 17 (80 mg, 0.13 mmol) using an analogous method to that used for Example 7 and gave the desired compound as an electrostatic solid (44 mg) following chromatographic purification (HPLC system 1).

LC-MS (Method 3):) Rt = 3.52 min, m/z = 569.3 $[M]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.40 (1H, bs), 8.49 (1H, s, formate), 8.11 (1H, s), 7.95-7.87 (2H, m), 7.85-7.79 (1H, m), 7.74-7.70 (1H, m), 7.70-7.61 (2H, m), 6.18 (1H, s), 3.52 (3H, s), 3.43-3.35 (2H, m) 3.28-3.18 (1H, m), 3.09 (9H, s), 3.18-3.05 (1H, m, obscured),

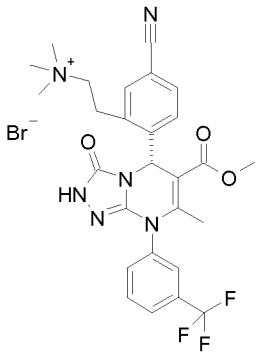
2.14 (3H, s), 1.95-1.80 (3H, m), 1.80-1.67 (1H, m).

The following examples were prepared from Intermediate 17 and the appropriately substituted tertiary amines using an analogous method to Example 44:

Ex	Structure	Name	LC-MS (Method 3)	NMR
45		1-(4-{5-Cyano-2-[(R)-6-methoxy-carbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-butyl)-1-azonia-bicyclo[2.2.2] octane formate	Rt = 3.53 min, m/z = 611.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.41 (1H, bs), 8.45 (1.4H, s, formate), 8.11 (1H, s), 7.95-7.86 (2H, m), 7.85-7.79 (1H, m), 7.73-7.70 (1H, m), 7.72-7.61 (2H, m), 6.19 (1H, s), 4.00-3.89 (4H, m), 3.59-3.50 (2H, m), 3.51 (3H, s), 3.48-3.39 (4H, m), 3.30-3.19 (1H, m), 3.16 (3H, s), 3.13-3.00 (1H, m), 2.15 (3H, s), 1.97-1.72 (4H, m).
46		1-(4-{5-Cyano-2-[(R)-6-methoxy-carbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-butyl)-1-azonia-bicyclo[2.2.2] octane formate	Rt = 3.68 min, m/z = 621.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.39 (1H, bs), 8.41 (1.8H, s, formate), 8.11 (1H, bs), 7.96-7.87 (2H, m), 7.85-7.79 (1H, m), 7.72-7.70 (1H, m), 7.70-7.60 (2H, m), 6.17 (1H, s), 3.51 (3H, s), 3.44-3.56 (6H, m), 3.28-3.15 (3H, m), 3.11-3.00 (1H, m), 2.14 (3H, s), 2.08 (1H, m), 1.93-1.67 (10H, m).

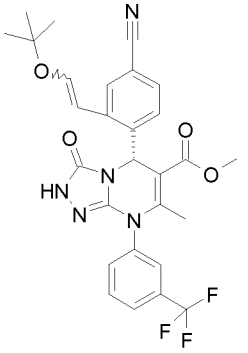
5

Example 47



(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-trimethyl-ammonium bromide

Intermediate 18



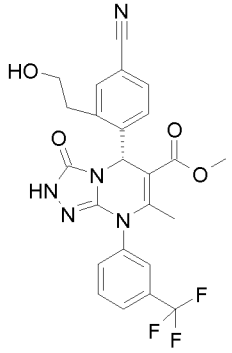
(R)-5-[2-(2-tert-Butoxy-vinyl)-4-cyano-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

An autoclave was charged with a mixture of Intermediate 4b (10 g, 18.72 mmol), 2-methyl-2-vinyloxy-propane (6.55 g, 65.50 mmol), tri-tertiary-butyl phosphonium tetrafluoroborate (540 mg, 1.86 mmol), Herrmann-Beller catalyst (trans-di(μ-acetotao)*bis*(0-di-o-tolyl-phosphino)benzyl)dipalladium (II)) (880 mg, 0.94 mmol), 1,2,2,6,6-pentamethylpiperidine (11.5 g, 74.20 mmol). Tetra-ethylene glycol (140 mL) was added and the resulting solution degassed under Argon. The mixture was then heated at 150°C for 1 h. The mixture was cooled, diluted with EtOAc and aqueous 10% citric acid and the organic extract was washed with water and brine, then dried (Na_2SO_4) and

concentrated *in vacuo*. The resultant residue was purified by chromatography, eluting with 25-75% EtOAc in cyclohexane to give the title compound as a [3:1] mixture of E/Z isomers and as a yellow foam (7.95 g).

LC-MS (Method 5):Rt = 3.87 min, m/z = 554.2 $[M+H]^+$

Intermediate 19



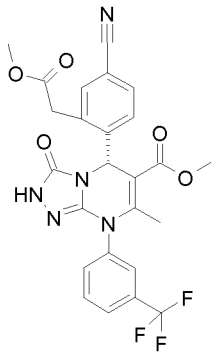
(R)-5-[4-Cyano-2-(2-hydroxy-ethyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

A solution of Intermediate 18 (7.87 g, 14.20 mmol) in DCM (130 mL) was cooled to -10°C using a salt/ice bath and treated drop-wise with TFA (6.35 mL, 85.47 mmol). After stirring the solution at -10°C for 2 h the resulting solution was poured into ice-cold aqueous Na_2CO_3 solution. The organic phase was separated and the aqueous phase was further extracted with DCM (70 mL) and the combined DCM extract returned to the salt/ice bath at -5°C. Sodium borohydride (1.57 g, 41.42 mmol) was added portion-wise and after stirring for 15 minutes, MeOH (32 mL) was added to the resulting mixture. The reaction was stirred at -5°C for 1.5 h, water was added and the resulting mixture allowed to stir vigorously for 15 minutes prior to separation of the organic phase. The aqueous phase was further extracted with DCM and the combined organic extract was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The resultant residue was purified by chromatography, eluting with EtOAc and gave the title compound as a cream solid (3.7 g).

LC-MS (Method 5):Rt = 3.17 min, m/z = 500.1 $[M+H]^+$

Alternative synthesis of Intermediate 19:

Intermediate 20



(R)-5-(4-Cyano-2-methoxycarbonylmethyl-phenyl)-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

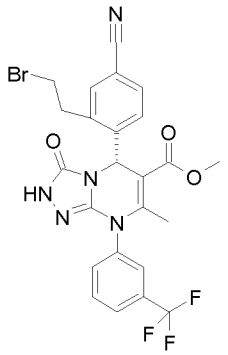
A microwave vial was charged with Intermediate 4b (2.5 g, 4.67 mmol), palladium(0)*bis*(dibenzylideneacetone) (132 mg, 0.23 mmol), zinc fluoride (242 mg, 2.34 mmol) and dry DMF (12 mL), then degassed under an argon atmosphere. A solution of tri(*tert*-butyl)phosphine (1 M in toluene; 475 µL, 0.19 mmol) and 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (3.05 mL, 14 mmol) were added to the reaction, followed by further degassing. The mixture was heated under microwave irradiation at 135°C for 4 h. Further 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (0.7 mL, 3.2 mmol) was added and the mixture heated under microwave irradiation for a further 1 h at 135°C. The resultant mixture was partitioned between EtOAc and water, and the aqueous layer was extracted with EtOAc. The combined organic extract was washed with brine, dried ($MgSO_4$) and then concentrated *in vacuo*. The resultant residue was dissolved in MeOH, treated with TFA (5 drops)and allowed to stir for 18 h at RT (this process removes the TBDMS group from the initially generated silylated product). The reaction mixture was concentrated *in vacuo* and then purified by chromatography, eluting with 0-100% EtOAc in cyclohexane, to afford the title compound as a white solid (1.82 g).

LC-MS (Method 4):Rt = 3.45 min, m/z = 528.3 $[M+H]^+$

(R)-5-[4-Cyano-2-(2-hydroxy-ethyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester (Intermediate 19)

A solution of Intermediate 20 (458 mg, 0.87 mmol) in anhydrous THF (5 mL) under argon was cooled to 0°C in an ice-bath. A solution of lithium borohydride (1 M in THF; 1.04 mL, 1.04 mmol) was added drop-wise. The resulting solution was stirred at 0°C for 3 h, then at RT for 18 h. The reaction was quenched with water and diluted with EtOAc. The aqueous layer was further extracted with EtOAc. The combined organic extract was washed with brine, dried ($MgSO_4$), and purified by chromatography, eluting with 0-5% MeOH in DCM, to afford the title compound as a white solid (115 mg).

Intermediate 21



(R)-5-[2-(2-Bromo-ethyl)-4-cyano-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

The title compound was prepared from Intermediate 19 (0.30 g, 0.60 mmol) using an analogous method to that used for Intermediate 13 and gave the desired compound as a white solid (0.24 g).

LC-MS (Method 4):Rt = 3.83 min, m/z = 562.1 $[M(^{79}Br)+H]^+$

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-trimethyl-ammonium bromide (Example 47)

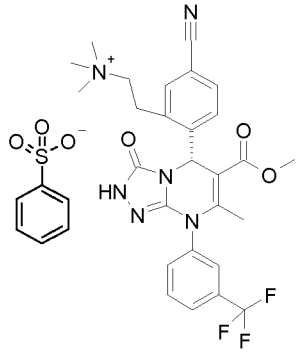
A cooled solution (ice bath) of Intermediate 21 (400 mg, 0.71 mmol) in MeCN (10

mL) was treated drop-wise with a solution of trimethylamine in EtOH (50wt%) and the resulting solution allowed to stir at RT for 18 h. The mixture was concentrated *in vacuo* then triturated with Et_2O and following sonication, a solid was collected and dried *in vacuo* at 35°C for 2 h. The solid product was partitioned between water (10 mL) and EtOAc (10 mL) and the aqueous layer separated and freeze dried to give the title compound as a white electrostatic solid.

LC-MS (Method 3) Rt = 3.46 min, m/z = 541.2 $[M]^+$

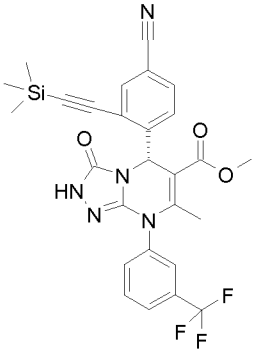
^{1}H NMR (400 MHz, DMSO) δ 11.30 (1H, bs), 8.13 (1H, bs), 7.97-7.87 (2H, m), 7.86-7.79 (2H, m), 7.78-7.67 (2H, m), 6.27 (1H, s), 4.03-3.93 (1H, m), 3.79-3.62 (2H, m) 3.53 (3H, s), 3.43-3.34 (1H, m, obscured), 3.21 (9H, s), 2.17 (3H, s).

Example 48



(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-trimethyl-ammonium bromide

Intermediate 22



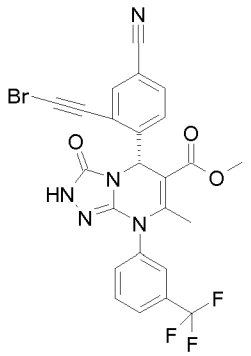
(R)-5-(4-Cyano-2-trimethylsilanylethynyl-phenyl)-7-methyl-3-oxo-8-(3-

trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

A microwave vial was charged with a mixture of Intermediate 4b (3.5 g, 6.57 mmol), ethynyl-trimethyl-silane (3.70 mL, 26.28 mmol), *bis*(triphenylphosphine) palladium(II) dichloride (461 mg, 0.66 mmol), copper(II)iodide (136 mg, 0.72 mmol) and DIPEA (3.40 mL, 19.71 mmol). Dioxane (16 mL) was added and the resulting solution degassed under Argon. The mixture was then heated at 130°C for 1.25 h. The reaction was cooled, diluted with water and the mixture was extracted with EtOAc (x 3) and the combined organic extract was washed with brine, then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by chromatography, eluting with 0-60% EtOAc in cyclohexane to give the title compound as a cream coloured foam (5.65 g).

LC-MS (Method 2):Rt = 4.18 min, m/z = 552.3 $[M+H]^+$

Intermediate 23



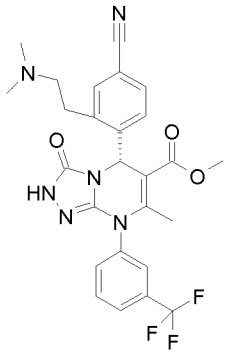
(R)-5-(2-Bromoethynyl-4-cyano-phenyl)-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

A cooled (ice bath) stirred solution of Intermediate 22 (2.14 g, 3.88 mmol) in acetone (40 mL) was treated with silver nitrate (66 mg, 0.39 mmol) followed by NBS (829 mg, 4.66 mmol). The cooling bath was removed after 1 h and after a further 1 h the mixture was diluted EtOAc and poured into water. The aqueous layer was separated and further extracted with EtOAc (x 3) and the combined organic extract was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was

purified by chromatography, eluting with 0-100% EtOAc in cyclohexane to give the title compound as a pale yellow foam (1 g).

LC-MS (Method 5):Rt = 3.63 min, m/z = 558.1 $[M(^{79}Br)+H]^+$

Intermediate 24

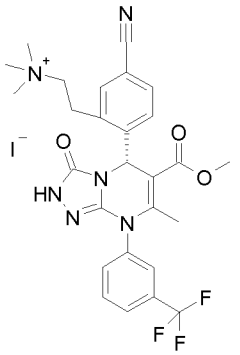


(R)-5-[4-Cyano-2-(2-dimethylamino-ethyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

A solution of Intermediate 23 (210 mg, 0.38 mmol) in MeCN (0.40 mL) was treated with a solution of dimethylamine (2 M in THF; 1.90 mL, 3.80 mmol) and the resulting mixture stirred for 18 h. The reaction mixture was cooled to 0°C and MeOH (3 mL) was added, followed by sodium borohydride (71 mg, 1.88 mmol). After stirring for 1 h the resultant mixture was poured into EtOAc and then washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant residue was purified by chromatography, eluting with 2-8% (2M NH_3 in MeOH) in DCM to give the title compound as clear oil.

LC-MS (Method 4):Rt = 3.52 min, m/z = 527.2 $[M+H]^+$

Intermediate 25



(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-trimethyl-ammonium iodide

To a solution of Intermediate 24 (0.59 g, 1.12 mmol) in MeCN (10 mL) was added methyl iodide (0.25 mL, 4.0 mmol). The resultant mixture was warmed to 50°C and stirred for 1.5 h. The solvent was evaporated *in vacuo* to yield the title compound as a pale orange solid (0.68 g).

LC-MS (Method 1):Rt = 2.39 min, m/z = 541.3 $[M]^+$

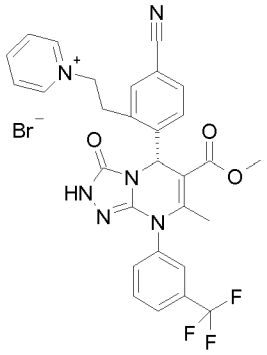
(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-trimethyl-ammonium benzenesulfonate (Example 48)

The title compound was prepared from Intermediate 25 (0.68 g, 1.02 mmol) using an analogous method to that used for Example 42 and gave the desired compound as a pale yellow electrostatic solid (0.72 g).

LC-MS (Method 3): Rt = 3.45 min, m/z = 541.2 $[M]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.30 (1H, bs), 8.13 (1H, bs), 7.97-7.87 (2H, m), 7.86-7.79 (2H, m), 7.78-7.67 (2H, m), 7.62-6.56 (2H, m. besylate), 7.35-7.28 (3H, m, besylate), 6.27 (1H, s), 4.03-3.93 (1H, m), 3.79-3.62 (2H, m), 3.53 (3H, s), 3.46-3.34 (1H, m, obscured), 3.21 (9H, s), 2.17 (3H, s).

Example 49



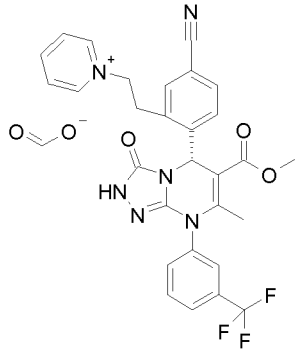
1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-pyridinium bromide

A mixture of Intermediate 21 (0.40 g, 0.71 mmol) and pyridine was warmed to 50°C for 3 h then concentrated *in vacuo*. The crude product was partitioned between water and EtOAc and the aqueous layer separated and freeze dried to give the title compound as a white electrostatic solid (0.39 g).

LC-MS (Method 3): Rt = 3.48 min, m/z = 561.2 $[M]^+$

^{1}H NMR (400 MHz, DMSO)δ 11.38 (1H, bs), 9.10 (2H, d, J = 5.6 Hz), 8.67 (1H, t, J = 7.7 Hz), 8.23 (2H, t, J = 7.2 Hz), 8.15 (1H, bs), 7.97-7.87 (2H, m), 7.86-7.80 (1H, m), 7.79-7.70 (2H, m), 7.61 (1H, m), 6.43 (1H, s), 5.26-5.07 (2H, m), 3.97-3.84 (1H, m), 3.65-3.52 (1H, m), 3.49 (3H, s), 2.16 (3H, s).

Example 50



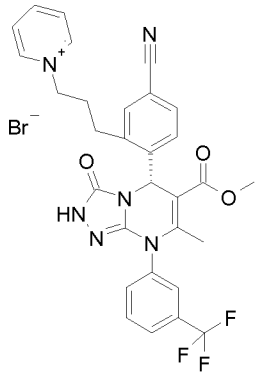
1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-pyridininium formate

A solution of Intermediate 21 (100 mg, 0.18 mmol) in a mixture of MeCN (2.5 mL) and pyridine (0.15 mL, 1.78 mmol) was warmed to 70°C for 18 h in a sealed vial. The resultant solution was concentrated *in vacuo* and the crude product was purified directly by DMAP to give the title compound as a white electrostatic solid (54 mg).

LC-MS (Method 3):Rt = 3.52 min, m/z = 561.2 $[M]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.67 (1H, bs), 9.11 (2H, d, J = 5.7 Hz), 8.67 (1H, t, J = 7.8 Hz), 8.46 (1.4H, bs, formate), 8.23 (2H, t, J = 7.2 Hz), 8.15 (1H, bs), 7.97-7.87 (2H, m), 7.86-7.80 (1H, m), 7.79-7.69 (2H, m), 7.61 (1H, m), 6.43 (1H, s), 5.27-5.09 (2H, m), 3.97-3.85 (1H, m), 3.65-3.52 (1H, m), 3.49 (3H, s), 2.16 (3H, s).

Example 51



1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-pyridinium bromide

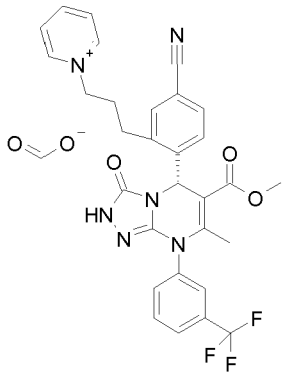
The title compound was prepared from Intermediate 13 (0.68 g, 1.02 mmol) and pyridine using an analogous method to that used for Example 19 and gave the desired compound as a pale yellow electrostatic solid (0.72 g).

LC-MS (Method 3):Rt = 3.53 min, m/z = 575.22 $[M]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.18 (1H, bs), 9.18 (2H, d, J = 6.6 Hz), 8.64 (1H, t, J = 7.8 Hz), 8.21 (2H, t, J = 7.2 Hz), 8.12 (1H, bs), 7.96-7.86 (2H, m), 7.86-7.80 (1H, m),

7.76-7.72 (1H, m), 7.72-7.60 (2H, m), 6.12 (1H, s), 4.79 (2H, t, J = 7.5 Hz), 3.50 (3H, s), 3.35-3.24 (1H, m, obscured), 3.12-2.99 (1H, m), 2.65-2.53 (1H, m), 2.51-2.40 (1H, m, obscured), 2.14 (3H, s).

