Bioorganic & Medicinal Chemistry Letters 19 (2009) 6682–6685

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Histamine H_3 and H_4 receptor affinity of branched 3-(1*H*-imidazol-4-yl)propyl *N*-alkylcarbamates

Dorota Łażewska [a], Małgorzata Więcek [a], Xavier Ligneau [b], Tim Kottke [c], Lilia Weizel [c], Roland Seifert [d], Walter Schunack [e], Holger Stark [c], Katarzyna Kieć-Kononowicz [a,*]

[a] Department of Technology and Biotechnology of Drugs, Jagiellonian University Medical College, ul. Medyczna 9, 30-688 Kraków, Poland
[b] Bioprojet-Biotech, 4 rue du Chesnay Beauregard, BP 96205, 35762 Saint-Grégoire, France
[c] Institute of Pharmaceutical Chemistry, Johann Wolfgang Goethe-University, Max-von-Laue-Strasse 9, 60438 Frankfurt/Main, Germany
[d] Institute of Pharmacology, Medical School of Hannover, Carl-Neuberg-Strasse 1, 30625 Hannover, Germany
[e] Institute of Pharmacy, Free University of Berlin, Königin-Luise-Strasse 2+4, 14195 Berlin, Germany

ARTICLE INFO

Article history:
Received 23 June 2009
Revised 30 September 2009
Accepted 1 October 2009
Available online 6 October 2009

Keywords:
Histamine H_3 receptor
Histamine H_4 receptor
Imidazole derivatives

ABSTRACT

A series of imidazole-containing (non-)chiral carbamates were tested at human histamine H_3 receptor (H_3R). All compounds displayed K_i values below 100 nM. A trend for a stereoselectivity at human H_3R was observed for the chiral α-branched ligands. Selected compounds were also tested at human histamine H_4 receptor and showed moderate to weak affinities (118–1460 nM).

© 2009 Elsevier Ltd. All rights reserved.

Imidazole moiety is present in many biologically active compounds (for review see[1]). One of the most important of them is histamine. Histamine exerts tremendous influence over a variety of physiological processes by the four known receptors subtypes: H_1, H_2, H_3 and H_4.

Histamine H_3 receptors (H_3Rs) are widely expressed in CNS and play the main role in many important processes. Nowadays, the current interest in the area of H_3R ligands (inverse agonists, antagonists) is focused on non-imidazole compounds (for review see[2–7]), whereas the first generation H_3R active structures contained the imidazole moiety (for review see[8]). These compounds were analogues of histamine with the 4-substituted imidazole ring. However, despite their high potency and clinical studies none of them have entered the market as a drug. The main drawback of these compounds was inhibition of numerous CYP450 enzymes[9,10] (although recently some studies suggested the possibilities to minimize these activities[11]), reduced oral bioavailability and poor brain penetration (e.g., thioperamide[12]). Actually, imidazole-based ligands like thioperamide, clobenpropit, and ciproxifan (Fig. 1) are mainly used as reference structures in a variety of preclinical animal models.

Despite that imidazole-containing ligands are further the subject of investigations and quite recently, Jablonowski et al. described a series of *N*-methylimidazole-containing compounds—potent H_3R ligands with improved metabolic stability. (e.g., **1**, Fig. 2)[13]

Histamine H_4 receptors (H_4Rs) are preferentially expressed on hematopoietic and immune cells (e.g., eosinophils, mast cells, macrophages) and play a role in immunological and inflammatory processes.[14]

The human H_4R is closely related to the human H_3R. These two proteins have a sequence identity of 31% and their homology in the transmembrane region is 54%.[15]

Therefore, it is not surprising, that numerous imidazole-containing H_3R ligands have also significant affinity for the human H_4R (e.g., Table 1)[16] and some of them (e.g., thioperamide, clobenpropit) have been used to characterize the H_4R. While the current medicinal chemistry efforts are concerned at finding more selective compounds, AstraZeneca continues to develop imidazole derivatives acting as dual H_3R and H_4R ligands (e.g., Fig. 3).[17] These compounds are considered as potential drugs for the treatment of histamine H_4 mediated diseases especially asthma. Also, very recently, Igel et al. described N^G-alkanoyl-imidazolylpropylguanidines as high-affinity human H_3R antagonists/partial agonists and full H_4R agonists.[18] For example, UR-PI294 with N^G-propionyl group, was tritiated, resulting the radioligand [^{3}H]UR-PI294.[19] This radioligand is considered a valuable pharmacological tool for the determination of human H_3R and human H_4R affinities.

In this Letter, we describe human H_3R affinity of branched 3-(1*H*-imidazol-4-yl)-propyl *N*-alkylcarbamates (Scheme 1). Most

* Corresponding author. Tel.: +48 12 620 55 81; fax: +48 12 620 55 96.
E-mail address: mfkonono@cyf-kr.edu.pl (K. Kieć-Kononowicz).

