ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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Novel Pyrazine Amide Compounds

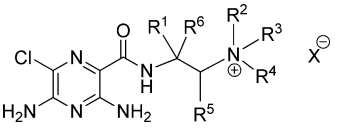
Benjamin Blass*

Temple University School of Pharmacy, 3307 North Broad Street, Philadelphia, Pennsylvania 19140, United States

Title:	Novel Pyrazine Amide Compounds		
Patent/Patent Application Number:	WO2015018754A1	**Publication date:**	February 12, 2015
Priority Application:	EP13179737.5	**Priority date:**	August 8, 2014
Inventors:	Wiedenmayer, D.; Hamprecht, D.; Heckel, A.		
Assignee Company:	Boehringer Ingelheim International GMBH		
Disease Area:	Respiratory and allergy disease	**Biological Target:**	Epithelial sodium channel (ENaC)

Summary: The epithelial sodium channel (ENaC), also referred to as the sodium channel non-neuronal 1 (SCNN1) and the amiloride-sensitive sodium channel (ASSC) is a membrane bound ion channel that is formed by three separate subunits designated α, β, and γ. Each subunit consists of two transmembrane regions connected by an extracellular loop. It has been reported that functional channels have an $\alpha 2\beta 1\gamma 1$ stoichiometry, although alternative functionally active arrangements have not been ruled out. Passage of Na^+ through ENaC is the rate limiting step in epithelial Na^+ transport, a key process in the control of various bodily functions such as maintaining fluid covering on apical surface of alveolar epithelial cells in lung tissue. Tight control of the fluid volume covering apical epithelial cells in airways is required in order to prevent infection and facilitate normal gas exchange. Aberrant ENaC activity has been linked to respiratory conditions such as bronchitis, chronic obstructive bronchitis (COPD), asthma, bronchiectasis, allergic alveolitis, rhinitis, chronic sinusitis, cystic fibrosis, α-I-antitrypsin deficiency, cough, pulmonary emphysema, interstitial lung diseases, alveolitis, hyperactive airways, nasal polyps, pulmonary edema, and pneumonitis of different origins. The present disclosure describes a series of novel pyrazine amides capable of inhibiting ENaC, which may be useful for the treatment of the aforementioned conditions.

Important Compound Classes:



Definitions:

R^1 is selected from methyl, HO(O)C−CH_2−, C_{1-4}−alkyl−O(O)C−CH_2−, Cl(C_{1-4}−alkyl)$_3$N−CH_2−CH_2−HN(O)C−CH_2−, or aryl;

R^6 is selected from H or C_{1-4}−alkyl;

R^2 is selected from C_{1-4}−alkyl;

R^3 is selected from C_{1-4}−alkyl, optionally substituted with one or two groups selected from C_{5-6}−cycloalkyl, indolyl, HO(O)C−, C_{1-4}−alkyl−O(O)C−, C_{5-6}−cycloalkyl−O(O)C−, aryl-O− optionally substituted with C_{1-4}−alkyl−O−, aryl-C_{1-4}−alkyl optionally substituted with C_{1-4}−alkyl−O−, or aryl optionally substituted with one or two $R^{3.1}$−, $R^{3.1}$−O−, $R^{3.1}$−CH_2−, $R^{3.1}$−CH_2−O−, halogen, or NC−, wherein

$R^{3.1}$ is selected independently from H, C_{1-4}−alkyl, benzyl, HO(O)C−, C_{1-4}−alkyl−O(O)C−, HO−CH_2−, C_{1-4}−alkyl−O−CH_2−, (C_{1-4}−alkyl)$_2$N−CH_2−, C_{1-4}−alkyl−$(O)_2$S, H−[O−CH_2−CH_2]$_n$−, $R^{3.1.1}$HN(O)C−, ($R^{3.1.1}$)$_2$N(O)C−, $R^{3.1.2}$HN(O)C−, or ($R^{3.1.2}$)$_2$N(O)C-, wherein

n is 3, 4, or 5,

$R^{3.1.1}$ is selected independently from H, H−[O−CH_2−CH_2]$_2$−, H−[O−CH_2−CH_2]$_3$− or a five-, six-, or nine-membered heterocyclyl, wherein one, two, or three elements are replaced by an element independently selected from N, O, or S; each five-, six-, or nine-membered heterocyclyl optionally substituted with one or two substituents independently selected from C_{1-4}−alkyl−, HO−, HO−C_{1-4}−alkyl−, or O= or