Example 52



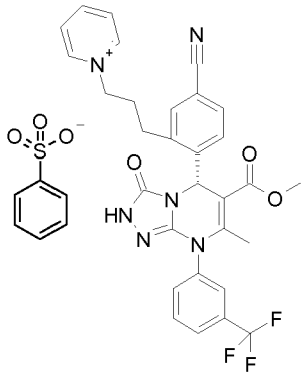
1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-pyridinium formate

The title compound was prepared from Example 51 (91 mg, 0.14 mmol) following MDAP purification and gave the title compound as a white electrostatic solid (59 mg).

LC-MS (Method 3):Rt = 3.52 min, m/z = 575.22 $[M]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.50 (1H, bs), 9.20 (2H, d, J = 5.7 Hz), 8.64 (1H, t, J = 7.8 Hz), 8.46 (1.4H, bs, formate), 8.21 (2H, t, J = 6.8 Hz), 8.12 (1H, bs), 7.96-7.87 (2H, m), 7.86-7.79 (1H, m), 7.76-7.72 (1H, m), 7.72-7.61 (2H, m), 6.12 (1H, s), 4.80 (2H, t, J = 7.4 Hz), 3.49 (3H, s), 3.37-3.24 (1H, m, obscured), 3.12-2.99 (1H, m), 2.65-2.53 (1H, m), 2.51-2.40 (1H, m, obscured), 2.14 (3H, s).

Example 53



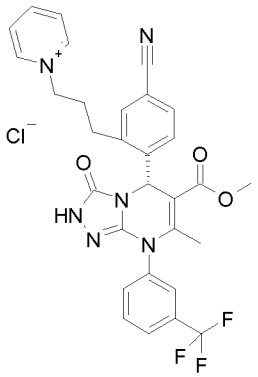
1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-pyridinium benzenesulfonate

The title compound was prepared from Example 51 (0.51 g, 0.78 mmol) using an analogous method to that used for Example 42 and gave the desired compound as a pale yellow electrostatic solid (0.55 g).

LC-MS (Method 3):Rt = 3.50 min, m/z = 575.2 $[M]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.23 (1H, bs), 9.18 (2H, d, J = 6.5 Hz), 8.64 (1H, t, J = 7.7 Hz), 8.21 (2H, t, J = 7.4 Hz), 8.12 (1H, bs), 7.95-7.88 (2H, m), 7.86-7.78 (1H, m), 7.76-7.72 (1H, m), 7.72-7.61 (2H, m), 7.61-7.57 (2H, m, besylate), 7.35-7.27 (3H, m, besylate), 6.12 (1H, s), 4.80 (2H, t, J = 7.4 Hz), 3.49 (3H, s), 3.37-3.24 (1H, m, obscured), 3.12-2.99 (1H, m), 2.65-2.53 (1H, m), 2.51-2.40 (1H, m, obscured), 2.14 (3H, s).

Example 54



1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-

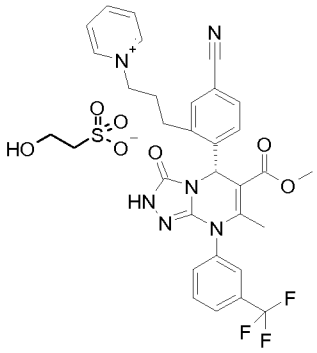
phenyl}-propyl)-pyridinium chloride

The title compound was prepared from Example 53 (0.51 g, 0.70 mmol) using Amberlite IRA 458 'chloride' resin (40 g, wet) and an analogous method to that used for Example 42 and gave the desired compound as a white electrostatic solid (0.44 g).

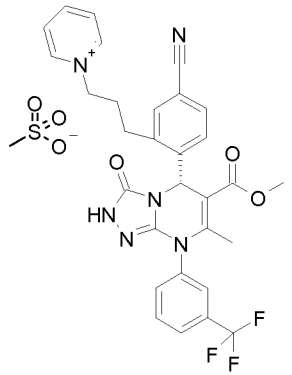
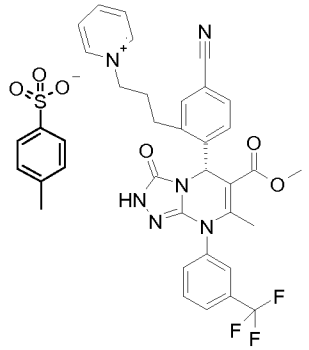
LC-MS (Method 3):Rt = 3.50 min, m/z = 575.2 $[M]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.25 (1H, bs), 9.19 (2H, d, J = 6.7 Hz), 8.64 (1H, t, J = 7.8 Hz), 8.21 (2H, t, J = 7.0 Hz), 8.12 (1H, bs), 7.95-7.88 (2H, m), 7.86-7.78 (1H, m), 7.76-7.72 (1H, m), 7.71-7.61 (2H, m), 6.12 (1H, s), 4.80 (2H, t, J = 7.4 Hz), 3.49 (3H, s), 3.36-3.23 (1H, m, obscured), 3.12-2.99 (1H, m), 2.65-2.53 (1H, m), 2.51-2.40 (1H, m, obscured), 2.14 (3H, s).

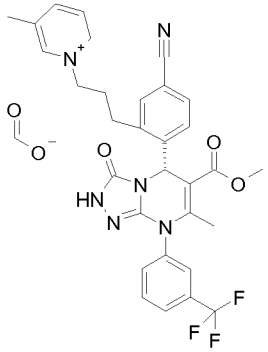
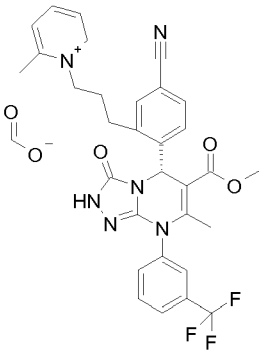
The following compounds were prepared from Example 51 using an analogous method to that used for Example 42, utilising an appropriate acid to prepare the desired IRA-458 resin, and gave the desired compounds as white electrostatic solids:

Ex	Structure	Name	LC-MS (Method 3)	NMR
55		1-(3-{5-Cyano-2-[(R)-6-methoxy-carbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-pyridinium 2-hydroxy-ethanesulfonate	Rt = 3.53 min, m/z = 575.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.20 (1H, bs), 9.18 (2H, d, J = 6.6 Hz), 8.64 (1H, t, J = 7.9 Hz), 8.20 (2H, t, J = 7.1 Hz), 8.12 (1H, bs), 7.95-7.88 (2H, m), 7.86-7.78 (1H, m), 7.76-7.72 (1H, m), 7.72-7.60 (2H, m), 6.12 (1H, s), 4.78 (2H, t, J = 7.4 Hz), 4.45 (1H, t, J = 5.8 Hz, isethionate), 3.62 (2H, q, J = 6.5 Hz, isethionate), 3.49 (3H, s), 3.37-3.24 (1H, m, obscured), 3.12-2.99 (1H, m), 2.63-2.53 (1H, m, obscured), 2.60 (1H, t, J = 6.7 Hz, isethionate), 2.53-2.40 (1H, m, obscured), 2.14 (3H, s).

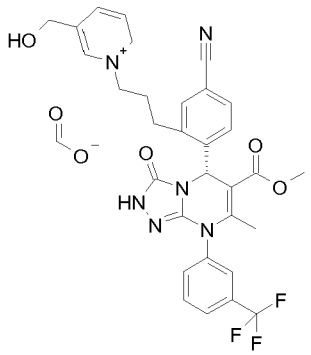
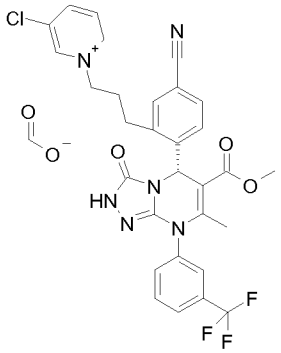
(continued)

56		1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-pyridinium methanesulfonate	Rt = 3.52 min, m/z = 575.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.24 (1H, bs), 9.18 (2H, d, J = 6.7 Hz), 8.64 (1H, t, J = 7.9 Hz), 8.21 (2H, t, J = 7.2 Hz), 8.12 (1H, bs), 7.96-7.87 (2H, m), 7.86-7.78 (1H, m), 7.76-7.73 (1H, m), 7.72-7.60 (2H, m), 6.12 (1H, s), 4.79 (2H, t, J = 7.4 Hz), 3.49 (3H, s), 3.36-3.25 (1H, m, obscured), 3.12-3.00 (1H, m), 2.63-2.54 (1H, m), 2.53-2.42 (1H, m, obscured), 2.30 (3H, s), 2.14 (3H, s).
57		1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-3-hydroxymethyl-pyridinium tosylate	Rt = 3.49 min, m/z = 575.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.24 (1H, bs), 9.18 (2H, d, J = 6.2 Hz), 8.64 (1H, t, J = 7.9 Hz), 8.21 (2H, t, J = 7.4 Hz), 8.12 (1H, bs), 7.95-7.88 (2H, m), 7.85-7.78 (1H, m), 7.76-7.72 (1H, m), 7.72-7.61 (2H, m), 7.50-7.45 (2H, m, tosylate), 7.13-7.08 (2H, m, tosylate), 6.12 (1H, s), 4.79 (2H, t, J = 7.5 Hz), 3.49 (3H, s), 3.37-3.25 (1H, m, obscured), 3.12-2.99 (1H, m), 2.66-2.53 (1H, m), 2.51-2.40 (1H, m, obscured), 2.28 (3H, s), 2.14 (3H, s).

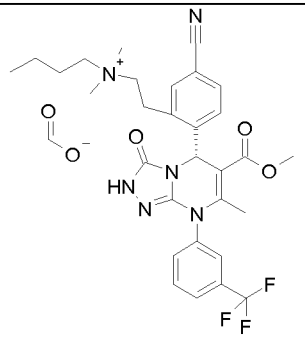
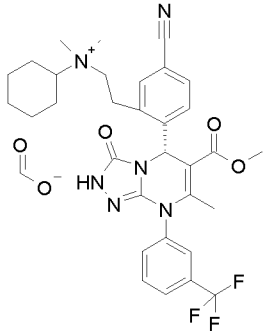
The following examples were prepared from Intermediate 13 and the appropriately substituted pyridines using an analogous method to Example 19:

Ex	Structure	Name	LC-MS (Method 3)	NMR
58		1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-3-methyl-pyridinium formate	Rt = 3.61 min, m/z = 589.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.46 (1H, bs), 9.09 (1H, s), 9.01 (1H, d, J = 5.9 Hz), 8.49 (1.3H, bs, formate), 8.46 (1H, s), 8.12 (1H, bs), 8.12-8.05 (1H, m), 7.97-7.87 (2H, m), 7.85-7.79 (1H, m), 7.74-7.71 (1H, m), 7.71-7.60 (2H, m), 6.11 (1H, s), 4.73 (2H, t, J = 7.3 Hz), 3.49 (3H, s), 3.37-3.25 (1H, m, obscured), 3.11-2.99 (1H, m), 2.64-2.52 (1H, m, obscured), 2.51 (3H, bs, obscured), 2.51-2.41 (1H, m, obscured), 2.14 (3H, s).
59		1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-2-methyl-pyridinium formate	Rt = 3.59 min, m/z = 589.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.43 (1H, bs), 9.08 (1H, d, J = 6.1 Hz), 8.50 (1H, t, J = 7.7 Hz), 8.46 (1.4H, bs, formate), 8.12 (1H, bs), 8.08 (1H, d, J = 7.9 Hz), 8.04-7.98 (1H, m), 7.96-7.88 (2H, m), 7.85-7.77 (2H, m), 7.72-7.60 (2H, m), 6.17 (1H, s), 4.74 (2H, t, J = 7.7 Hz), 3.50 (3H, s), 3.40-3.28 (1H, m), 3.14-3.03 (1H, m), 2.92 (3H, s), 2.61-2.48 (1H, m, obscured), 2.43-2.28 (1H, m), 2.15 (3H, s).

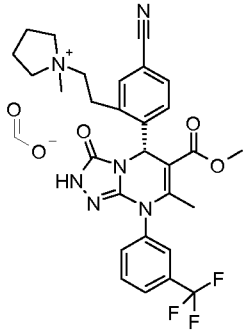
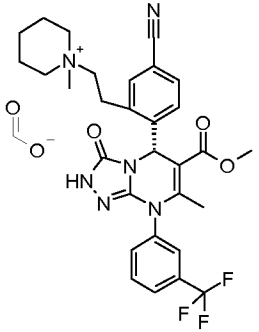
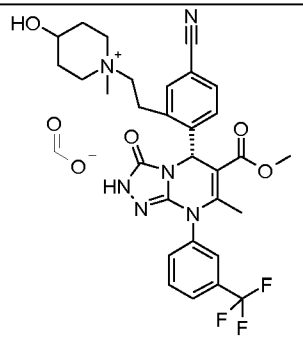
(continued)

60		1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-3-hydroxymethyl-pyridinium formate	Rt = 3.47 min, m/z = 605.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.32 (1H, bs), 9.15 (1H, s), 9.06 (1H, d, J = 5.9 Hz), 8.53 (1H, t, J = 7.9 Hz), 8.46 (1.4H, bs, formate), 8.19-8.13 (1H, m), 8.12 (1H, bs), 7.95-7.87 (2H, m), 7.85-7.78 (1H, m), 7.75-7.72 (1H, m), 7.71-7.60 (2H, m), 6.12 (1H, s), 4.79 (2H, t, J = 7.3 Hz), 4.75 (2H, s), 3.49 (3H, s), 3.36-3.25 (1H, m), 3.12-3.2.99 (1H, m), 2.61-2.52 (1H, m), 2.49-2.39 (1H, m, obscured), 2.14 (3H, s).
61		3-Chloro-1-(3-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-pyridinium formate	Rt = 3.62 min, m/z = 609.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.27 (1H, bs), 9.56 (1H, s), 9.25-9.14 (1H, m), 8.81 (1H, d, J = 7.6 Hz), 8.43 (1.5H, bs, formate), 8.28-8.20 (1H, m), 8.12 (1H, bs), 7.96-7.88 (2H, m), 7.86-7.78 (1H, m), 7.76-7.72 (1H, m), 7.71-7.61 (2H, m). 6.13 (1H, s), 4.79 (2H, t, J = 7.1 Hz), 3.51 (3H, s), 3.38-3.27 (1H, m), 3.13-3.01 (1H, m), 2.65-2.54 (1H, m), 2.53-2.45 (1H, m, obscured), 2.15 (3H, s).

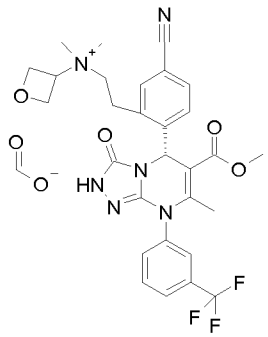
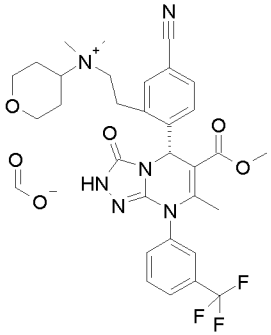
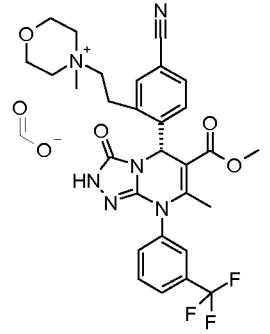
The following examples were prepared from Intermediate 23 and the appropriately substituted secondary amines using analogous methods to those used for Intermediate 24 and Intermediate 25, respectively. Following purification by MDAP and lyophilisation, the title compounds were obtained as white electrostatic solids:

Ex	Structure	Name	LC-MS (Method 3)	NMR
62		Butyl-(3-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-dimethyl-ammonium formate	Rt = 3.75 min, m/z = 583.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.55 (1H, bs), 8.53 (1H, s, formate), 8.14 (1H, s), 7.97-7.88 (2H, m), 7.87-7.80 (2H, m), 7.78-7.73 (1H, m), 7.73-7.67 (1H, m), 6.24 (1H, s), 4.04-3.95 (1H, m), 3.74-3.60 (2H, m), 3.54 (3H, s), 3.18 (6H, s), 3.44-3.29 (3H, m, obscured), 2.16 (3H, s), 1.82-1.71 (2H, m), 1.41-1.29 (2H, m), 0.96 (3H, t, J = 8 Hz).
63		(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-cyclohexyl-dimethyl-ammonium formate	Rt = 3.80 min, m/z = 609.4 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.52 (1H, bs), 8.43 (1.6H, s, formate), 8.14 (1H, s), 7.97-7.87 (3H, m), 7.87-7.79 (1H, m), 7.78-7.73 (1H, m), 7.73-7.66 (1H, m), 6.23 (1H, s), 4.08-3.97 (1H, m), 3.73-3.24 (4H, m, obscured), 3.54 (3H, s), 3.18-3.12 (6H, m), 2.28-2.18 (2H, m), 2.16 (3H, s), 1.94-1.83 (2H, m), 1.69-1.44 (3H, m), 1.43-1.22 (2H, m), 1.22-1.04 (1H, m).

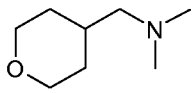
(continued)

64		1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-1-methyl-pyrrolidinium formate	Rt = 3.51 min, m/z = 567.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.32 (1H, very broad s), 8.44 (1.4H, s, formate), 8.13 (1H, bs), 7.97-7.86 (3H, m), 7.86-7.79 (1H, m), 7.79-7.67 (2H, m), 6.27 (1H, s), 4.07-3.95 (1H, m), 3.83-3.28 (7H, m, obscured), 3.53 (3H, s), 3.21 (3H, s), 2.22-2.12 (7H, m).
65		1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-1-methyl-piperidinium formate	Rt = 3.59 min, m/z = 581.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.46 (1H, bs), 8.38 (1.7H, s, formate), 8.08 (1H, bs), 7.92-7.82 (3H, m), 7.82-7.74 (1H, m), 7.74-7.68 (1H, m), 7.68-7.62 (1H, m), 6.18 (1H, s), 4.17-4.05 (1H, m), 3.67-3.21 (7H, m, obscured), 3.49 (3H, s), 3.18 (3H, s), 2.11 (3H, s), 1.96-1.72 (4H, m), 1.58-1.48 (2H, m).
66		1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-4-hydroxy-1-methyl-piperidinium formate	Rt = 3.44 min, m/z = 597.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.52 (1H, bs), 8.43 (1.4H, s, formate), 8.13 (1H, bs), 7.97-7.87 (3H, m), 7.87-7.79 (1H, m), 7.79-7.73 (1H, m), 7.73-7.66 (1H, m), 6.23 & 6.26 (1H total, 2s, isomers), 4.21-4.05 (1H, m), 3.93-3.17 (9H, m, obscured), 3.53 (3H, s), 3.27 & 3.22 (3H total, 2s, isomers), 2.16 (3H, s), 2.19-1.99 (2H, m), 1.89-1.69 (2H, m).

(continued)

67		(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-dimethyl-oxetan-3-yl-ammonium formate	Rt = 3.44 min, m/z = 583.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.58 (1H, bs), 8.52 (1H, s, formate), 8.13 (1H, bs), 7.93 (2H, m), 7.86 (1H, d, J = 1.4 Hz), 7.83 (1H, t, J = 7.9 Hz), 7.76 (1H, dd, J = 1.6, 7.9 Hz), 7.70 (1H, d, J = 8.2 Hz), 6.26 (1H, s), 4.98 (2H, m), 4.92-4.83 (3H, m), 4.00 (1H, m), 3.73-3.58 (2H, m), 3.53 (3H, s), 3.39-3.31 (1H, obscured), 3.28 (3H, s), 3.27 (3H, s), 2.16 (3H, s).
68		(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-dimethyl-(tetrahydro-pyran-4-yl)-ammonium formate	Rt = 3.51 min, m/z = 611.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.54 (1H, bs), 8.41 (1.1H, s, formate), 8.14 (1H, bs), 7.92 (3H, m), 7.83 (1H, t, J = 7.9 Hz), 7.76 (1H, dd, J = 1.6, 8.1 Hz), 7.70 (1H, d, J = 8.1 Hz), 6.25 (1H, s), 4.04 (3H, m), 3.80-3.59 (2H, m, obscured), 3.54 (3H, s), 3.43-3.28 (4H, m), 3.16 (3H, s), 3.15 (3H, s), 2.16 (3H, s), 2.11 (2H, m), 1.82 (2H, m).
69		4-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-4-methyl-morpholin-4-ium formate	Rt = 3.47 min, m/z = 583.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.54 (1H, bs), 8.43 (1.5H, s, formate), 8.14 (1H, bs), 7.96-7.88 (3H, m), 7.87-7.80 (1H, m), 7.79-7.74 (1H, m), 7.74-7.68 (1H, m), 6.27 (1H, s), 4.34-4.21 (1H, m), 4.11-3.90 (4H, m), 3.83-3.27 (7H, m, obscured), 3.53 (3H, s), 3.35 (3H, s), 2.16 (3H, s).