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.10.005

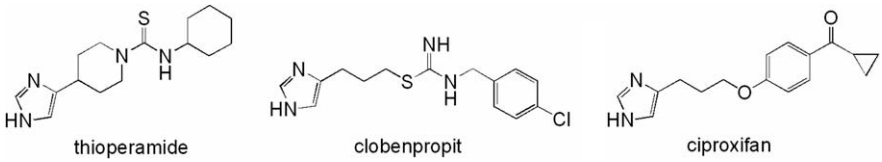
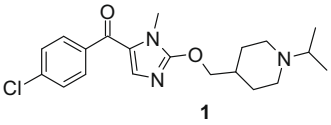


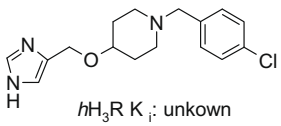
Figure 1. Some reference imidazole-containing histamine H_3 receptor ligands.



1

H_3R:
human K_i = 3 nM
rat pA_2 = 8.0
human pA_2 = 9.2
IC_{50}s > 10 mM for CYP: 1A2, 2C9, 2C19, 2D6 and 3A4

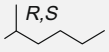
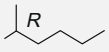
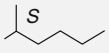
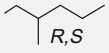
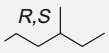
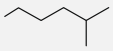
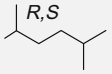
Figure 2. Structure and potency profile of **1**.[13]



hH_3R K_i: unkown
hH_4R K_i: unkown

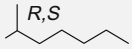
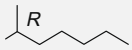
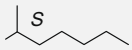
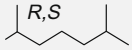
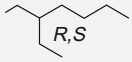
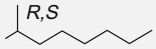
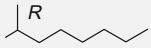
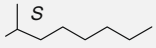
Figure 3. Structure of one of the compounds developed by AstraZeneca.[17]

Table 1
Affinities of compounds **2**–**22** at human histamine H_3 and H_4 receptor

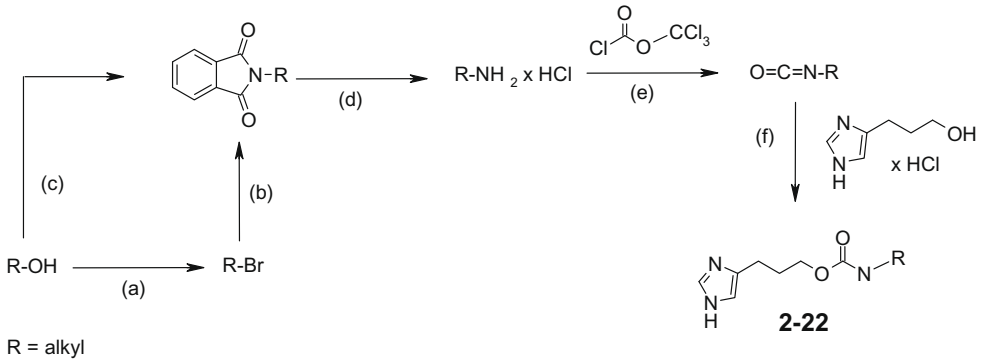
Compds	R	K_i[a] (nM)	hH_3R K_i[b] (nM)	hH_4R K_i[c] (nM)	Selectivity ratio hH_4R/hH_3R
2		20 ± 5	49	nt[d]	
3		19 ± 5	12	290 ± 98	24
4		23 ± 5	31	nt[d]	
5		25 ± 4	21	nt[d]	
6		12 ± 2	15	nt[d]	
7		18 ± 4	4.7 ± 0.9	118 ± 38	25
8		8.7 ± 2.9	29	695 ± 51	24
9		19 ± 4	19	426 ± 147	22
10		12 ± 5	42	nt[d]	
11		15 ± 5	8.3	162 ± 34	20
12		5.1 ± 1.9	13	123 ± 17	9
13		nt[d]	13	nt[d]	
14		nt[d]	30	nt[d]	

(*continued on next page*)

Table 1 (*continued*)

Compds	R	K_i[a] (nM)	hH_3R K_i[b] (nM)	hH_4R K_i[c] (nM)	Selectivity ratio hH_4R/hH_3R
15		18 ± 4	52	nt[d]	
16		23 ± 8	41	636 ± 150	16
17		18 ± 3	74	1460 ± 240	20
18		22 ± 5	75	nt[d]	
19		nt[d]	37	779 ± 85	21
20		18 ± 5	91	nt[d]	
21		nt[d]	28 ± 3[e]	nt[d]	
22		nt[d]	43 ± 17[e]	nt[d]	
Ciproxifan			46 ± 4[f]	612 ± 32[g]	13
Clobenpropit			2.4 ± 0.6[f]	4.3 ± 0.2[g]	1.8
Thioperamide			60 ± 12[f]	43 ± 3[g]	0.7