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two substituents $R^{3.1.1}$ together with the nitrogen atom they are bound to form a five-, six-, or nine-membered heterocyclyl, wherein one or two further elements are replaced by an element independently selected from N, O, or S; each five-, six-, or nine-membered heterocyclyl optionally substituted with one or two substituents independently selected from C_{1-4}−alkyl, C_{1-4}−alkyl−O− or O=, and

$R^{3.1.2}$ is independently branched or unbranched C_{1-4}−alkyl, optionally substituted with one or two substituents selected independently from O=, NC−, HO−, C_{1-4}−alkyl−O−, $(C_{1-4}\text{−alkyl})_2N$−, $Cl(C_{1-4}\text{−alkyl})_3N$−, HO(O)C−, C_{1-4}−alkyl−O(O)C−, $HO(O)_2S$−, C_{1-4}−alkyl−$(O)_2S$−, C_{1-4}−alkyl−$(O)_2S$−, $(C_{1-4}\text{−alkyl})_2OP$− or a five- or six-membered heterocyclyl or heteroaryl, wherein one or two elements are replaced by an element independently selected from N or O;

each five- or six-membered heterocyclyl or heteroaryl being optionally substituted with one or two substituents independently selected from C_{1-4}−alkyl or O=;

R^4 is independently selected from C_{1-4}−alkyl, optionally substituted with one or two groups selected from C_{5-6}−cycloalkyl, indolyl, HO(O)C−, C_{1-4}−alkyl−O(O)C−, C_{5-6}−cycloalkyl−OO(0)C−, aryl−O− optionally substituted with C_{1-4}−alkyl−O−, aryl−C_{1-4}−alkyl optionally substituted with C_{1-4}−alkyl−O−, or

aryl optionally substituted with one or two $R^{4.1}$, [$R^{4.1}$−O−, $R^{4.1}$−CH_2−], $R^{4.1}$−CH_2−O−, halogen or NC−, wherein $R^{4.1}$ is selected independently from H, C_{1-4}−alkyl, benzyl, HO(O)C−, C_{1-4}−alkyl−O(O)C−, HO−CH_2−, C_{1-4}−alkyl−O−CH_2−, $(C_{1-4}\text{−alkyl})_2N-CH_2$−, C_{1-4}−alkyl−$(O)_2S$, H−[O−CH_2−CH_2]$_n$−, $R^{4.1.1}$HN(O)C−, $(R^{4.1.1})^2N(O)C$−, $R^{4.1.2}$HN(O)C− or $(R^{4.1.2})_2N(O)C$−, wherein

n is 3, 4 or 5,

$R^{4.1.1}$ is selected independently from H, H−[O−CH_2−CH_2]$_2$−, H−[O−CH_2−CH_2]$_3$− or

a five-, six- or nine-membered heterocyclyl, wherein one, two, or three elements are replaced by an element independently selected from N, O, or S; each five-, six-, or nine-membered heterocyclyl being optionally substituted with one or two substituents independently selected from C_{1-4}−alkyl−, HO−,HO−C_{1-4}−alkyl−, O= or

two substituents $R^{4.1.1}$ together with the nitrogen atom they are bound to form a five-, six-, or nine-membered heterocyclyl, wherein one or two further elements are replaced by an element independently selected from N, O, or S; each five-, six-, or nine-membered heterocyclyl being optionally substituted with one or two substituents independently selected from C_{1-4}−alkyl−, HO−, HOC_{1-4}−alkyl−, O=, and

$R^{4.1.2}$ is branched or unbranched C_{1-4}−alkyl, optionally substituted with one or two substituents selected independently from O=, NC−, HO−, C_{1-4}−alkyl−O−, $(C_{1-4}\text{−alkyl})_2N$−, $Cl(C_{1-4}\text{−alkyl})_3N$−, HO(O)C−, C_{1-4}−alkyl−O(O)C−, $HO(O)_2S$−, C_{1-4}−alkyl−$(O)_2S$−, C_{1-4}−alkyl−$(O)_2S$−, $(C_{1-4}\text{−alkyl})_2OP$− or

a five- or six-membered heterocyclyl or heteroaryl, wherein one or two elements are replaced by

an element independently selected from N or O; each five- or six-membered heterocyclyl or heteroaryl being optionally substituted with one or two substituents independently selected from C_{1-4}−alkyl or O=;

R^5 is H;