Intermediate 26

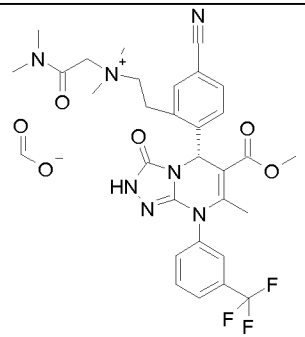
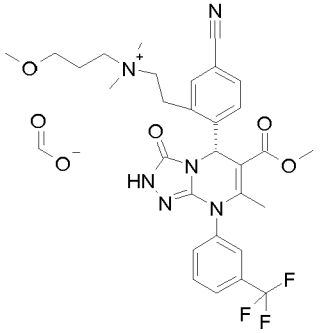


Dimethyl-(tetrahydro-pyran-4-ylmethyl)-amine

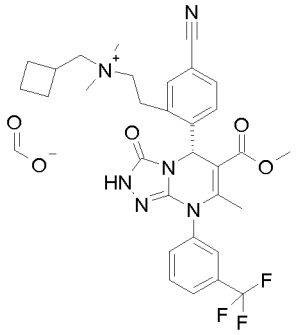
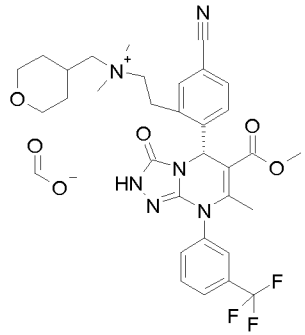
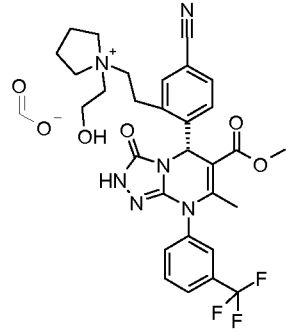
4-(Bromomethyl)tetrahydro-2*H*-pyran (0.50 g, 2.8 mmol) was dissolved in dimethylamine (40% in water, 5 mL) and the reaction mixture was stirred at RT for 18 h. The mixture was saturated with NaCl and extracted into Et_2O (2x). The combined organic extract was dried (K_2CO_3), filtered and concentrated *in vacuo* to give the title compound as a colourless oil (0.40 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (2H, dd, J = 11.6, 4.4 Hz), 3.39 (2H, td, J = 11.6, 1.6 Hz), 2.20 (6H, s), 2.12 (2H, d, J = 6.5 Hz), 1.75-1.62 (3H, m), 1.33-1.21 (2H, m).

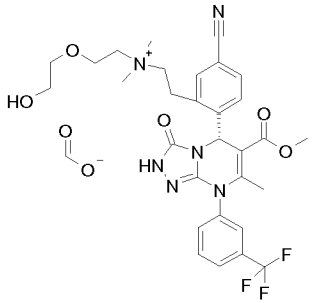
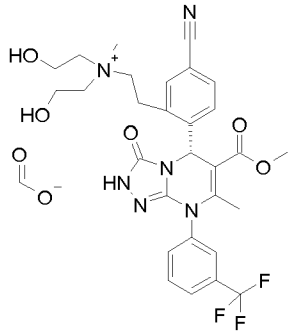
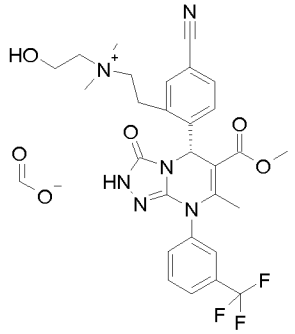
The following examples were prepared from Intermediate 21 and the appropriately substituted tertiary amines or basic heterocycles using an analogous method to that used in Example 50 (all tertiary amines were known or commercially available unless otherwise stated). Following purification by MDAP and lyophilisation, the title compounds were obtained as white electrostatic solids:

Ex	Structure	Name	LC-MS (Method 3)	NMR
70		(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-dimethylcarbamoylmethyl-dimethyl-ammonium formate	Rt = 3.52 min, m/z = 612.4 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.46 (1H, bs), 8.40 (1.7 H, s, formate), 8.14 (1H, bs), 7.93 (2H, m), 7.82 (2H, m), 7.77 (1H, m), 7.71 (1H, m), 6.24 (1H, s), 4.58 (2H, m), 4.17 (1H, m), 4.03 (1H, m), 3.67 (2H, m, obscured), 3.37 (9H, s), 2.99 (3H, s), 2.90 (3H, s), 2.17 (3H, s).
71		(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-(3-methoxy-propyl)-dimethyl-ammonium formate	Rt = 3.58 min, m/z = 599.4 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.52 (1H, bs), 8.45 (1.5 H, s, formate), 8.14 (1H, bs), 7.93 (2H, m), 7.88-7.79 (2H, m), 7.76 (1H, m), 7.70 (1H, m), 6.24 (1H, s), 4.03 (1H, m), 3.66 (2H, m), 3.53 (3H, s), 3.60-3.23 (5H, m, obscured) 3.27 (3H, s), 3.19 (6H, s), 2.16 (3H, s), 2.06 (2H, m).

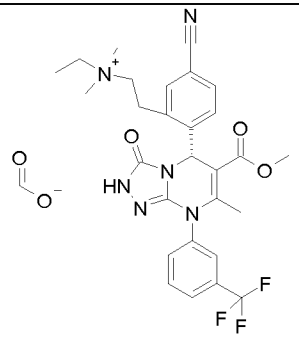
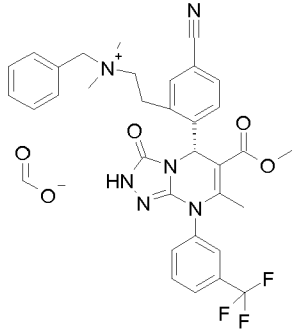
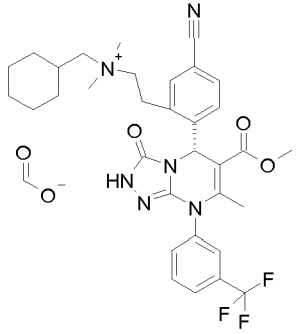
(continued)

72		(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-cyclobutylmethyl-dimethyl-ammonium formate	Rt = 3.75 min, m/z = 595.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.54 (1H, bs), 8.42 (1.5H, bs, formate), 8.14 (1H, bs), 7.97-7.87 (2H, m), 7.87-7.79 (2H, m), 7.79-7.74 (1H, m), 7.74-7.67 (1H, m), 6.25 (1H, s), 4.00-3.91 (1H, m), 3.71-3.60 (2H, m, obscured), 3.51-3.42 (2H, m, obscured), 3.53 (3H, s, obscured), 3.38-3.27 (1H, m), 3.13 (3H, s), 3.12 (3H, s), 3.02-2.90 (1H, m), 2.17 (3H, s), 2.08-2.19 (2H, m), 1.98-1.74 (4H, m).
73*		(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-dimethyl-(tetrahydro-pyran-4-ylmethyl)-ammonium formate	Rt = 3.55 min, m/z = 625.4 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.58 (1H, bs), 8.46 (1.4 H, s, formate), 8.13 (1H, bs), 7.93 (2H, m), 7.83 (2H, m), 7.76 (1H, dd, J = 8.1, 1.6 Hz), 7.70 (1H, d, J = 8.1 Hz), 6.24 (1H, s), 4.08 (1H, m), 3.83 (2H, m), 3.72-3.32 (10H, m, obscured), 3.22 (6H, s), 2.32 (1H, m), 2.16 (3H, s), 1.75 (2H, m), 1.38 (2H, m).
74		1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-1-(2-hydroxy-ethyl)-pyrrolidinium formate	Rt = 3.48 min, m/z = 597.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.56 (1H, bs), 8.46 (1.4 H, s, formate), 8.13 (1H, bs), 7.92 (2H, m), 7.86 (1H, d, J = 1.5 Hz), 7.83 (1H, t, J = 7.9 Hz), 7.75 (1H, dd, J = 8.1, 1.5 Hz), 7.69 (1H, d, J = 8.1 Hz), 6.27 (1H, s), 4.08-3.92 (4H, m), 3.80-3.35 (11H, m, obscured) 2.16 (3H, s), 2.13 (4H, m).

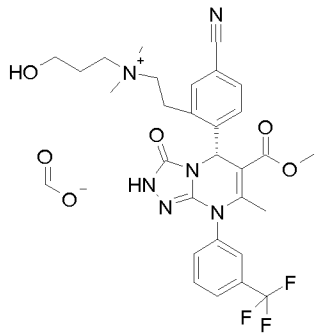
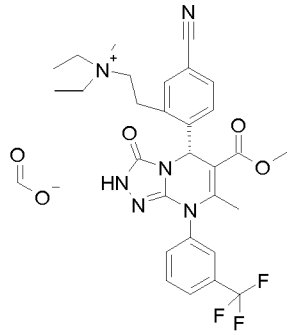
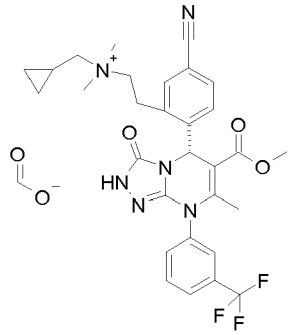
(continued)

75		(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-[2-(2-hydroxy-ethoxy)-ethyl]-dimethyl-ammonium formate	Rt = 3.39 min, m/z = 615.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.55 (1H, bs), 8.49 (1H, s, formate), 8.14 (1H, s), 7.97-7.87 (2H, m), 7.88-7.79 (2H, m), 7.79-7.73 (1H, m), 7.73-7.66 (1H, m), 6.26 (1H, s), 4.11-3.99 (1H, m), 3.94 (2H, s), 3.82-3.61 (4H, m), 3.59-3.30, (9H, m, obscured), 3.34 (6H, s), 2.17 (3H, s).
76		(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-bis-(2-hydroxy-ethyl)-methyl-ammonium formate	Rt = 3.37 min, m/z = 601.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.45 (1H, bs), 8.50 (1H, s, formate), 8.15 (1H, s), 7.98-7.89 (2H, m), 7.89-7.80 (2H, m), 7.79-7.74 (1H, m), 7.74-7.68 (1H, m), 6.28 (1H, s), 4.18-4.06 (1H, m), 3.96 (4H, s), 3.84-3.73 (1H, m), 3.73-3.58 (4H, m), 3.54 (3H, s), 3.28 (3H, s), 2.17 (3H, s). 2 xO<u>H</u>'s not observed.
77		(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-(2-hydroxy-ethyl)-dimethyl-ammonium forma	Rt = 3.42 min, m/z = 571.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.54 (1H, bs), 8.52 (1.1H, s, formate), 8.14 (1H, bs), 7.97-7.87 (2H, m), 7.87-7.79 (2H, m), 7.79-7.73 (1H, m), 7.73-7.67 (1H, m), 6.27 (1H, s), 4.09-3.99 (1H, m), 3.94 (2H, bs), 3.81-3.62 (2H, m), 3.61-3.51 (2H, m), 3.53 (3H, s), 3.44-3.34 (assumed 2H, m, obscured) 3.24 (6H, s), 2.16 (3H, s).

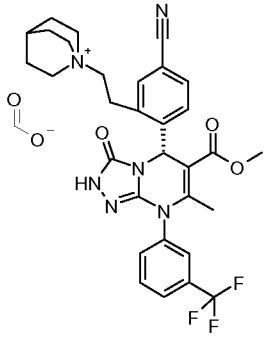
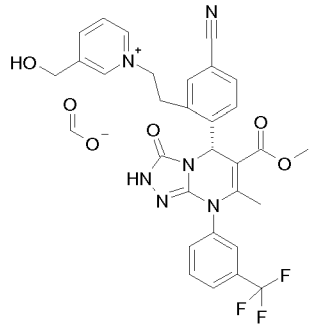
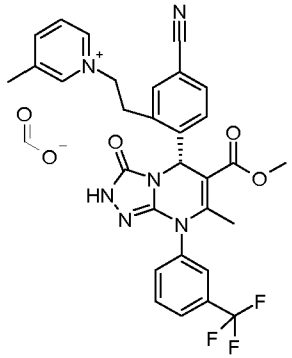
(continued)

78		(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-ethyl-dimethyl-ammonium format	Rt = 3.49 min, m/z = 555.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.51 (1H, bs), 8.43 (1.3H, s, formate), 8.13 (1H, bs), 7.96-7.88 (2H, m), 7.88-7.79 (2H, m), 7.79-7.73 (1H, m), 7.73-7.67 (1H, m), 6.25 (1H, s), 4.04-3.94 (1H, m), 3.73-3.27 (5H, m, obscured), 3.53 (3H, s), 3.16 (6H, s), 2.16 (3H, s), 1.34 (3H, t, J = 7 Hz).
79		Benzyl-(2-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-dimethyl-ammonium forma	Rt = 3.477 min, m/z = 617.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.53 (1H, bs), 8.40 (1.8 H, s, formate), 8.13 (1H, bs), 7.93 (2H, m), 7.86 (1H, d, J = 1.5 Hz), 7.83 (1H, t, J = 8.0 Hz), 7.77 (1H, dd, J = 1.6, 8.1 Hz), 7.65 (2H, m), 7.54 (3H, m), 6.28 (1H, s), 4.66 (2H, J = 12.8 Hz), 4.04 (2H, m, obscured), 3.51 (3H, s), 3.48 (2H, m), 3.13 (6H, s), 2.16 (3H, s).
80		(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-cyclohexylmethyl-dimethyl-ammonium formate	Rt = 3.96 min, m/z = 623.4 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.53 (1H, bs), 8.40 (1.7 H, s, formate), 8.13 (1H, bs), 7.93 (2H, m), 7.83 (2H, m), 7.76 (1H, dd, J = 1.6, 8.0 Hz), 7.71 (1H, d, J = 8.1 Hz), 6.23 (1H, s), 4.05 (2H, m), 3.54 (3H, s, obscured), 3.36 (2H, m, obscured), 3.27 (2H, m), 3.19 (6H, s), 2.16 (3H, s), 2.04 (1H, m), 1.84 (2H, m), 1.66 (2H, m), 1.58 (1H, m), 1.39-1.25 (2H, m), 1.20-1.07 (3H, m).

(continued)

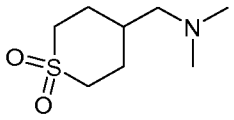
81		(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-(3-hydroxy-propyl)-dimethyl-ammonium formate	Rt = 3.40 min, m/z = 585.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.50 (1H, bs), 8.44 (1.5 H, s, formate), 8.13 (1H, bs), 7.93 (2H, m), 7.86 (1H, d, J = 1.2 Hz), 7.83 (1H, t, J = 7.9 Hz), 7.76 (1H, dd, J = 8.1, 1.7 Hz), 7.70 (1H, d, J = 8.1 Hz), 6.25 (1H, s), 4.02 (1H, m), 3.66-3.30 (10H, m, obscured), 3.19 (3H, s), 3.18 (3H, s), 2.16 (3H, s), 1.95 (2H, m).
82		(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-diethyl-methyl-ammonium forma	Rt = 3.55 min, m/z = 569.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.52 (1H, bs), 8.42 (1.6 H, s, formate), 8.13 (1H, bs), 7.93 (2H, m), 7.87 (1H, d, J = 1.2 Hz), 7.83 (1H, t, J = 7.8 Hz), 7.76 (1H, dd, J = 8.0, 1.6 Hz), 7.70 (1H, d, J = 8.2 Hz), 6.22 (1H, s), 4.00 (1H, m), 3.67-3.28 (10H, m, obscured), 3.11 (3H, s), 2.16 (3H, s), 1.32 (6H, m).
83		(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-cyclopropylmethyl-dimethyl-ammonium formate	Rt = 3.62 min, m/z = 581.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.51 (1H, bs), 8.41 (1.6 H, s, formate), 8.13 (1H, bs), 7.92 (2H, m), 7.86 (1H, d, J = 1.3 Hz), 7.82 (1H, t, J = 7.9 Hz), 7.76 (1H, dd, J = 8.1, 1.7 Hz), 7.70 (1H, d, 8.1 Hz), 6.25 (1H, s), 4.08 (2H, m), 3.53 (3H, s), 3.41-3.31 (4H, m), 3.21 (6H, s), 2.16 (3H, s), 1.28 (1H, m), 0.73 (2H, m), 0.46 (2H, m).

(continued)

84		1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-1-azonia-bicyclo[2.2.2]octane formate	Rt = 3.56 min, m/z = 593.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.53 (1H, bs), 8.41 (1.7 H, s, formate), 8.13 (1H, bs), 7.93 (2H, m), 7.83 (2H, m), 7.75 (1H, dd, J = 8.1, 1.8 Hz), 7.70 (1H, d, J = 8.2 Hz), 6.25 (1H, s), 3.88-3.47 (11H, m, obscured), 3.32 (2H, m), 2.16 (3H, s), 2.12 (1H, m), 1.94 (6H, m).
85		1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-3-hydroxymethyl-pyridinium formate	Rt = 3.45 min, m/z = 591.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.57 (1H, bs), 9.17 (1H, s), 9.00 (1H, d, J = 8 Hz), 8.57 (1H, d, J = 8 Hz), 8.47 (1.3H, s, formate), 8.22-8.10 (2H, m), 7.99-7.89 (2H, m), 7.88-7.72 (4H, m), 6.45 (1H, s), 5.27-5.06 (2H, m), 4.78 (2H, s), 3.69-3.52 (2H, m, obscured), 3.94-3.82 (1H, m), 3.50 (3H, s), 2.17 (3H, s).
86		1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-3-methyl-pyridinium formate	Rt = 3.58 min, m/z = 575.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.58 (1H, bs), 9.06 (1H, s), 8.90 (1H, d, J = 6 Hz), 8.51 (1H, d, J = 8 Hz), 8.43 (1.5H, s, formate), 8.19-8.08 (2H, m), 7.97-7.88 (2H, m), 7.86-7.71 (3H, m), 7.68 (1H, m), 6.43 (1H, s), 5.22-5.00 (2H, m), 3.94-3.50 (2H, m, obscured), 3.47 (3H, s), 2.54 (3H, s), 2.16 (3H, s).

* = for tertiary amine preparation see Intermediate 26.

Intermediate 27

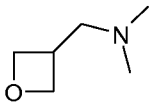


(1,1-Dioxo-hexahydro-1lambda*6*-thiopyran-4-ylmethyl)-dimethylamine

[(1,1-Dioxotetrahydro-2*H*-thiopyran-4-yl)methyl]amine (500 mg, 3.07 mmol) was dissolved in formic acid (1 mL) and formaldehyde (37% in water, 1 mL) and the reaction mixture was heated to 65°C for 4 h. The mixture was cooled and carefully poured onto aqueous $NaHCO_3$ and washed with EtOAc. The aqueous layer was basified to pH 13 with NaOH and extracted into 2-MethylTHF (3x). The combined organic extract was dried ($MgSO_4$), filtered and concentrated *in vacuo* and resultant residue was purified by chromatography eluting from 0-10% (2M NH_3 in MeOH) in DCM to give the title compound as a clear oil (80 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11 (4H, m), 2.20 (6H, s), 2.24-2.12 (4H, m), 1.88-1.57 (3H, m).

Intermediate 28

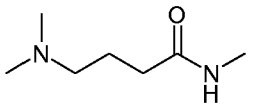


Dimethyl-oxetan-3-ylmethyl-amine

Oxetan-3-yl-methylamine (0.25 g, 2.87 mmol) was dissolved in a mixture of formaldehyde (37% solution in water; 1 mL) and formic acid (1 mL) then heated at 65°C for 4 h. The reaction mixture was poured into aqueous sodium hydroxide/brine and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered and carefully concentrated *in vacuo* to afford the title compound as a residue still containing traces of Et_2O (0.11 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.80 (2H, m), 4.38-4.45 (2H, m), 3.09-3.28 (1H, m), 2.62 (2H, d, J = 7.4 Hz), 2.20 (6H, s).

Intermediate 29

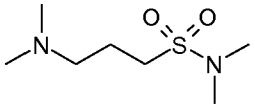


4-Dimethylamino-N-methyl-butyramide

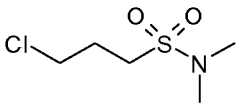
A stirred solution of 4-dimethylamino-butyric acid hydrochloride salt (0.50 g, 2.98 mmol; for reference procedure from 4-aminobutyric acid see *JACS*, **1963**, *85*, 1-8) and DIPEA (3.22 mL, 18.50 mmol) in DMF (5 mL) was treated with a methylamine solution (2 M in THF; 5.96 mL, 11.93 mmol) and then HATU (1.42 g, 3.73 mmol). The mixture was stirred at RT for 4 h before being diluted with MeOH (15 mL). This resultant solution was purified *via* a SCX-2 cartridge and the relevant fractions were concentrated *in vacuo* to afford the title compound as a colourless oil (0.31 g).

^{1}H NMR (300 MHz, DMSO): δ 7.66 (1H, bs), 2.54 (3H, d, J = 4.6 Hz), 2.15 (2H, t, J = 7.2 Hz), 2.09 (6H, s), 2.04 (2H, t, J = 7.5 Hz), 1.53-1.65 (2H, m).

Intermediate 30



3- Dimethylamino-propane-1-sulfonic acid dimethylamide

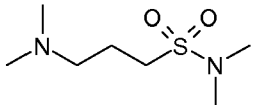


a) 3-Chloro-propane-1-sulfonic acid dimethylamide

A stirred solution of 3-chloropropylsulfonylchloride (6.00 g, 33.90 mmol) in THF (35 mL) was cooled in an ice bath to 0-5°C. Dimethylamine (2 M in THF; 36 mL, 72 mmol) was added drop-wise, maintaining the temperature below 10°C, and the resultant suspension stirred at 5°C for 30 min then allowed to warm to RT. After 1 h, the mixture was diluted with water and extracted into EtOAc and the extract washed with water, brine and then dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound

as a pale yellow oil (5.19 g).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70 (2H, t, J 6.2 Hz), 3.06-3.12 (2H, m), 2.90 (6H, s), 2.25 (2H, m).

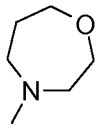


b) 3- Dimethylamino-propane-1-sulfonic acid dimethylamide

A solution of 3-chloro-propane-1-sulfonic acid dimethylamide (0.55 g, 3.00 mmol) in MeCN (5 mL) was treated with dimethylamine (2 M in THF; 10 mL, 20 mmol), potassium carbonate (455 mg, 3.30 mmol) and a catalytic amount of potassium iodide (50 mg, 0.03 mmol). This mixture was heated in a sealed tube at 65°C for 18 h, then cooled and diluted with water and extracted into EtOAc. The organic extract was washed with brine then dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound as a pale brown oil (0.40 g).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.01-2.95 (2H, m), 2.88 (6H, s), 2.38 (2H, t, J = 6.8 Hz), 2.22 (6H, s), 2.02-1.92 (2H, m).

Intermediate 31

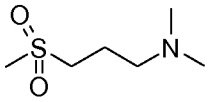


4-Methyl-[1,4]oxazepane

1,4] Oxazepane hydrochloride (730 mg, 5.3 mmol), and $NaHCO_3$ (450 mg, 5.3 mmol) were suspended in formic acid (2 mL) and a formaldehyde solution (37 wt% in water; 1 mL) and heated to reflux for 5.5 h. The reaction was cooled, and a solution of NaOH (2 g in 5 mL water) was added cautiously. The product was then extracted with Et_2O (50 mL), dried (Na_2SO_4) and the solvent removed by distillation at atmospheric pressure to afford of a light brown liquid that contained some residual Et_2O (680 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85-3.78 (2H, m), 3.76-3.70 (2H, m), 2.68-2.59 (4H, m), 2.41-2.37 (3H, m), 1.98-1.88 (2H, m).

Intermediate 32

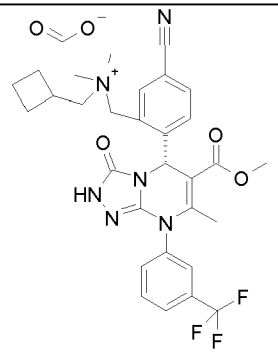
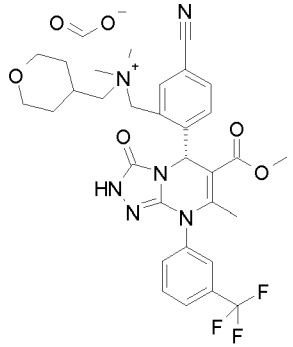


(3-Methanesulfonylpropyl)dimethylamine

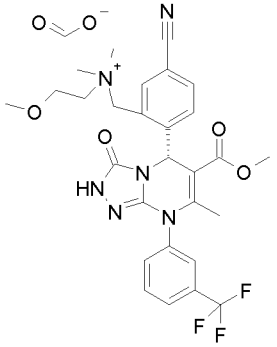
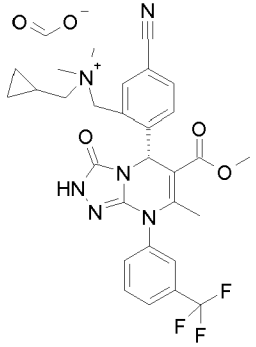
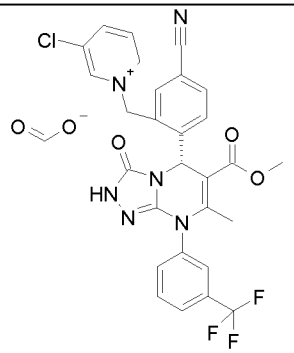
1-Bromo-3-methanesulfonylpropane (500 mg, 2.5 mmol) was suspended in a dimethylamine solution (2 M in THF; 10 mL, 20 mmol) and stirred at RT, resulting in a crystalline solid. The reaction was left to stand overnight and the reaction mixture was then diluted with Et_2O (10 mL) and filtered. The filtrate was concentrated *in vacuo* resulting in an orange oily solid which was redissolved in Et_2O (10 mL), filtered and concentrated *in vacuo* to give the title compound as an orange oil (420 mg).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.07-2.99 (2H, m), 2.84 (3H, m), 2.34 (2H, t, J = 6.7 Hz), 2.16 (6H, s), 2.00-1.88 (2H, m).

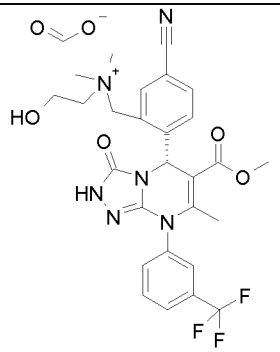
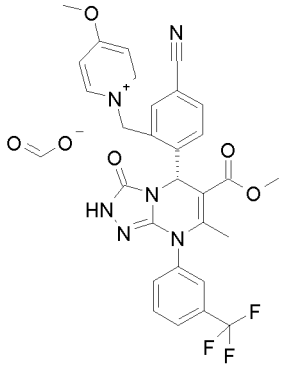
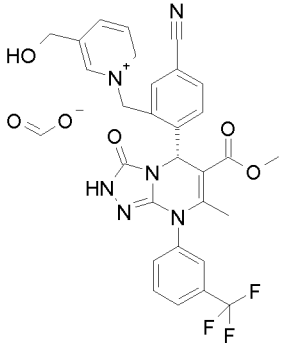
The following examples were prepared from Intermediate 14 and the appropriately substituted tertiary amines or basic heterocycles using an analogous method to that used in Example 24 (all tertiary amines/basic heterocycles were known or commercially available unless otherwise stated). Where the tertiary amine used was limiting, the reaction mixture was diluted further with MeCN. Following purification by MDAP and lyophilisation, the title compounds were obtained as white electrostatic solids:

Ex	Structure	Name	LC-MS (Method 3)	NMR
87		{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-cyclobutylmethyl-dimethyl-ammonium formate	Rt = 3.66 min, m/z = 581.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.63 (1H, bs), 8.46 (1.5H, s, formate), 8.10 (2H, m), 8.02 (1H, dd, J = 8.3, 1.5 Hz), 7.95-7.79 (4H, m), 6.45 (1H, s), 5.06 (1H, d, J = 14.3 Hz), 4.91 (1H, d, J = 14.3 Hz), 3.67-3.56 (2H, m, obscured), 3.53 (3H, s), 3.16 (3H, s), 3.12 (3H, s), 3.07-2.94 (1H, m), 2.23-2.12 (2H, m), 2.07 (3H, s), 2.02-1.88 (3H, m), 1.86-1.75 (1H, m).
88*		{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-(tetrahydro-pyran-4-ylmethyl)-ammonium formate	Rt = 3.45 min, m/z = 611.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.54 (1H, bs), 8.46 (1.4 H, s, formate), 8.13 (1H, d, J = 1.7 Hz), 8.12-8.08 (1H, m), 8.03 (1H, dd, J = 8.2, 1.7 Hz), 7.95-7.79 (4H, m), 6.49 (1H, s), 5.15 (1H, d, J = 14.2 Hz), 4.97 (1H, d, J = 14.2 Hz), 3.90-3.82 (2H, m, obscured), 3.53 (3H, s, obscured), 3.57-3.35 (4H, m, obscured), 3.25 (3H, s), 3.18 (3H, s), 2.45-2.35 (1H, m), 2.07 (3H, s), 1.82-1.73 (2H, m), 1.51-1.38 (2H, m).

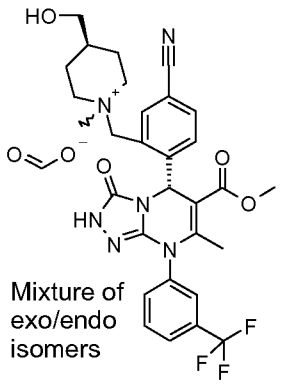
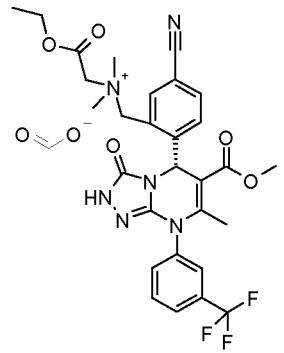
(continued)

89		{{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(2-methoxy-ethyl)-dimethyl-ammonium formate	Rt = 3.45 min, m/z = 571.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.58 (1H, bs), 8.41 (1.7 H, s, formate), 8.14 (1H, d, J = 1.6 Hz), 8.11 (1H, bs), 8.02 (1H, dd, J = 8.3, 1.6 Hz), 7.95-7.79 (4H, m), 6.48 (1H, s), 5.15-5.05 (2H, m), 3.91-3.77 (4H, m), 3.53 (3H, s), 3.36 (3H, s), 3.25 (3H, s), 3.23 (3H, s), 2.06 (3H, s).
90		{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-cyclopropylmethyl-dimethyl-ammonium formate	Rt = 3.52 min, m/z = 567.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.60 (1H, bs), 8.43 (1.6 H, s, formate), 8.13 (1H, d, J = 1.6 Hz), 8.10 (1H, bs), 8.02 (1H, dd, J = 8.3, 1.6 Hz), 7.95-7.79 (4H, m), 6.45 (1H, s), 5.15 (1H, d, J = 14.2 Hz), 5.01 (1H, d, J = 14.2 Hz), 3.54 (3H, s), 3.52-3.46 (2H, m), 3.27 (3H, s), 3.22 (3H, s), 2.07 (3H, s), 1.33-1.21 (1H, m), 0.79-0.72 (2H, m), 0.54-0.45 (2H, m).
91		3-Chloro-1-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-pyridinium formate	Rt = 3.50 min, m/z = 581.1 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.63 (1H, bs), 9.74 (1H, s), 9.33 (1H, d, J = 5.9 Hz), 8.86 (1H, dd, J = 8.5, 1.3 Hz), 8.44 (1.5 H, s, formate), 8.31-8.24 (1H, m), 8.23-8.10 (1H, bm), 7.98-7.89 (4H, m), 7.87-7.79 (2H, m), 6.56 (1H, d, J = 15.4 Hz), 6.42 (1H, s), 6.11 (1H, d, J = 15.4 Hz), 3.57 (3H, s), 2.18 (3H, s).

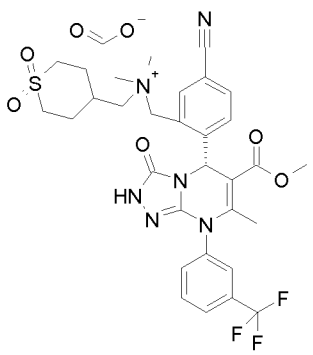
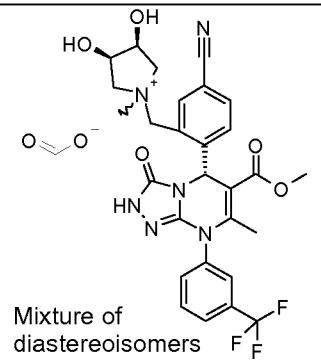
(continued)

92		{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(2-hydroxy-ethyl)-dimethyl-ammonium formate	Rt = 3.28 min, m/z = 557.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.55 (1H, bs), 8.46 (1.3 H, s, formate), 8.16 (1H, d, J = 1.63 Hz), 8.11 (1H, bs), 8.02 (1H, dd, J = 8.3, 1.6 Hz), 7.96-7.79 (4H, m), 6.50 (1H, s), 5.19-5.07 (2H, m), 3.99 (2H, t, J = 4.7 Hz), 3.72-3.65 (2H, m, obscured), 3.53 (3H, s, obscured), 3.27 (3H, s), 3.25 (3H, s), 2.06 (3H,s).
93		1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methoxy-pyridinium formate	Rt = 3.49 min, m/z = 577.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.72 (1H, bs), 9.16-9.11 (2H, m), 8.46 (1.3H, s, formate), 8.17 (1H, bs), 7.98-7.79 (5H, m), 7.76-7.71 (2H, m), 7.60 (1H, d, J = 1.1 Hz), 6.47-6.40 (2H, m), 5.92 (1H, d, J = 15.4 Hz), 4.14 (3H, s), 3.57 (3H, s), 2.19 (3H, s).
94		1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-3-hydroxymethyl-pyridinium formate	Rt = 3.34 min, m/z = 577.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.62 (1H, bs), 9.35 (1H, s), 9.24 (1H, d, J = 6.0 Hz), 8.60 (1H, d, J = 7.8 Hz), 8.44 (1.4 H, s, formate), 8.23-8.16 (2H, m), 7.98-7.79 (5H, m), 7.70 (1H, d, J = 1.2 Hz), 6.59 (1H, d, J = 15.2 Hz), 6.43 (1H, s), 6.14 (1H, d, J = 15.2 Hz), 4.76 (2H, s), 3.55 (3H, s, obscured 2.19 (3H, s).

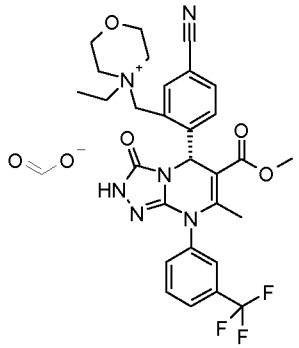
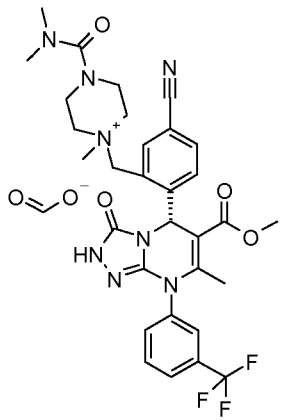
(continued)

95	 Mixture of exo/endo isomers	{1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-hydroxymethyl-1-methyl-piperidinium formate	Rt = 3.30 min, m/z = 597.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.44 (1H, bs), 8.37 (1.4H, s, formate), 8.15-8.08 (1.6H, m), 8.05-7.99 (1.4H, m), 7.96-7.99 (4H, m), 6.52, 6.38 (1H, 2 x s), 5.17-4.96 (2H, m), 4.01-3.81 (2H, m), 3.73-3.23 (4H, m), 3.56, 3.53 (3H, 2 x s), 3.14, 3.06 (3H, 2 x s), 2.08, 2.06 (3H, 2 x s), 2.03-1.57 (5H, m).
96		{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-ethoxycarbonylmethyl-dimethyl-ammonium formate	Rt = 3.61 min, m/z = 599.4 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.56 (1H, bs), 8.41 (1.5 H, s, formate), 8.14 (1H, d, J = 1.6 Hz), 8.12 (1H, bs), 8.04 (1H, dd, J = 8.4, 1.6 Hz), 7.96-7.79 (4H, m), 6.42 (1H, s), 5.33-5.24 (2H, m), 4.64-4.56 (2H, m), 4.29 (2H, q, J = 7.1 Hz), 3.54 (3H, s, obscured 3.41 (3H, s), 3.36 (3H, s), 2.08 (3H, s), 1.28 (3H, t, J = 7.2 Hz).

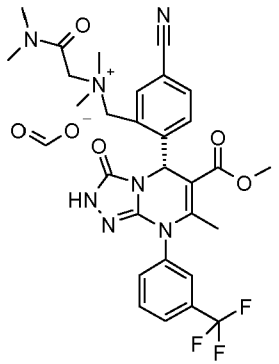
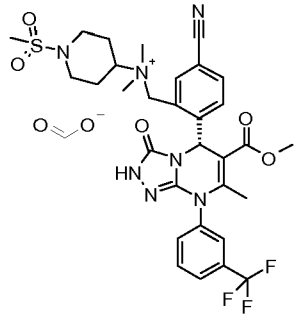
(continued)

97*		{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(1,1-dioxo-hexahydro-1lambda*6*-thiopyran-4-ylmethyl)-dimethyl-ammonium formate	Rt = 3.38 min, m/z = 659.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO TFA-D added) δ 8.14 (1.2H, s), 8.12 (1H, d, J = 1.6 Hz), 8.10 (1H, bs), 8.04 (1H, dd, J = 8.3, 1.6 Hz), 7.95-7.80 (4H, m), 6.51 (1H, s), 5.18 (1H, d, J = 14.0 Hz), 5.02 (1H, d, J = 14.0 Hz), 3.64-3.52 (2H, m), 3.56 (3H, s), 3.27 (3H, s), 3.23 (3H, s), 3.21-3.10 (4H, m), 2.56-2.51 (1H, m, obscured), 2.24-2.14 (2H, m), 2.10 (3H, s), 2.05-1.91 (2H, m).
98	 Mixture of diastereoisomers	1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-3,4-dihydroxy-1-methyl-pyrrolidinium formate	Rt = 3.28 min, m/z = 585.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.38 (1H, bs), 8.47 (1.1H, s, formate), 8.19-8.06 (2H, m), 8.02-7.78 (5H, m), 6.49-6.45 (1H, 2 x s), 5.95 (1H, bs), 5.25, 5.10 (2H, 2 x d, J = 14.5 Hz, 1 x s), 4.49-4.37 (2H, m), 4.19-4.06 (2H, m), 3.90 (1H, d, J = 5.7 Hz), 3.81-3.64 (2H, m), 3.53 (3H, s), 3.37, 3.17 (3H, 2 x s), 2.09, 2.08 (3H, 2 x s).