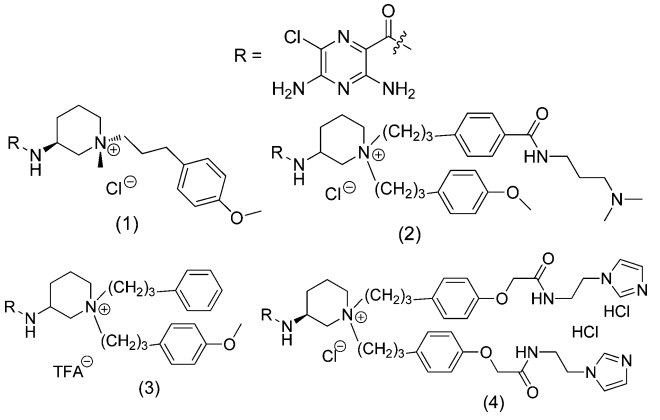
or R^1 and R^2 are together R^{12}, wherein R^{12} is selected from C_{2-4}−alkylene each optionally partially or fully substituted with $R^{12.1}$, wherein $R^{12.1}$ is selected independently from phenyl, optionally substituted with C_{1-4}−alkyl;

or R^1, R^2, and R^4 together with the atoms connecting them form an aza-bicyclo[2.2.2]octane;

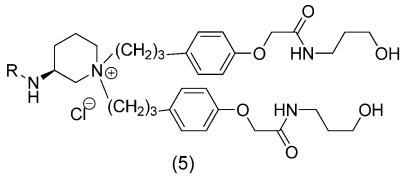
or R^1 and R^5 are together −CH_2−;

and X is selected independently from chloride, bromide, iodide, hydroxide, hydrogensulfate, nitrate, formate, acetate, trifluoroacetate, methanesulfonate, or *p*-toluenesulfonate; or a pharmaceutically acceptable salt thereof.

Key Structures:



Key Structures (Continued):



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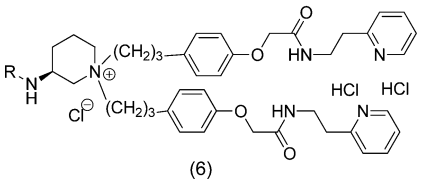

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Recent Review Articles:

1. Marunaka, Y. Characteristics and pharmacological regulation of epithelial Na^+ channel (ENaC) and epithelial Na^+ transport. *J. Pharmacol. Sci.* **2014**, *126* (1), 21−36.
2. Schoenberger, M.; Althaus, M. Novel small molecule epithelial sodium channel inhibitors as potential therapeutics in cystic fibrosis - a patent evaluation. *Expert Opin. Ther. Pat.* **2013**, *23* (10), 1383−1389.
3. Mall, M. A. Role of the amiloride-sensitive epithelial Na^+ channel in the pathogenesis and as a therapeutic target for cystic fibrosis lung disease. *Exp. Physiol.* , *94* (2), 171−174.

Biological Assay:

IC_{50} values were determined in the Ussing Chamber assay. Mouse kidney M-l cells were cultivated in DMEM containing 5% FCS and 5 μM dexamethasone for 10 to 12 days on polyester transwell filters. The filters were inserted into a Teflon-coated wellplate, which fit into the Ussing chamber system. Prior to measurement the medium of M-1 cells was replaced with Caco-2 transport buffer (Invitrogen, Germany). During measurements, the Ussing chamber temperature was maintained at 37 °C. Short circuit currents (I_{sc}) were measured in the voltage-clamp mode with the software package Lab View for data acquisition and analysis. The trans epithelial electrical resistance (TEER) was determined by the application of voltage steps of ±5 mV every 5 s. Compounds were administered at a final concentration of 3 μM or at increasing concentrations (l-3−10 μM) to the apical solution. At the end of each experiment the amiloride sensitive 1_ SC was measured by adding 3 μM amiloride to the apical compartment. Results are expressed as inhibition in percent of the amiloride effect or as IC_{50}.

Biological Data:

Entry	IC_{50} (nM)	Entry	IC_{50} (nM)
1	70	4	9
2	20	5	13
3	6	6	6

Claims:

23 Total claims
20 Composition of matter claims
3 Method of use claims.

AUTHOR INFORMATION

Corresponding Author
*Tel: 215-707-1085. E-mail: benjamin.blass@temple.edu.

Notes
The authors declare no competing financial interest.