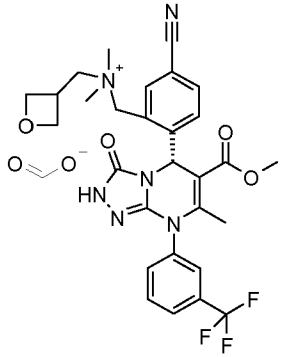
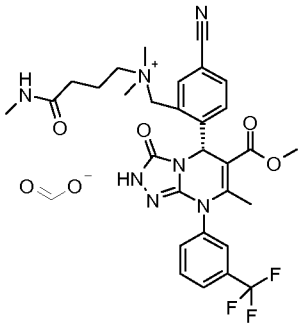
(continued)

99		4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-ethyl-morpholin-4-ium formate	Rt = 3.42 min, m/z = 583.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.59 (1H, bs), 8.49 (1.2 H, s, formate), 8.14-7.99 (3H, m), 7.97-7.76 (4H, m), 6.40 (1H, s), 5.23-4.97 (2H, m), 4.12-3.75 (7H, m), 3.69-3.57 (3H, m), 3.56 (3H, s), 2.07 (3H, s), 1.45-1.34 (3H, m).
100		1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-dimethylcarbamoyl-1-methyl-piperazin-1-ium formate	Rt = 3.38 min, m/z = 639.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.69 (1H, bs), 8.48 (1.3 H, s, formate), 8.16-8.06 (2H, m), 8.04-7.99 (1H, m), 7.95-7.79 (4H, m), 6.48 (1H, s), 5.24-4.95 (2H, m), 3.80-3.60 (7H, m), 3.44-3.18 (10H, m), 2.67 (3H, s), 2.07 (3H, s).

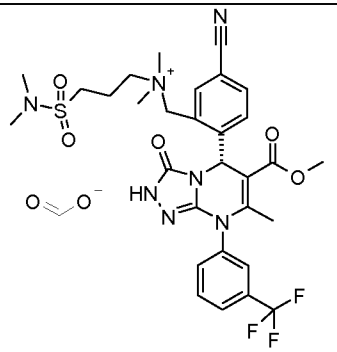
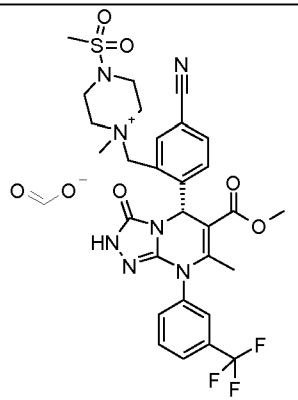
(continued)

101		{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethylcarbamoylmethyl-dimethyl-ammonium formate	Rt = 3.44 min, m/z = 598.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.57 (1H, bs), 8.39 (1.8 H, s, formate), 8.16-8.08 (2H, m), 8.04-7.99 (1H, m), 7.96-7.78 (4H, m), 6.42 (1H, s), 5.51-5.23 (2H, m), 4.79-4.56 (2H, m), 3.53 (3H, s), 3.41 (3H, s), 3.34 (3H, s), 3.00 (3H, s), 2.94 (3H, s), 2.06 (3H, s).
102		{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(1-methanesulfonyl-piperidin-4-yl)-dimethyl-ammonium formate	Rt = 3.46 min, m/z = 674.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.58 (1H, bs), 8.45 (1.5 H, s, formate), 8.15-8.06 (2H, m), 8.05-7.99 (1H, m), 7.96-7.79 (4H, m), 6.37 (1H, s), 5.27-4.81 (2H, m), 3.98-3.79 (3H, m), 3.54 (3H, s, obscured), 3.22 (3H, s), 3.09 (3H, s), 2.91 (3H, s), 2.92-2.80 (2H, m), 2.48-2.39 (2H, m), 2.09 (3H, s), 2.07-1.91 (2H, m).

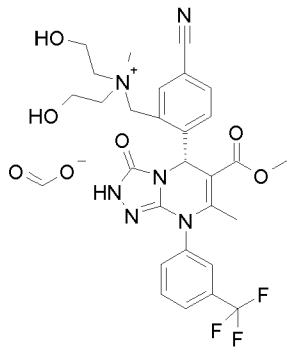
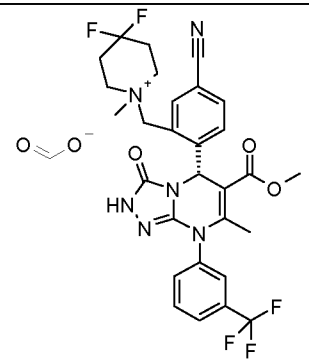
(continued)

103*		{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-oxetan-3-ylmethyl-ammonium formate	Rt = 3.32 min, m/z = 583.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.60 (1H, bs), 8.50 (1.2 H, s, formate), 8.14-8.06 (2H, m), 8.04-7.99 (1H, m), 7.95-7.78 (4H, m), 6.50 (1H, s), 5.13-4.87 (2H, m), 4.77-4.66 (2H, m), 4.59-4.50 (2H, m), 3.98-3.74 (3H, s), 3.54 (3H, s), 3.15 (3H, s), 3.11 (3H, s), 2.07 (3H, s).
104*		{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-(3-methylcarbamoyl-propyl)-ammonium formate	Rt = 3.28 min, m/z = 612.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.42 (1H, bs), 8.38 (1.5H, s, formate), 8.09-8.07 (1H, m), 8.05 (1H, bs), 7.99-7.94 (1H, m), 7.90-7.74 (5H, m), 6.42 (1H, s), 5.08-4.88 (2H, m), 3.52-3.46 (5H, m, obscured), 3.16 (3H, s), 3.11 (3H, s), 2.55 (3H, d, J 4.5 Hz), 2.20-2.14 (2H, m), 2.08-1.99 (5H, m).

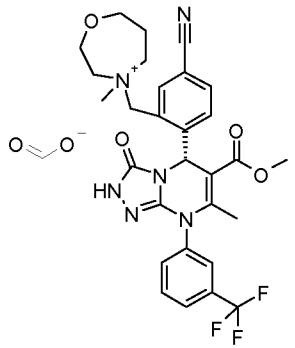
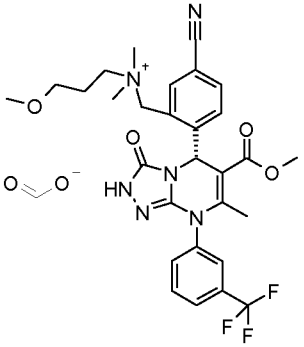
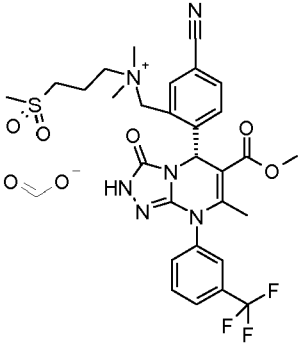
(continued)

105*		{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(3-dimethylsulfamoyl-propyl)-dimethyl-ammonium formate	Rt = 3.52 min, m/z = 662.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.50 (1H, bs), 8.44 (1.5H, s, formate), 8.13-8.08 (2H, m), 8.05-8.00 (1H, m), 7.95-7.79 (4H, m), 6.48 (1H, s), 5.18-4.98 (2H, m), 3.68-3.60 (2H, m), 3.54 (3H, s), 3.25 (3H, s), 3.22 (3H, s), 3.15 (2H, t, J = 7.5 Hz), 2.81 (6H, s), 2.28-2.17 (2H, m), 2.07 (3H, s).
106		1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methanesulfonyl-1-methyl-piperazin-1-ium formate	Rt = 3.40 min, m/z = 646.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.62 (1H, bs), 8.45 (1.4H, s, formate), 8.14-8.07 (2H, m), 8.06-8.01 (1H, m), 7.95-7.79 (4H, m), 6.55 (1H, s), 5.28-5.09 (2H, m), 3.96-3.84 (2H, m), 3.80-3.66 (4H, m, obscured), 3.57-3.43 (2H, m, obscured), 3.54 (3H, s), 3.27 (3H, s), 3.05 (3H, s), 2.07 (3H, s).

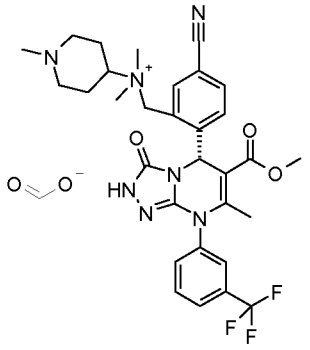
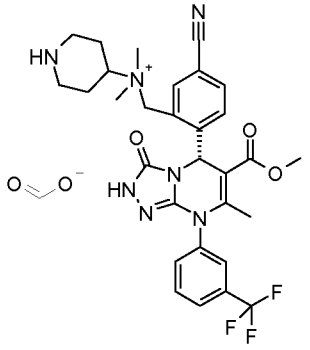
(continued)

107		5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-bis-(2-hydroxy-ethyl)-methyl-ammonium formate	Rt = 3.26 min, m/z = 587.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.52 (1H, bs), 8.49 (1.2H, s, formate), 8.24-8.18 (1H, m), 8.11 (1H, bs), 8.03-7.98 (1H, m), 7.95-7.78 (4H, m), 6.50 (1H, s), 5.31-5.16 (2H, m), 4.06-3.79 (6H, m), 3.72-3.62 (2H, m), 3.53 (3H, s), 3.23 (3H, s), 2.05 (3H, s).
108		1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4,4-difluoro-1-methyl-piperidinium formate	Rt = 3.52 min, m/z = 603.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.59 (1H, bs), 8.41 (1.7H, s, formate), 8.14-8.08 (2H, m), 8.06-8.01 (1H, m), 7.95-7.79 (4H, m), 6.55 (1H, s), 5.28-5.11 (2H, m), 3.94-3.73 (5H, m, obscured), 3.54 (3H, s), 3.27 (3H, s), 2.67-2.54 (1H, m), 2.46-2.35 (2H, m), 2.06 (3H, s). (98007)

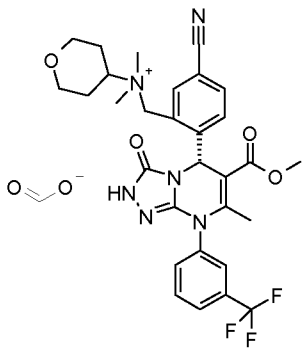
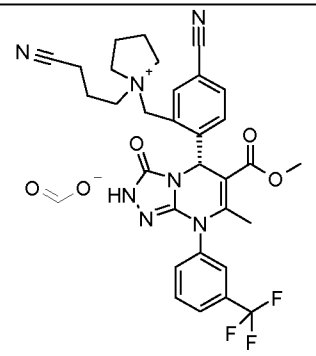
(continued)

109*		4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methyl-[1,4]oxazepan-4-ium formate	Rt = 3.37 min, m/z = 583.4 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11. 25 (1H, very bs), 8.43 (1.4H, s, formate), 8.14 (1H, d, J = 1.3 Hz), 8.11 (1H, bs), 8.05-8.01 (1H, m), 7.95-7.79 (4H, m), 6.46 (1H, s), 5.22-5.05 (2H, m), 4.09-3.87 (4H, m), 3.82-3.63 (4H, m), 3.54 (3H, d, J = 2.8 Hz), 3.25 (3H, m), 2.31-2.19 (1H, m), 2.15-2.10 (1H, m), 2.06 (3H, d, J 1.9).
110		{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(3-methoxy-propyl)-dimethyl-ammonium formate	Rt = 3.49 min, m/z = 585.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.61 (1H, bs), 8.44 (1.4H, s, formate), 8.12 (1H, d, J = 1.6 Hz), 8.11 (1H, bs), 8.02 (1H, dd, J = 8.3, 1.8 Hz), 7.95-7.78 (4H, m), 6.47 (1H, s), 5.13 (1H, d, J = 14.2 Hz), 4.96 (1H, d, J = 14.2 Hz), 3.66-3.59 (2H, m), 3.53 (3H, s), 3.47 (2H, t, J = 5.7 Hz), 3.30 (3H, s), 3.21 (3H, s), 3.16 (3H, s), 2.19-2.09 (2H, m), 2.07 (3H, s).
111*		{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(3-methanesulfonyl-propyl)-dimethyl-ammonium formate	Rt = 3.36 min, m/z = 633.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.63 (1H, bs), 8.53 (1H, s, formate), 8.12 (1H, d, J = 1.6 Hz), 8.11 (1H, bs), 8.03 (1H, dd, J = 8.2, 1.6 Hz), 7.95-7.79 (4H, m), 6.49 (1H, s), 5.15 (1H, d, J = 14 Hz), 5.04 (1H, d, J = 14 Hz), 3.69-3.61 (2H, m), 3.55 (3H, s), 3.28-3.19 (8H, m), 3.06 (3H, s), 2.35-2.22 (2H, m), 2.07 (3H, s).

(continued)

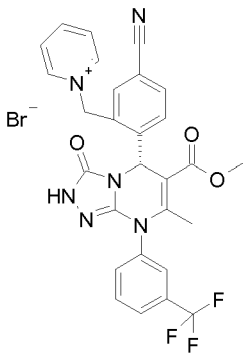
112		{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-(1-methyl-piperidin-4-yl)-ammonium formate	Rt = 2.76 min, m/z = 610.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.47 (1H, bs), 8.37 (2H, s, formate), 8.11 (1H, d, J = 1.7 Hz), 8.09 (1H, bs), 8.02 (1H, dd, J = 8.2, 1.7 Hz), 7.95-7.91 (1H, m), 7.90-7.74 (3H, m), 6.36 (1H, s), 5.18 (1H, d, J = 14.2 Hz), 4.86 (1H, d, J = 14.2 Hz), 3.76-3.66 (2H, m), 3.53 (3H, s), 3.18 (3H, s), 3.09-2.99 (2H, m), 3.05 (3H, s), 2.31-2.24 (2H, m), 2.22 (3H, s), 2.09 (3H, s), 2.04-1.87 (3H, m).
113		{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-piperidin-4-yl-ammonium formate	Rt = 2.79 min, m/z = 596.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.48 (1H, bs), 8.35 (2H, s, formate), 8.12 (1H, d, J = 1.6 Hz), 8.09 (1H, bs), 8.02 (1H, dd, J = 8.2, 1.7 Hz), 7.95-7.91 (1H, m), 7.90-7.79 (3H, m), 6.36 (1H, s), 5.13 (1H, d, J = 14.3 Hz), 4.85 (1H, d, J = 14.3 Hz), 3.85-3.75 (3H, m, obscured), 3.53 (2H, s, obscured), 3.24-3.17 (2H, m), 3.15 (3H, s), 3.03 (3H, s), 2.60-2.53 (2H, m, obscured), 2.29-2.20 (2H, m), 2.09 (3H, s), 1.82-1.65 (2H, m).

(continued)

114		{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium formate	Rt = 3.41 min, m/z = 597.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.56 (1H, bs), 8.42 (1.5H, s, formate), 8.13 (1H, d, J = 1.8 Hz), 8.09 (1H, bs), 8.03 (1H, dd, J = 8.4, 1.8 Hz), 7.95-7.91 (1H, m), 7.90-7.79 (3H, m), 6.37 (1H, s), 5.18 (1H, d, J = 14.2 Hz), 4.87 (1H, d, J = 14.0 Hz), 4.17-4.09 (2H, m), 4.06-3.97 (1H, m), 3.54 (3H, s), 3.42 (2H, t, J = 11.6 Hz), 3.19 (3H, s), 3.05 (3H, s), 2.25 (2H, t, J = 11 Hz), 2.09 (3H, s), 2.05-1.89 (2H, m).
115		1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-1-(3-cyano-propyl)-pyrrolidinium formate	Rt = 3.52 min, m/z = 606.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.50 (1H, bs), 8.44 (1.4H, s, formate), 8.14-8.06 (2H, m), 8.02-7.97 (1H, m), 7.95-7.79 (4H, m), 6.35 (1H, s), 5.21-5.07 (2H, m), 3.93-3.75 (4H, m), 3.62-3.53 (5H, m, obscured), 2.66 (2H, t, J 7.3 Hz), 2.29-2.14 (2H, m), 2.12-2.02 (7H, s).

* = for tertiary amine preparations see Intermediates 27-32.

Example 116



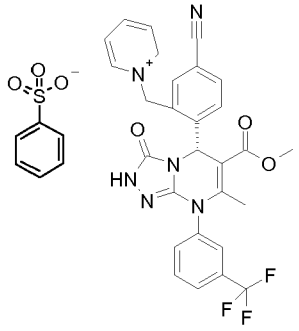
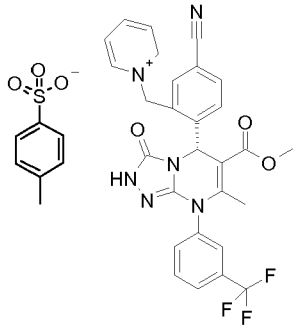
1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-pyridinium bromide

A solution of Intermediate 14 (1.30 g, 2.37 mmol) in MeCN (10 mL) was treated with pyridine (1.91 mL, 23.72 mmol) and warmed to 50°C for 3 h. The resultant mixture was concentrated *in vacuo* and the crude product partitioned between water (30 mL) and EtOAc (25 mL) and the aqueous layer separated and lyophilised to give the desired product as a white electrostatic solid.

LC-MS (Method 3):Rt = 3.42 min, m/z = 547.2 $[M]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.39 (1H, bs), 9.35 (2H, d, J = 6.4 Hz), 8.69 (1H, t, J = 7.8 Hz), 8.24 (2H, m), 8.18 (1H, bs), 8.04-7.89 (3H, m), 7.88-7.79 (2H, m), 7.79-7.75 (1H, m), 6.56 (1H, d, J = 15.3 Hz), 6.42 (1H, s), 6.14 (1H, d, J = 15.1 Hz), 3.55 (3H, s) and 2.18 (3H, s).

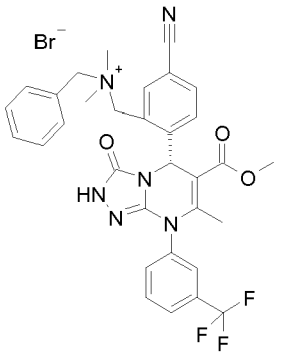
The following compounds were prepared from Intermediate 14 using an analogous method to that used for Example 116, utilising an appropriate acid to prepare the desired IRA-458 resin (see Example 42 for the quat exchange method), and gave the desired compounds as a white electrostatic solids:

Ex	Structure	Name	LC-MS (Method 3)	NMR
117		1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-pyridinium benzenesulphonate	Rt = 3.40 min, m/z = 547.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.40 (1H, bs), 9.35 (2H, d, J = 6.6 Hz), 8.69 (1H, t, J = 7.8 Hz), 8.26-8.21 (2H, m), 8.17 (1H, bs), 8.00-7.89 (3H, m), 7.88-7.79 (2H, m), 7.78-7.74 (1H, m), 7.62-7.57 (2H, m, besylate), 7.34-7.27 (3H, m, besylate), 6.56 (1H, d, J = 15.1 Hz), 6.42 (1H, s), 6.13 (1H, d, J = 15.1 Hz), 3.54 (3H, s) and 2.18 (3H, s).
118		1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-pyridinium tosylate	Rt = 3.43 min, m/z = 547.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.39 (1H, bs), 9.34 (2H, d, J = 6.7 Hz), 8.69 (1H, t, J = 7.8 Hz), 8.26-8.20 (2H, m), 8.17 (1H, bs), 8.00-7.89 (3H, m), 7.88-7.79 (2H, m), 7.78-7.74 (1H, m), 7.47 (2H, d, J = 8.1 Hz, tosylate), 7.11 (2H, d, J = 8.1 Hz, tosylate), 6.56 (1H, d, J = 15.2 Hz), 6.42 (1H, s), 6.13 (1H, d, J = 15.2 Hz), 3.54 (3H, s), 2.29 (3H, s) and 2.18 (3H, s).

(continued)

119		1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-pyridinium chloride	Rt = 3.42 min, m/z = 547.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.41 (1H, bs), 9.36 (2H, d, J = 6.3 Hz), 8.68 (1H, tt, J = 7.8, 1.3 Hz), 8.24 (2H, dd, J = 7.6, 6.7 Hz), 8.16 (1H, bs), 7.96-7.90 (3H, m), 7.83 (2H, t, J = 7.8 Hz), 7.70 (1H, d, J = 1.5 Hz), 6.56 (1H, d, AB-system, J = 15.2 Hz), 6.42 (1H, s), 6.15 (1H, d, AB-system, J = 15.1 Hz), 3.54 (3H, s), 2.18 (3H, s).

Example 120



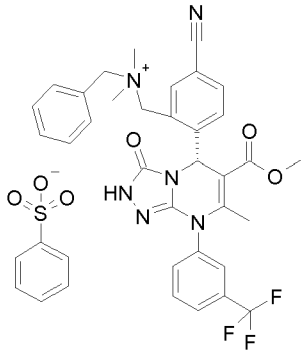
Benzyl-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-ammonium bromide

N-benzyl dimethylamine (1.80 mL, 12.0 mmol) was added to a solution of Intermediate 14 (1.26 g, 2.36 mmol) in MeCN (8 mL) and toluene (4 mL) contained in a large microwave vial. This was sealed and heated at 50°C with stirring for 21 h. Solvents were removed *in vacuo* and the resultant green residue triturated with Et_2O. The organics were decanted off and the residue slurried in EtOAc (50 mL) for 1 h then filtered and dried *in vacuo* to afford an off-white solid. The resultant solid was partitioned between water and a [1:1] mixture of EtOAc/Et_2O and the hazy aqueous phase was separated, purged with a stream of air to remove volatile solvent residues. MeCN (25 mL) was added and the resulting solution was lyophilised to afford the title compound as a cream coloured electrostatic solid (0.66 g).

LC-MS (Method 3):Rt = 3.72 min, m/z = 603.4 $[M]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.36 (1H, bs), 8.17 (1H, d, J = 1.6 Hz), 8.11 (1H, bs), 8.04 (1H, dd, J = 1.6, 8.3 Hz), 7.95-7.85 (3H, m), 7.84-7.78 (1H, m), 7.66-7.60 (2H, m), 7.58-7.51 (3H, m), 6.50 (1H, s), 5.27 (1H, d, J = 14.5 Hz), 5.03 (1H, d, J = 14.1 Hz), 4.87 (1H, d, J = 12.4 Hz), 4.75 (1H, d, J = 12.4 Hz), 3.50 (3H, s) 3.14 (3H, s), 3.12 (3H, s) and 2.08 (3H, s).

Example 121



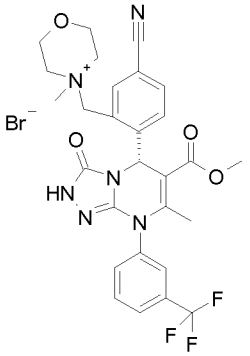
Benzyl-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-ammonium benzenesulfonate

The title compound was prepared from Example 120 (0.53 g, 0.77 mmol) using an analogous method to that used for Example 42 and gave the desired compound as a white electrostatic solid. This was suspended in water (5.0 mL) with warming at 45°C, then cooled to RT, filtered and dried *in vacuo* to afford the title compound as a white solid (0.32 g).

LC-MS (Method 3):Rt = 3.69 min, m/z = 603.2 $[M]^+$

^{1}H NMR (400 MHz, DMSO) δ 11.36 (1H, bs), 8.17 (1H, d, J = 1.6 Hz), 8.10 (1H, bs), 8.04 (1H, dd, J = 1.6, 8.3 Hz), 7.95-7.85 (3H, m), 7.84-7.78 (1H, m), 7.66-7.51 (7H, m), 7.34-7.26 (3H, m), 6.49 (1H, s), 5.26 (1H, d, J = 14.5 Hz), 5.02 (1H, d, J = 14.1 Hz), 4.86 (1H, d, J = 12.4 Hz), 4.74 (1H, d, J = 12.4 Hz), 3.50 (3H, s) 3.14 (3H, s), 3.11 (3H, s) and 2.08 (3H, s).

Example 122



4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-

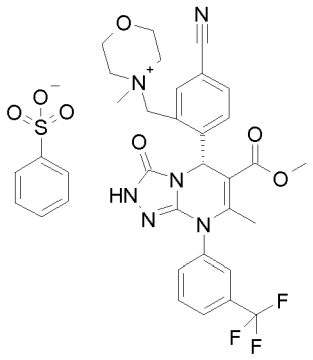
phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methyl-morpholin-4-ium bromide

The title compound was prepared from Intermediate 14 (1.20 g, 2.19 mmol) using an analogous method to that used for Example 120. The semi-pure solid product was further stirred in EtOAc (30 mL) at 40°C for 2 h and sonicated for 5 min. The resultant solid was filtered to give a beige cake, which was dissolved in MeCN/H_2O (10 mL) and lyophilised to give the title compound as an off-white electrostatic solid (0.43 g).

LC-MS (Method 3): Rt = 3.33 min, m/z = 569.2 [M]+

1H NMR (400 MHz, DMSO-D_6) δ 11.36 (1H, s), 8.15-8.08 (2H, m), 8.04 (1H, dd, J = 8.2, 1.7 Hz), 7.95-7.79 (4H, m), 6.55 (1H, s), 5.24 (1H, d J = 14.1 Hz), 5.11 (1H, d, J = 14.1 Hz), 4.10-3.92 (4H, m), 3.91-3.79 (2H, m), 3.64-3.54 (2H, m, obscured),3.54 (3H, s), 3.28 (3H, s) and 2.07 (3H, s).

Example 123



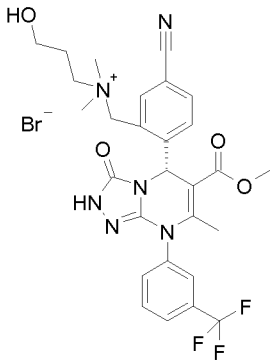
4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methyl-morpholin-4-ium bromide

The title compound was prepared from Example 122 (0.47 g, 0.72 mmol) using an analogous method to that used for Example 42. The semi-pure solid product was further purified by HPLC (System 1) and was then lyophilised to give the title compound as a white electrostatic solid (0.23 g).

LC-MS (Method 3): Rt = 3.33 min, m/z = 569.2 [M]+

1H NMR (400 MHz, DMSO-D_6) δ 11.36 (1H, s), 8.14-8.08 (2H, m), 8.03 (1H, dd, J = 8.2, 1.8 Hz), 7.95-7.78 (4H, m), 7.62-7.57 (2H, m, besylate), 7.34-7.27 (3H, m, besylate), 6.54 (1H, s), 5.22 (1H, d J = 14.2 Hz), 5.10 (1H, d, J = 14.2 Hz), 4.09-3.91 (4H, m), 3.91-3.79 (2H, m), 3.64-3.54 (2H, m, obscured), 3.54 (3H, s), 3.27 (3H, s) and 2.07 (3H, s).

Example 124



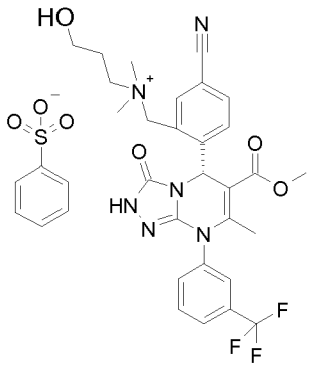
4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methyl-morpholin-4-ium bromide

The title compound was prepared from Intermediate 14 (0.76 g, 1.38 mmol) using an analogous method to that used for Example 120. A C_{18} Isolute cartridge (50 g) was pre-conditioned by elution with MeCN (150 mL) followed by 75%-0.5% MeCN in 0.01M aqueous HBr (100 mL). The crude product (650 mg) was dissolved in 0.5% MeCN: 0.01M HBr (10 mL), loaded onto the cartridge and eluted from 0.5%-40% MeCN in 0.01M aqueous HBr. The title compound was obtained as an electrostatic solid following lyophilisation (0.42 g).

LC-MS (Method 3): Rt = 3.26 min, m/z = 571.2 [M]+

1H NMR (400 MHz, DMSO-D_6) δ 11.36 (1H, bs), 8.14 (1H, d, J = 1.6 Hz), 8.11 (1H, bs), 8.02 (1H, dd, J = 8.1, 1.5 Hz). 7.95-7.78 (4H, m), 6.49 (1H, s), 5.12 (1H, d, J = 14.0 Hz), 4.97 (1H, d, J = 14.0 Hz), 3.68-3.60 (2H, m), 3.59-3.53 (2H, m, obscured), 3.53 (3H, s), 3.22 (3H, s), 3.17 (3H, s), 2.07 (3H, s) and 2.07-1.97 (2H, m), OH not observed.

Example 125



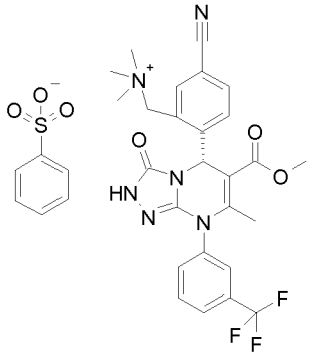
4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methyl-morpholin-4-ium bromide

The title compound was prepared from Example 124 (0.72 g, 1.31 mmol) using an analogous method to that used for Example 42. The semi-pure solid product was further purified by HPLC (System 1) and was then lyophilised to give the title compound as a white electrostatic solid (0.23 g).

LC-MS (Method 3): Rt = 3.27 min, m/z = 571.3 [M]+

1H NMR (400 MHz, DMSO-D_6) δ 11.36 (1H, bs), 8.12 (1H, d, J = 1.6 Hz), 8.10 (1H, bs), 8.02 (1H, dd, J = 8.2, 1.6 Hz). 7.95-7.78 (4H, m), 7.62-7.57 (2H, m, besylate), 7.34-7.27 (3H, m, besylate), 6.48 (1H, s), 5.11 (1H, d, J = 14.0 Hz), 4.96 (1H, d, J = 14.0 Hz), 4.85 (1H, bs), 3.68-3.60 (2H, m), 3.59-3.53 (2H, m, obscurred), 3.53 (3H, s), 3.21 (3H, s), 3.16 (3H, s), 2.07 (3H, s) and 2.07-1.97 (2H, m).

Example 126



{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-trimethyl-

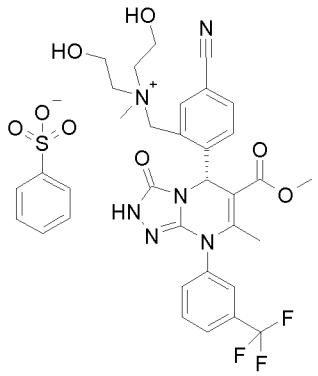
ammonium benzenesulfonate

The title compound was prepared from Example 9 (0.85 g, 1.37 mmol) using an analogous method to that used for Example 42. The semi-pure solid product was further purified by HPLC (System 1) and was then lyophilised to give the title compound as a white electrostatic solid (0.90 g).

LC-MS (Method 3): Rt = 3.27 min, m/z = 571.3 [M]+

1H NMR (400 MHz, DMSO-D_6) δ 11.36 (1H, bs), 8.12 (1H, d, J = 1.6 Hz), 8.10 (1H, bs), 8.02 (1H, dd, J = 8.2, 1.6 Hz). 7.95-7.78 (4H, m), 7.62-7.57 (2H, m, besylate), 7.34-7.27 (3H, m, besylate), 6.48 (1H, s), 5.11 (1H, d, J = 14.0 Hz), 4.96 (1H, d, J = 14.0 Hz), 4.85 (1H, bs), 3.68-3.60 (2H, m), 3.59-3.53 (2H, m, obscured), 3.53 (3H, s), 3.21 (3H, s), 3.16 (3H, s), 2.07 (3H, s) and 2.07-1.97 (2H, m).

Example 127



{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-bis-(2-hydroxy-ethyl)-methyl-ammonium benzenesulfonate

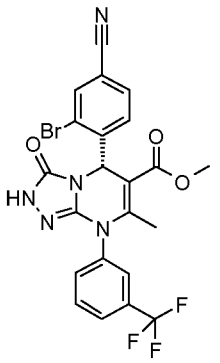
The title compound was prepared from Example 107 (0.60 g, 0.95 mmol) using an analogous method to that used for Example 42 and gave the title compound as a white electrostatic solid (0.54 g).

LC-MS (Method 3): Rt = 3.28 min, m/z = 587.2 $[M]^+$

1H NMR (400 MHz, DMSO-D_6) δ 1H NMR (400 MHz, DMSO) δ 11.36 (1H, bs), 8.23-8.18 (1H, m), 8.11 (1H, bs), 8.03-7.98 (1H, m), 7.95-7.78 (4H, m), 7.61-7.56 (2H, m, besylate), 7.34-7.27 (3H, m, besylate), 6.50 (1H, s), 5.47-5.39 (2H, m, 2 x OH), 5.30-

5.13 (2H, m), 4.06-3.79 (6H, m), 3.72-3.62 (2H, m), 3.53 (3H, s), 3.23 (3H, s), 2.05 (3H, s).

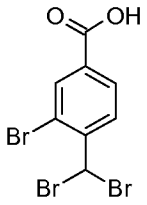
Route B to Intermediate 4b



(4b)

(S)-5-(2-Bromo-4-cyanophenyl)-7-methyl-3-oxo-8-(3-trifluoromethylphenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester

Intermediate 33



3-Bromo-4-dibromomethylbenzoic acid

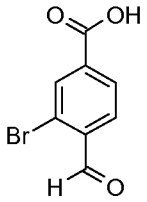
3-Bromo-4-methylbenzoic acid (910 g, 4.23 mol, 1.0 eq.) and NBS (2010 g, 11.29 mol, 2.67 eq.) were dissolved in DCM (8.5 L) in a 20 L flange flask fitted with a mechanical stirrer. A slurry of AIBN (50 g, 0.3 mol, 0.07 eq.) in DCM (1 L) was then added, and the mixture irradiated under strong light (500W) under a reflux condenser under an N_2 atmosphere. The internal temperature of the reaction rose from 17°C to 41°C and the initial white suspension became a pale orange suspension as it reached gentle reflux. After a total of 72 h. the reaction was complete and water (5 L) was added to the cloudy orange solution, which was stirred at RT for 1 h. The orange biphasic mixture was then left to stand overnight and was then concentrated *in vacuo* to give an orange distillate and a tan suspended solid. The solid was then collected by filtration, washed with water

(2 L) and suction dried for 2 h to give the title compound as a tan coloured damp solid (1860 g).

LCMS (Method 1):Rt = 3.39 min, m/z 369, 371, 373, 375 [M-H]

^{1}H NMR (300 MHz, DMSO): δ 8.14-8.03 (3H, m), 7.36 (1H, s).

Intermediate 34



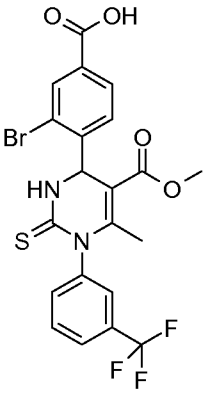
3-Bromo-4-formylbenzoic acid

Intermediate 33 (1860 g, 4.23 mol, 1.0 eq.) was suspended in water (5 L) and the slurry was heated to an internal temperature of 40°C. Solid Na_2CO_3 (1460 g, 13.77 mol, 3.25 eq.) was then added in small portions over a period of 20 min. Foaming resulted on initial addition, so EtOAc (0.2 L) was added to collapse the foam and suppress any further foaming. Once addition was complete, the brown suspension was heated to 90°C over 40 min, then stirred at 90°C for 90 min, then cooled to 40°C over 90 min. EtOAc (1.5 L) was added, followed by addition of aqueous concentrated HCl via dropping funnel (0.7 L), resulting in vigorous evolution of CO_2 gas and evaporation of most of the EtOAc. Further EtOAc (1 L) was added to wash the foaming product from the condenser and the walls of the reactor, then additional EtOAc (0.3 L) was added and the thick slurry was stirred at RT overnight. The slurry was then heated to 40°C and further aqueous concentrated HCl was added via dropping funnel with vigorous stirring over 45 min, resulting in CO_2 gas evolution, evaporation of most of the EtOAc and formation of a solid. Stirring was ceased, and the solid floated to the top of the aqueous mixture (pH 1). The majority of the aqueous layer was separated (*ca.* 5 L) and then 2-MeTHF (5 L) was added. The clear aqueous layer was then removed, and the organic layer diluted to 10 L with additional 2-MeTHF, and warmed to 50°C to give a dark orange solution. The organic layer was then washed with 1 M HCl (0.5 L), evaporated, and azeotroped with toluene to afford the title compound as a tan coloured solid (960.3 g).

LCMS (Method 4):Rt 2.73 min, m/z 227, 229 [M-H]

^{1}H NMR (300 MHz, DMSO): δ 10.26 (1H, d, J = 0.8 Hz), 8.20 (1H, d, J = 1.5 Hz), 8.08-8.04 (1H, m), 7.95 (1H, d, J = 8.0 Hz).

Intermediate 35



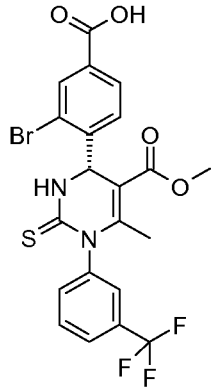
4-(2-Bromo-4-carboxyphenyl)-6-methyl-2-thioxo-1-(3-trifluoromethylphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

Intermediate 34 (458 g, 2 mol, 1.0 eq.), methyl acetoacetate (274.4 g, 255 mL, 2.36 mol, 1.18 eq.) and 3-trifluoromethylphenyl thiourea (519 g, 2.36 mol, 1.18 eq.), were charged to a 10 L jacketed reactor under a N_2 atmosphere, and suspended in THF (4.6 L) and while stirring, was cooled to -10°C (internal temperature -3°C). Polyphosphoric acid (1650 g, 3.6 wt eq.), was prewarmed in a water bath at 50°C, then added in one portion, resulting in an immediate exotherm, and the internal temperature rose to 19°C. The resulting orange mixture was then warmed to 75°C in 10°C increments to a gentle reflux, and the reaction stirred at this temperature for 20 h. The reaction was then cooled to 20°C and the bulk of THF removed *in vacuo* to give a dark orange viscous oil, which was then diluted with water (5 L) and Et_2O (5 L). The aqueous layer was separated and extracted again with Et_2O (2 x 2 L) and the combined organics were subsequently washed with water (1 L), brine (1 L) and dried (Na_2SO_4) and filtered through Celite to remove any fine particulates. The filtered solution was then concentrated *in vacuo* to give a viscous orange gum which was resuspended in Et_2O (ca. 1.5 L) and left to stand overnight. The resulting suspension was filtered and the solid collected was rinsed with Et_2O (0.5 L) and dried in a vacuum oven at 50°C (8 mbar) for 4 days to afford the title compound (754 g).

LCMS (Method 1):Rt 3.52 min, m/z 529, 531 $[M+H]^+$

^1H NMR (300 MHz, DMSO): δ 10.15 (1H, d, J = 3.5 Hz), 8.11 (1H, d, J = 1.6 Hz), 8.05 (1H, dd, J = 8.1, 1.7 Hz), 7.92-7.64 (5H, m), 5.80 (1H, d, J = 2.9 Hz), 3.53 (3H, s), 2.07 (3H, s).

Intermediate 36



(S)-4-(2-Bromo-4-carboxy-phenyl)-6-methyl-2-thioxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester

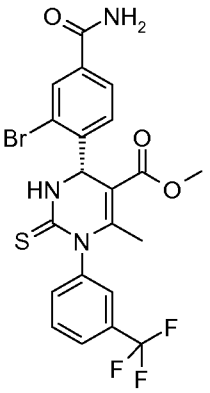
Intermediate 35 (151.7 g, 0.29 mol, 1.0 eq.) was dissolved in dioxane (2 L) and heated to 80°C. The resulting suspension was filtered to remove any inorganic residues and the clear solution was again heated to 80°C and (+)-Cinchonine (88 g, 0.29 mol, 1.0 eq,) was added, resulting in a clear solution. The resultant mixture was allowed to cool slowly and crystallise. After 3 h, the resulting solid was filtered and washed with cold dioxane. The solid was resuspended in hot dioxane (85°C) and allowed to cool and crystallise overnight. The resulting crystals were filtered off, washed with cold dioxane, and the solid recrystallised again from hot dioxane. The final recrystallization solids were filtered off and air-dried to give the intermediate (+)-Cinchonine salt as a white solid 83.2 g (68%).

The optical purity of the resolved (+)-Cinchonine salt was determined by partitioning between 1 M HCl and EtOAc; the organic layer was separated, concentrated *in vacuo* and then redissolved in 20% IPA / n-heptane with 0.1% TFA and subjected to chiral analytical HPLC (ChiralPak IA, 5 μM 4.6 x 250 mm), eluting with 20% IPA/n-heptane (+ 0.1% TFA) at 1 mL/min and a wavelength of 254 nm. The racemic product

was also checked by chiral HPLC; Retention times of 14.8 and 42.5 mins were observed for a racemic sample and the desired enantiomer was eluted at 42.5 mins and was found to be greater than 99.5ee%.

The intermediate (+)-Cinchonine salt (83.2 g, 101.75 mmol) was liberated by partitioning between EtOAc (1 L) and 1 M HCl (1 L). The aqueous layer was extracted again with EtOAc (2 x 0.5 L) and the combined organic layers washed with 1 M HCl (0.5 L), then brine (0.25 L), dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as a white solid (45.45 g).

Intermediate 37



(S)-4-(2-Bromo-4-carbamoyl-phenyl)-6-methyl-2-thioxo-1-(3-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester

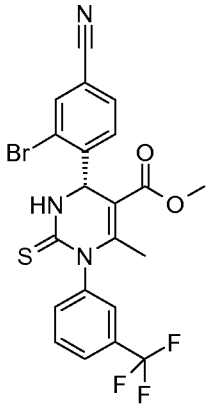
Intermediate 36 (93.8 g, 0.18 mol) was dissolved in THF (1 L) and 1,1'-carbonyldiimidazole (57.5 g, 0.35 mol, 2.0 eq.) was added portion-wise and left to stir at RT until gas evolution had ceased. Aqueous ammonia solution (33%, 330 mL) was then added drop-wise, ensuring the internal temperature did not exceed 10°C (exotherm observed on initial addition). The reaction was left to stir at RT for 2 h, then brine was added and the layers were separated. The organic phase was washed with aqueous 1 M HCl (2 x) and the acidic layer further extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound as a colourless foam (87.3 g).

LCMS (Method 2):Rt 3.44 min, m/z 528, 530 $[M+H]^+$

^1H NMR (300 MHz, DMSO): δ 10.12 (1H, d, J = 2.6 Hz), 8.12 (1H, s), 8.11 (1H, d, J =

1.7 Hz), 7.96 (1H, dd, J = 8.1, 1.7 Hz), 7.88-7.77 (2H, m), 7.75-7.63 (3H, m), 7.54 (1H, s), 5.78 (1H, s), 3.54 (3H, s), 2.07 (3H, s).

Intermediate 38



(S)-4-(2-Bromo-4-cyanophenyl)-6-methyl-2-thioxo-1-(3-trifluoromethylphenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester

Intermediate 37 (87.3 g, 0.165 mol) was dissolved in DMF (400 mL) and cooled to 0-5°C in an ice bath. Phosphorous oxychloride (62.0 g, 37.0 mL, 2.5 eq.) was then added drop-wise, ensuring the internal temperature did not exceed 10°C. Once addition was complete, the yellow solution was stirred at 0-5°C for 15 min, then poured into a mixture of solid 2 M Na_2CO_3 and ice. A yellow precipitate formed and the slurry was aged for 1 h, then the solid was filtered, washed with water and dried in a vacuum oven over P_2O_5 at 40-45°C. NMR analysis of the resultant product still showed starting material remaining so the reaction was repeated again using a further 20 mL phosphorous oxychloride. NMR of the resulting solid showed the product to be an adduct with $POCl_3$. Therefore, the solid was dissolved in absolute EtOH (1000 mL) and the suspension warmed to aid dissolution. Saturated aqueous $NaHCO_3$ solution (250 mL) was then added and the mixture was heated to 40°C and stirred for 2 h. The resultant mixture was then poured into water (500 mL) and the resulting white solid filtered off, washed with water and air dried to afford the title compound (77.5 g).

LCMS (Method 2):Rt 3.94 min, m/z 510, 512 $[M+H]^+$

^{1}H NMR (300 MHz, DMSO): δ 10.18 (1H, d, J = 2.7 Hz), 8.24 (1H, d, J = 1.5 Hz), 7.96

(1H, dd, J = 8.0, 1.6 Hz), 7.89-7.76 (3H, m), 7.74-7.64 (2H, m), 5.8 (1H, s), 3.53 (3H, s), 2.06 (3H, s).

(S)-5-(2-Bromo-4-cyanophenyl)-7-methyl-3-oxo-8-(3-trifluoromethylphenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester (Intermediate 4b)

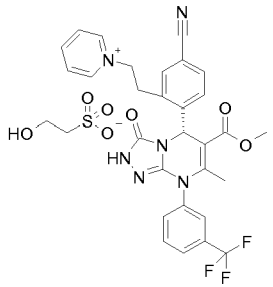
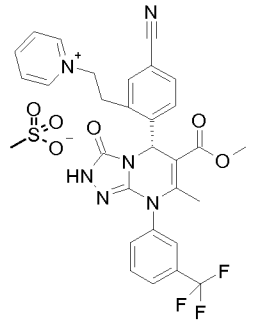
Intermediate 38 (49.8 g, 98 mmol) was dissolved in DCM (830 mL), 2,6-lutidine (32.4 mL, 278 mmol, 2.85 eq.) was added and the solution was cooled to 2°C. While stirring, triphosgene (9.17 g, 30.9 mmol, 0.32 eq) was then added slowly over a period of 3 min. After 5 min, the reaction was warmed to RT and stirred for 25 min. The reaction was cooled to 8°C and the solution was then transferred *via* cannula to a cooled (7°C) mixture of hydrazine solution (1 M in THF, 278 mL) and MeCN (250 mL). The reaction was stirred at 7°C for a further 10 min and then allowed to warm to RT. After 2.25 h, the reaction mixture was washed with water, then with 50% saturated brine and the organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting gum was azeotroped with toluene and triturated with Et_2O (200 mL) to afford a solid which was filtered off, washed with Et_2O and dried to afford the title compound as a cream coloured solid (31.75 g).

LCMS (Method 5):Rt 3.51 min, m/z 534, 536 $[M+H]^+$

^1H NMR (300 MHz, $CDCl_3$): δ 8.36 (1H, s), 7.88 (1H, d, J = 1.5 Hz), 7.83-7.79 (1H, m), 7.73 (1H, t, J = 8.0 Hz), 7.65-7.60 (2H, m), 7.59-7.50 (2H, m), 6.39 (1H, d, J = 1.0 Hz), 3.62 (3H, s), 2.25 (3H, d, J = 1.0 Hz).

The chiral purity was analysed by Chiralpak IC chiral HPLC column (5 μm particle size, 5% MeOH/DCM, flow rate 5 mL/min) and gave Rt = 5.83 min. (100%ee). A racemic sample (Intermediate 4) gave Rt for first and second eluting enantiomers of 3.58 and 5.85 min, respectively.

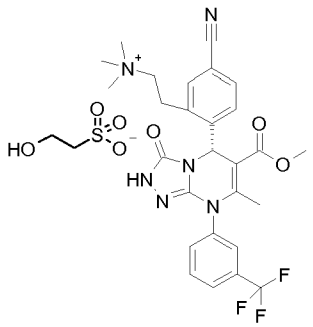
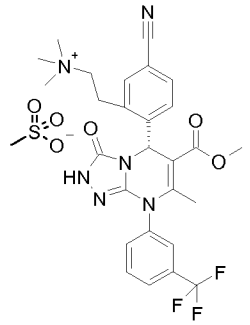
The following compounds were prepared from Example 49 using an analogous method to that used for Example 42, utilising an appropriate acid to prepare the desired IRA-458 resin, and gave the desired compounds as white electrostatic solids:

Ex	Structure	Name	LC-MS (Method 3)	NMR
128		1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-pyridinium 2-hydroxy-ethanesulfonate	Rt = 3.48 min, m/z = 561.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.38 (1H, bs), 9.10 (2H, d, J = 5.6 Hz), 8.67 (1H, t, J = 7.7 Hz), 8.23 (2H, t, J = 7.2 Hz), 8.15 (1H, bs), 7.97-7.87 (2H, m), 7.86-7.80 (1H, m), 7.79-7.70 (2H, m), 7.61 (1H, m), 6.43 (1H, s), 5.26-5.07 (2H, m), 4.45 (1H, t, J = 5.7 Hz), 3.97-3.84 (1H, m), 3.62 (2H, q, J = 6.6 Hz), 3.65-3.52 (1H, m, obscured), 3.49 (3H, s), 2.60 (2H, t, J = 6.8 Hz), 2.16 (3H, s).
129		1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-pyridinium methanesulfonate	Rt = 3.48 min, m/z = 561.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.39 (1H, bs), 9.10 (2H, d, J = 5.5 Hz), 8.67 (1H, t, J = 7.9 Hz), 8.23 (2H, t, J = 7.2 Hz), 8.15 (1H, bs), 7.97-7.87 (2H, m), 7.86-7.80 (1H, m), 7.79-7.70 (2H, m), 7.62 (1H, m), 6.43 (1H, s), 5.25-5.09 (2H, m), 3.97-3.84 (1H, m), 3.65-3.52 (1H, m), 3.49 (3H, s), 2.30 (3H, s), 2.16 (3H, s).

(continued)

130		1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-pyridinium benzenesulfonate	Rt = 3.50 min, m/z = 561.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.39 (1H, bs), 9.10 (2H, d, J = 5.5 Hz), 8.67 (1H, t, J = 7.9 Hz), 8.23 (2H, t, J = 7.2 Hz), 8.15 (1H, bs), 7.97-7.87 (2H, m), 7.86-7.80 (1H, m), 7.79-7.70 (2H, m), 7.62 (1H, m), 7.60-7.55 (2H, m, besylate), 7.35-7.27 (3H, m, besylate), 6.43 (1H, s), 5.25-5.09 (2H, m), 3.97-3.84 (1H, m), 3.65-3.52 (1H, m), 3.49 (3H, s), 2.30 (3H, s), 2.16 (3H, s).

The following compounds (Examples 131 and 132) were prepared from Example 47 and Example 133 was prepared from Example 48, using an analogous method to that used for Example 42, utilising an appropriate acid to prepare the desired IRA-458 resin, and gave the desired compounds as white electrostatic solids:

Ex	Structure	Name	LC-MS (Method 3)	NMR
131		(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-trimethyl-ammonium 2-hydroxy-ethanesulfonate	Rt = 3.48 min, m/z = 561.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.30 (1H, bs), 8.13 (1H, bs), 7.95-7.88 (2H, m), 7.85-7.80 (2H, m), 7.76 (1H, dd, J = 8.1, 1.7 Hz), 7.71 (1H, d, J = 8.1 Hz), 6.26 (1H, s), 4.44 (1H, t, J = 5.7 Hz, isoethionate), 4.01-3.93 (1H, m), 3.78-3.64 (2H, m), 3.62 (2H, dt, J = 6.7, 5.7 Hz, isoethionate), 3.53 (3H, s), 3.45-3.34 (1H, m), 3.21 (9H, s), 2.59 (2H, t, J = 6.7 Hz, isoethionate), 2.16 (3H, s).
132		(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-trimethyl-ammonium methanesulfonate	Rt = 3.48 min, m/z = 561.2 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.30 (1H, bs), 8.13 (1H, bs), 7.95-7.88 (2H, m), 7.85-7.80 (2H, m), 7.76 (1H, dd, J = 8.1, 1.7 Hz), 7.71 (1H, d, J = 8.1 Hz), 6.26 (1H, s), 4.01-3.93 (1H, m), 3.78-3.63 (2H, m), 3.53 (3H, s), 3.43-3.34 (1H, m), 3.21 (9H, s), 2.29, (3H, s, mesylate), 2.16 (3H, s).

(continued)

133		(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-trimethyl-ammonium chloride	Rt = 3.50 min, m/z = 561.3 $[M]^+$	^{1}H NMR (400 MHz, DMSO) δ 11.32 (1H, bs), 8.13 (1H, bs), 7.95-7.88 (2H, m), 7.85-7.80 (2H, m), 7.76 (1H, dd, J = 8.1, 1.7 Hz), 7.71 (1H, d, J = 8.1 Hz), 6.26 (1H, s), 4.02-3.94 (1H, m), 3.79-3.63 (2H, m), 3.53 (3H, s), 3.43-3.36 (1H, m), 3.21 (9H, s), 2.16 (3H, s).

Biological Assay

Compounds of this invention were tested for potency in a human neutrophil elastase (HNE) enzyme activity assay.

HNE Enzyme Assay

Assays were performed in 96-well plates in a total assay volume of 100 µL. The final concentration of elastase enzyme (human leukocyte elastase, Sigma E8140) was 0.00072 U/mL. The peptide substrate (MeOSuc-Ala-Ala-Pro-Val-AMC, Calbiochem #324740) was used at a final concentration of 100 µM. The final concentration of DMSO was 1% in the assay buffer (0.05M Tris.HCl, 0.1M NaCl, 0.1M $CaCl_2$, 0.0005% brij-35, pH 7.5). The enzymatic reaction was started by addition of the enzyme and incubated at 25°C for 30 minutes. After incubation, the reaction was stopped by addition of soybean trypsin inhibitor (Sigma T9003) at a final concentration of 50 µg/well. Fluorescence was measured using a Molecular Devices fluorescence plate reader using 380 nm excitation and 460 nm emission wavelengths.

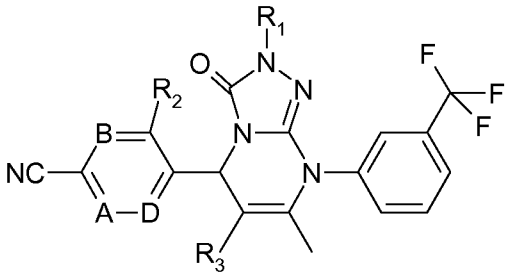
A dose response to each compound was performed and the effect of compound in each experiment was expressed as a percentage inhibition of the control enzyme fluorescence. Dose response curves were plotted and compound potency (IC_{50}) was determined. Compounds were tested in at least two separate experiments.
IC_{50}s for tested Examples, representative of the invention, are shown in the following table:

Example	HNE inhibition
1-15, 17-20, 22, 24-40, 42-133	++++

In the table above, HNE enzyme inhibition (IC_{50} values) are indicated as follows: > 500 nM '+'; 100-500 nM '++'; 20-100 nM '+++'; <20 nM '++++'.

CLAIMS

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

A is CH or N;

B is CH or N;

D is CH or N;

R_1 is selected in the list consisting of:

- hydrogen;
- $(C_1\text{-}C_6)$alkyl;
- $NR_7R_8(C_1\text{-}C_6)$alkyl;
- $(C_1\text{-}C_4)$alkenyl;
- phenyl$(C_1\text{-}C_6)$alkyl wherein such phenyl ring is optionally substituted by a group $NR_{15}R_{16}(C_1\text{-}C_6)$alkyl or by $N^+R_{15}R_{16}R_{17}(C_1\text{-}C_6)$alkyl;
- a group $-CH_2(CH_2)_nOH$;
- a group $-(CH_2)_nCONR_5R_6$;
- a group $-(CH_2)_nSO_2NR_5R_6$;
- a group $-CH_2\text{-}(CH_2)_nNR_5SO_2R_6$;
- a group $-(CH_2)_t\text{-}(C_6H_4)\text{-}SO_2(C_1\text{-}C_4)$alkyl;
- a group $-(CH_2)_rSO_2(C_1\text{-}C_4)$alkyl wherein such $(C_1\text{-}C_4)$alkyl is optionally substituted by a group $-NR_{15}R_{16}$ or $-N^+R_{15}R_{16}R_{17}$;
- a group $-SO_2$-phenyl wherein such phenyl ring is optionally substituted by $NR_7R_8(C_1\text{-}C_6)$alkyl; and

- a group -$(CH_2)_n$-W wherein **W** is a 5-6-membered heteroaryl ring which is optionally substituted by a group -$SO_2(C_1$-$C_4)$alkyl;

n is 1, 2 or 3;

t is zero, 1, 2 or 3;

r is zero, 1, 2 , 3 or 4;

$\mathbf{R_5}$ is selected in the group consisting of: hydrogen, $(C_1$-$C_6)$alkyl, $NR_{16}R_{15}(C_1$-$C_6)$alkyl and $N^+R_{17}R_{15}R_{16}(C_1$-$C_6)$alkyl;

$\mathbf{R_6}$ is hydrogen or $(C_1$-$C_6)$alkyl;

$\mathbf{R_7}$ is selected in the group consisting of: hydrogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylcarbonyl, -$SO_2(C_1$-$C_4)$alkyl and $NR_{16}R_{15}(C_1$-$C_6)$alkyl;

$\mathbf{R_8}$ is hydrogen or $(C_1$-$C_6)$alkyl;

alternatively, $\mathbf{R_7}$ and $\mathbf{R_8}$ together with the nitrogen atom they are linked to may form a $(C_5$-$C_7)$heterocycloalkyl ring system which is optionally substituted by one or more groups $(C_1$-$C_6)$ alkyl and oxo;

$\mathbf{R_{16}}$ is hydrogen or $(C_1$-$C_6)$alkyl;

$\mathbf{R_{15}}$ is hydrogen or $(C_1$-$C_6)$alkyl;

$\mathbf{R_{17}}$ is hydrogen or $(C_1$-$C_6)$alkyl;

$\mathbf{R_3}$ is a group cyano or a group –C(O)-XR_4;

X is a divalent group selected from: -O-, -(CH_2)- and -NH-;

$\mathbf{R_4}$ is a group selected in the list consisting of:

- hydrogen;

-$(C_1$-$C_6)$alkyl;

-a group of formula -[Alk^1]-Z wherein $\mathbf{Alk^1}$ represents a $(C_1$-$C_4)$alkylene radical and **Z** is:

(i) -NR_9R_{10} wherein R_9 and R_{10} are independently hydrogen, $(C_1$-$C_6)$alkyl or $(C_3$-$C_6)$cycloalkyl group, wherein such $(C_1$-$C_6)$alkyl or $(C_3$-$C_6)$cycloalkyl group are optionally substituted by one to four group R_{35} which are at each occurrence independently selected in the group consisting of: $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxyl, hydroxyl, hydroxyl-C_1-C_6-alkyl,

halo, trifluoromethyl, trifluoromethoxy; or, taken together with the nitrogen to which they are attached, form a monocyclic (C_5-C_7)heterocyclic ring which may contain a further heteroatom selected from N, O and S and which is optionally substituted by one to four group R_{35} which are at each occurrence independently selected in the group consisting of: (C_1-C_6)alkyl, (C_1-C_6)alkoxyl, hydroxyl, hydroxyl-C_1-C_6-alkyl, halo, trifluoromethyl, trifluoromethoxy;

or

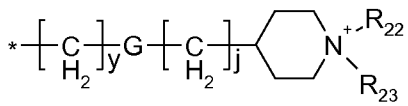
(ii) $-N^+R_{11}R_{12}R_{13}$ wherein R_{11}, R_{12} and R_{13} are each independently (C_1-C_6)alkyl or (C_3-C_6)cycloalkyl group, wherein such (C_1-C_6)alkyl or (C_3-C_6)cycloalkyl group are optionally substituted by one to four group R_{36} which are at each occurrence independently selected in the group consisting of: (C_1-C_6)alkyl, (C_1-C_6)alkoxyl, hydroxyl, hydroxyl-C_1-C_6-alkyl, halo, trifluoromethyl, trifluoromethoxy; or any two of R_{11}, R_{12} and R_{13} taken together with the nitrogen they are linked to form a monocyclic (C_5-C_7)heterocyclic ring which may contain a further heteroatom selected from N, O and S and the other of R_{11}, R_{12} and R_{13} is a (C_1-C_6)alkyl or an optionally substituted (C_3-C_6)cycloalkyl group, wherein such monocyclic (C_5-C_7)heterocyclic, (C_1-C_6)alkyl or (C_3-C_6)cycloalkyl group are optionally substituted by one to four group R_{36} which are at each occurrence independently selected in the group consisting of: (C_1-C_6)alkyl, (C_1-C_6)alkoxyl, hydroxyl, hydroxyl-C_1-C_6-alkyl, halo, trifluoromethyl, trifluoromethoxy;

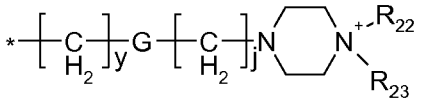
-a radical of formula $-(CH_2)_q$-[Q]–$(CH_2)_p$ Z wherein **Z** is as above defined, q is an integer ranging from zero to 3, p is an integer ranging from zero to 3 and Q represents a divalent group selected from: -O-, phenylene, (C_5-C_7)heterocycloalkylene, (C_3-C_6)cycloalkyl and pyridinylene, wherein such phenylene, (C_5-C_7)heterocycloalkylene, (C_3-C_6)cycloalkyl and pyridinylene are optionally substituted by one to four group R_{37} which are at each occurrence independently selected in the group consisting of: (C_1-C_6)alkyl, (C_1-C_6)alkoxyl, hydroxyl, hydroxyl-C_1-C_6-alkyl, halo, trifluoromethyl, trifluoromethoxy;

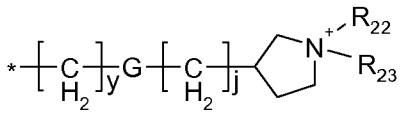
R_2 is selected from a group consisting of:

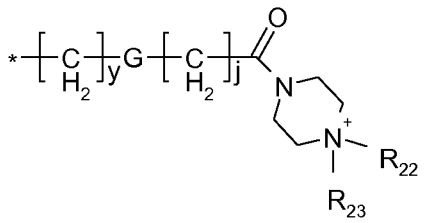
$R_{14}O(C_1\text{-}C_6)$alkyl; $NR_{18}R_{19}(C_1\text{-}C_6)$alkyl; -$CONR_{21}R_{20}$; $C_2\text{-}C_6$-alkenyl which $C_2\text{-}C_6$-alkenyl may be optionally substituted by a group –OH or -$NR_{18}R_{19}$; $C_2\text{-}C_6$-alkynyl which $C_2\text{-}C_6$-alkynyl may be optionally substituted by a group –OH or -$NR_{18}R_{19}$; and a group -$[CH_2]_y$-G-$[CH_2]_j$-CH_2-$N^+R_{22}R_{23}R_{24}$

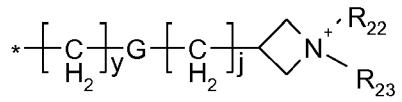
Or **R_2** is a group:



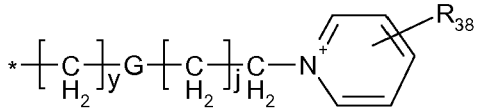








Or **R_2** is a group:



R_{14} is hydrogen or $(C_1\text{-}C_6)$alkyl which may be optionally substituted by a group $(C_1\text{-}C_4)$alkoxyl;

R_{18} is hydrogen or $(C_1\text{-}C_6)$alkyl;

R_{19} is hydrogen or $(C_1\text{-}C_6)$alkyl;

R_{20} is selected in the group consisting of: hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl$NR_{18}R_{19}$;

R_{21} is hydrogen or $(C_1\text{-}C_6)$alkyl;

j is an integer ranging from zero to 4;

y is an integer ranging from zero to 4;

G is a divalent linker selected from the group consisting of: -O-, -(SO_2)-, NR_{25}, a bond, $C_2\text{-}C_6$-alkenylene, $C_2\text{-}C_6$-alkynylene, $(C_3\text{-}C_6)$cycloalkylene, mono or bicyclic heterocycloalkylene, -$[CONR_{25}]$- and -$[NR_{25}CO]$-;

R_{25} is hydrogen or $(C_1\text{-}C_6)$alkyl;

$\mathbf{R_{22}}$ is selected in the group consisting of: $(C_1\text{-}C_6)$alkyl, which $(C_1\text{-}C_6)$alkyl is optionally substituted by one or more groups $(C_3\text{-}C_6)$cycloalkyl, phenyl, benzyl, CN, $-OR_{26}$, $-SO_2R_{26}$, $-CO_2R_{26}$, $-CONR_{26}R_{27}$ or $-SO_2NR_{26}R_{27}$; $(C_3\text{-}C_{10})$cycloalkyl which is optionally substituted by one or more groups $-OR_{26}$, $-SO_2R_{26}$, $-CO_2R_{26}$, $-CONR_{26}R_{27}$ or $-SO_2NR_{26}R_{27}$; and $(C_4\text{-}C_7)$heterocycloalkyl which is optionally substituted by one or more groups $-OR_{26}$, $-SO_2R_{26}$, $-CO_2R_{26}$, $-CONR_{26}R_{27}$ or $-SO_2NR_{26}R_{27}$;

$\mathbf{R_{26}}$ is hydrogen or $(C_1\text{-}C_6)$alkyl;

$\mathbf{R_{27}}$ is hydrogen or $(C_1\text{-}C_6)$alkyl;

$\mathbf{R_{23}}$ is hydrogen or $(C_1\text{-}C_6)$alkyl, which $(C_1\text{-}C_6)$alkyl is optionally substituted by one or more groups $-OR_{29}$, $-SO_2R_{29}$, $-CO_2R_{29}$, $-CONR_{29}R_{30}$ or $-SO_2NR_{29}R_{30}$;

$\mathbf{R_{24}}$ is hydrogen or $(C_1\text{-}C_6)$alkyl, which $(C_1\text{-}C_6)$alkyl is optionally substituted by one or more groups $-OR_{31}$, $-SO_2R_{31}$, $-CO_2R_{31}$, $-CONR_{31}R_{32}$ or $-SO_2NR_{31}R_{32}$;

alternatively, $\mathbf{R_{23}}$ and $\mathbf{R_{24}}$ together with the nitrogen atom they are linked to may form a 5-11- membered saturated monocyclic or bicyclic heterocyclic ring system which is optionally substituted by one or more groups $-OR_{28}$, halo, $C_1\text{-}C_6$ alkyl, $-SO_2R_{33}$, $-CO_2R_{33}$, $-CONR_{33}R_{34}$ or $-SO_2NR_{33}R_{34}$; and which 5-11- membered saturated monocyclic or bicyclic ring optionally contains a further heteroatom which is oxygen or nitrogen or a group $-SO_2$-;

or $\mathbf{R_{22}}$ together with $\mathbf{R_{23}}$, $\mathbf{R_{24}}$ and the nitrogen atom they are linked to, may form a bridged bicyclic heterocyclic ring system;

$\mathbf{R_{28}}$ is hydrogen or $(C_1\text{-}C_6)$alkyl;

$\mathbf{R_{29}}$ is hydrogen or $(C_1\text{-}C_6)$alkyl;

$\mathbf{R_{30}}$ is hydrogen or $(C_1\text{-}C_6)$alkyl;

$\mathbf{R_{31}}$ is hydrogen or $(C_1\text{-}C_6)$alkyl;

$\mathbf{R_{32}}$ is hydrogen or $(C_1\text{-}C_6)$alkyl;

$\mathbf{R_{33}}$ is hydrogen or $(C_1\text{-}C_6)$alkyl;

$\mathbf{R_{34}}$ is hydrogen or $(C_1\text{-}C_6)$alkyl;

$\mathbf{R_{38}}$ represents one or two optional substituents at each occurrence selected in the

list consisting of: (C_1-C_6)alkyl, (C_1-C_6)alkoxyl, hydroxyl, hydroxyl-C_1-C_6-alkyl, halo, trifluoromethyl, trifluoromethoxy;

wherein only two of A, B and D may be at the same time a nitrogen atom;

wherein if one or more groups $N^+R_{11}R_{12}R_{13}$- or $N^+R_{15}R_{16}R_{17}$- are present, they form quaternary salts with a pharmaceutically acceptable counter ion;

and wherein groups R_5 to R_{38}, and n may have the same or different meanings at each occurrence, if present in more than one group.

2. A compound as claimed in claim 1 wherein A is a group CH, B is a group CH and D is a group CH.

3. A compound as claimed in any of claims 1 or 2 wherein **R_2** is selected a group –$[CH_2]_y$-G-$[CH_2]_j$-CH_2-$N^+R_{22}R_{23}R_{24}$.

4. A compound as claimed in any of claims 1 to 3 wherein R_3 is a group –C(O)-XR_4.

5. A compound as claimed in any claims 1 to 4 wherein X is a divalent group -O- and R_4 is (C_1-C_6)alkyl .

6. A compound as claimed in any of claims 1 to 5, wherein **R_1** is hydrogen or a group -$(CH_2)_rSO_2$(C_1-C_4)alkyl;

7. A compound as claimed in any of claims 1 to 6, which is selected in the group consisting of:

5-[4-Cyano-2-(4-hydroxy-but-1-ynyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

5-[4-Cyano-2-(3-dimethylamino-prop-1-ynyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

5-[4-Cyano-2-(3-dimethylamino-prop-1-ynyl)-phenyl]-2-(3-methanesulfonyl-propyl)-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

(3-{5-Cyano-2-[2-(3-methanesulfonyl-propyl)-6-methoxycarbonyl-7-methyl-3-

oxo-8-m-tolyl-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-prop-2-ynyl)-trimethyl-ammonium formate;

5-[4-Cyano-2-(3-dimethylamino-propyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

5-(4-Cyano-2-dimethylaminomethyl-phenyl)-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

{5-Cyano-2-[6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-trimethyl-ammonium bromide;

(2-{5-Cyano-2-[6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzoylamino}-ethyl)-trimethyl-ammonium chloride;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-trimethyl-ammonium formate;

(R)-5-[4-Cyano-2-(3-dimethylamino-propyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-prop-2-ynyl)-trimethyl-ammonium iodide;

(R)-5-[4-Cyano-2-(3-dimethylamino-prop-1-ynyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3a]pyrimidine-6-carboxylic acid methyl ester;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-

trimethyl-ammonium iodide;

5-[4-Cyano-2-(4-hydroxy-but-1-ynyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

5-[4-Cyano-2-(3-dimethylamino-prop-1-ynyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

5-[4-Cyano-2-(3-dimethylamino-prop-1-ynyl)-phenyl]-2-(3-methanesulfonyl-propyl)-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

(3-{5-Cyano-2-[2-(3-methanesulfonyl-propyl)-6-methoxycarbonyl-7-methyl-3-oxo-8-m-tolyl-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-prop-2-ynyl)-trimethyl-ammonium formate;

5-[4-Cyano-2-(3-dimethylamino-propyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

5-(4-Cyano-2-dimethylaminomethyl-phenyl)-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

{5-Cyano-2-[6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-trimethyl-ammonium bromide;

(2-{5-Cyano-2-[6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzoylamino}-ethyl)-trimethyl-ammonium chloride;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-trimethyl-ammonium formate;

(R)-5-[4-Cyano-2-(3-dimethylamino-propyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-prop-2-ynyl)-trimethyl-ammonium iodide;

(R)-5-[4-Cyano-2-(3-dimethylamino-prop-1-ynyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3a]pyrimidine-6-carboxylic acid methyl ester;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-trimethyl-ammonium iodide;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-trimethyl-ammonium iodide;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-(3-methanesulfonyl-propyl)-dimethyl-ammonium formate;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-cyclopropylmethyl-dimethyl-ammonium formate;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-(3-hydroxy-propyl)-dimethyl-ammonium formate;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-(3-methoxy-propyl)-dimethyl-ammonium formate:

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-

phenyl)-2,3,5,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-dimethylcarbamoylmethyl-dimethyl-ammonium formate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-1-azonia-bicyclo[2.2.2]octane formate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-4-aza-1-azonia-bicyclo[2.2.2]octane formate;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-(4-hydroxy-cyclohexyl)-dimethyl-ammonium formate;

4-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-4-methyl-morpholin-4-ium formate;

Adamantan-1-yl-(3-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-ammonium formate;

4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methyl-morpholin-4-ium formate;

{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(3-hydroxy-propyl)-dimethyl-ammonium formate;

{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-ethyl-dimethyl-ammonium formate;

1-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-pyridinium

formate;

1-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-1-azonia-bicyclo[2.2.2]octane formate;

1-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-1,4-dimethyl-piperazin-1-ium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(4-hydroxy-cyclohexyl)-dimethyl-ammonium formate;

1-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-aza-1-azonia-bicyclo[2.2.2]octane formate;

1-{2-[(R)-6-carboxy-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-5-cyano-benzyl}-4-aza-1-azonia-bicyclo[2.2.2]octane formate;

Butyl-{5-cyano-2-[(R)-6-methoxy carbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-ammonium formate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-hydroxy-1-methyl-piperidinium formate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-1-methyl-pyrrolidinium formate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-1-methyl-piperidinium formate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-1-(2-hydroxy-ethyl)-pyrrolidinium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(3-dimethylcarbamoyl-propyl)-dimethyl-ammonium formate;

Benzyl-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-ammonium formate;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-trimethyl-ammonium bromide;

(S)-5-[4-Cyano-2-(5-hydroxypentyl)-phenyl]-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-6-carboxylic acid methyl ester; (Example 41)

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-trimethyl-ammonium benzenesulfonate;

(5-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-pentyl)-trimethyl-ammonium formate;

(4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-butyl)-trimethyl-ammonium formate;

1-(4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-butyl)-1-azonia-bicyclo[2.2.2]

octane formate;

1-(4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-butyl)-1-azonia-bicyclo[2.2.2]

octane formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-trimethyl-ammonium bromide;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-trimethyl-ammonium bromide;

1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-pyridinium bromide;

1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-pyridininium formate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-pyridinium bromide;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-pyridinium formate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-pyridinium benzenesulfonate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-pyridinium chloride;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-pyridinium 2-hydroxy-ethanesulfonate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-pyridinium methanesulfonate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-3-hydroxymethyl-pyridinium tosylate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-3-methyl-pyridinium formate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-2-methyl-pyridinium formate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-3-hydroxymethyl-pyridinium formate;

3-Chloro-1-(3-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-propyl)-pyridinium formate;

Butyl-(3-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-dimethyl-ammonium formate;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-cyclohexyl-dimethyl-ammonium formate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-

phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-1-methyl-pyrrolidinium formate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-1-methyl-piperidinium formate;

1-(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-4-hydroxy-1-methyl-piperidinium formate;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-dimethyl-oxetan-3-yl-ammonium formate;

(3-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-dimethyl-(tetrahydro-pyran-4-yl)-ammonium formate;

4-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-4-methyl-morpholin-4-ium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-dimethylcarbamoylmethyl-dimethyl-ammonium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-(3-methoxy-propyl)-dimethyl-ammonium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-cyclobutylmethyl-dimethyl-ammonium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-dimethyl-

(tetrahydro-pyran-4-ylmethyl)-ammonium formate;

1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-1-(2-hydroxy-ethyl)-pyrrolidinium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-[2-(2-hydroxy-ethoxy)-ethyl]-dimethyl-ammonium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-bis-(2-hydroxy-ethyl)-methyl-ammonium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-(2-hydroxy-ethyl)-dimethyl-ammonium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-ethyl-dimethyl-ammonium formate;

Benzyl-(2-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-dimethyl-ammonium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-cyclohexylmethyl-dimethyl-ammonium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-(3-hydroxy-propyl)-dimethyl-ammonium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-diethyl-methyl-ammonium formate;

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-cyclopropylmethyl-dimethyl-ammonium formate;

1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-1-azonia-bicyclo[2.2.2]octane formate;

1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-3-hydroxymethyl-pyridinium formate;

1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-3-methyl-pyridinium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-cyclobutylmethyl-dimethyl-ammonium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-(tetrahydro-pyran-4-ylmethyl)-ammonium formate;

{{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(2-methoxy-ethyl)-dimethyl-ammonium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-cyclopropylmethyl-dimethyl-ammonium formate;

3-Chloro-1-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-pyridinium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-

phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(2-hydroxy-ethyl)-dimethyl-ammonium formate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methoxy-pyridinium formate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-3-hydroxymethyl-pyridinium formate;

{1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-hydroxymethyl-1-methyl-piperidinium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-ethoxycarbonylmethyl-dimethyl-ammonium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(1,1-dioxo-hexahydro-1lambda*6*-thiopyran-4-ylmethyl)-dimethyl-ammonium formate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-3,4-dihydroxy-1-methyl-pyrrolidinium formate;

4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-ethyl-morpholin-4-ium formate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-dimethylcarbamoyl-1-methyl-piperazin-1-ium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-

dimethylcarbamoylmethyl-dimethyl-ammonium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(1-methanesulfonyl-piperidin-4-yl)-dimethyl-ammonium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-oxetan-3-ylmethyl-ammonium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-(3-methylcarbamoyl-propyl)-ammonium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(3-dimethylsulfamoyl-propyl)-dimethyl-ammonium formate

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methanesulfonyl-1-methyl-piperazin-1-ium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-bis-(2-hydroxy-ethyl)-methyl-ammonium formate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4,4-difluoro-1-methyl-piperidinium formate;

4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methyl-[1,4]oxazepan-4-ium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(3-methoxy-propyl)-dimethyl-ammonium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-(3-methanesulfonyl-propyl)-dimethyl-ammonium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-(1-methyl-piperidin-4-yl)-ammonium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-piperidin-4-yl-ammonium formate;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-(tetrahydro-pyran-4-yl)-ammonium formate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-pyridinium bromide;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-pyridinium benzenesulphonate;

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-pyridinium tosylate;

Benzyl-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-ammonium bromide;

Benzyl-{5-cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-dimethyl-ammonium benzenesulfonate;

4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-

phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methyl-morpholin-4-ium bromide;

4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methyl-morpholin-4-ium bromide;

4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methyl-morpholin-4-ium bromide;

4-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-4-methyl-morpholin-4-ium bromide;

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-trimethyl-ammonium benzenesulfonate;

1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-pyridinium 2-hydroxy-ethanesulfonate;

1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-pyridinium methanesulfonate.

1-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-pyridinium chloride

{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-benzyl}-bis-(2-hydroxy-ethyl)-methyl-ammonium benzenesulfonate

1-(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-

pyridinium benzenesulfonate

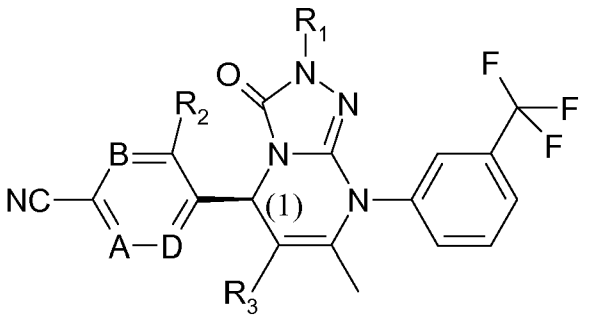
(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-trimethyl-ammonium 2-hydroxy-ethanesulfonate

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-trimethyl-ammonium methanesulfonate

(2-{5-Cyano-2-[(R)-6-methoxycarbonyl-7-methyl-3-oxo-8-(3-trifluoromethyl-phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl]-phenyl}-ethyl)-trimethyl-ammonium chloride

and pharmaceutically acceptable salts thereof.

8. A compound as claimed in any of claims 1 to 7 which is a compound of formula (I)' where the absolute configuration of carbon (1) is that shown here below:



(I)'

and wherein R_1, R_2, R_3, B and A are as defined for compounds of formula (I).

9. A compound as claimed in any of claims 1 to 8, in the form of a pharmaceutically acceptable salt.

10. A pharmaceutical composition comprising a compound as claimed in any of 1 to 9 and a pharmaceutically acceptable carrier or excipient.

11. A pharmaceutical composition as claimed in claim 10 which is adapted for oral administration or administration by the pulmonary route.

12. A compound as claimed in any of claims 1 to 9 for the treatment of, or for use in the manufacture of a medicament for use in the treatment of, a disease or condition in

which HNE is implicated.

13. A method of treatment of a disease or condition in which HNE is implicated, comprising administering to a subject suffering such disease an effective amount of a compound as claimed in any of claims 1 to 9.

14. A compound for use according to claim 12, or a method of treatment according to claim 13, wherein the disease or condition is chronic obstructive pulmonary disease (COPD), bronchiectasis, chronic bronchitis, lung fibrosis, pneumonia, acute respiratory distress syndrome (ARDS), pulmonary emphysema, smoking-induced emphysema or cystic fibrosis.

15. A compound for use according to claim 12 or a method of treatment according to claim 13, wherein the disease or condition is asthma, rhinitis, psoriasis, atopic dermatitis, non-atopic dermatitis, Crohn's disease, ulcerative colitis, or irritable bowel disease.