[a] [^{3}H]histamine release from synaptosomes of rat cerebral cortex,[25] mean ± sem of at least three independent experiments.
[b] [^{125}I]Iodoproxyfan binding to membranes of CHO-K1 cells expressing the human H_3R,[26] data from a single experiment with each concentrations tested at least in triplicate, except for **7** with mean ± sem of three independent experiments.
[c] [^{3}H]Histamine binding to membranes of Sf9 cells expressing the human H_4R, co-expressed with Gαi2 and $G\beta_1\gamma_2$ subunits,[27,28] mean ± sem of at least three independent experiments.
[d] Not tested.
[e] [^{125}I]Iodoproxyfan binding to membranes of HEK-293 cells expressing the human H_3R,[16] mean ± sem of three independent experiments.
[f] [^{125}I]Iodoproxyfan binding to membranes of CHO-K1 cells expressing the human H_3R, data from Ref. 26.
[g] [^{3}H]Histamine binding to membranes of HEK-293 cells expressing the human H_4R, data from Ref. 16.



Scheme 1. General synthesis of carbamates. Reagents and conditions: (a) 48% HBr, H_2SO_4 (concd); (b) potassium phthalimide, K_2CO_3, benzyltriethylammonium chloride, acetone 6 h reflux; (c) phthalimide, DEAD, triphenylphosphine, THF, 3 days rt; (d) (i) NH_2–NH_2, EtOH, 15 min reflux; (ii) HCl, EtOH; (e) ethyl acetate, catalytic amount of charcoal, 4–5 h reflux; (f) acetonitrile, 4–5 h reflux.

of these compounds had been previously studied in a functional test on synaptosomes of rat cortex and showed high histamine H_3R affinity.[20,21] Now some of the reported structures were also tested at the human H_4R. Results are collected in Table 1.

The synthetic route for these carbamates is illustrated in Scheme 1.[22] Commercially available or prepared amines were converted to the corresponding isocyanates by the reaction with an excess of diphosgene. Then, subsequently isocyanates reacted in acetonitrile with 3-(1*H*-imidazol-4-yl)-propanol hydrochloride to furnish the desired carbamates **2**–**22**. Non-commercially available amines were prepared from the corresponding alcohols as depicted in Scheme 1. Amines used to synthesize compounds **8**, **11** and **12** were obtained from the alkyl bromides via conventional Gabriel synthesis under phase-transfer conditions.[20,23] Subsequently, *N*-alkylphthalimides by means of hydrazinolysis gave the desired amines, isolated as hydrochlorides. Alkyl bromides for **8**, **11** and

12 were synthesized by standard procedures (48% HBr in concentrated H_2SO_4). Precursor *N*-alkylphthalimides for carbamates **9**, **10**, **13**, **14** and **22** were prepared via modified Gabriel procedure reported by Mitsunobu.[24] These reactions were carried out at room temperature in absolute THF in the presence of DEAD and triphenylphosphine.

All compounds reported here revealed high affinities for human H_3R (K_i values from 4.7 to 91 nM). The best acceptable for $h$$H_3R$ is the methyl substituent in the β position (**7** and **11**). It looks as if the ethyl group in this position (**19**) is also tolerated. However, the lack of the methyl analogue in the hexyl series did not let us confirm that.

A trend for a stereoselectivity at human H_3R was also observed for the chiral α-branched ligand. Indeed, the *R*-enantiomers (**3**, **9**, **16** and **21**) were slightly more potent than the corresponding *S*-enantiomers (**4**, **10**, **17** and **22**). In the *R*-eutomer series, the alkyl chain consisting of three to five carbons (compare **3**, **6** and **9**) was well tolerated by human H_3R. A six-carbon chain (compare **3**, **6** and **9** with **16**) was detrimental for H_3R binding and caused about threefold lost of in vitro affinity. Surprisingly, the seven-carbon compound **21** had again a better affinity than the six-carbon analogue **16**.

In the series of the pentyl derivatives (**8**–**14**), the methyl group was introduced into the different positions (α, β, γ and δ) and the dimethyl compound (**14**, α and δ position) was also prepared. Compounds with the methyl substituent in the β, γ or δ position were about twice more potent than α-branched ones (compare **11**, **12** and **13** with **8**). Interestingly, the introduction of a second methyl group in the δ position (**14**) did not influence the affinity when comparing with **8**, indicating that α-substituent determinated affinity and prevented the optimal interaction with the H_3R.

Comparing the results with those previously obtained in a functional test in rat cerebral cortex,[20,21] it is seen that most of the investigated compounds displayed lower or comparable affinity at the human H_3R. Surprisingly, **7** and **11** are more potent at the human H_3R than at the rat cortex (**7**: hK_i; 4.7 nM, rat K_i: 18 nM; **11**: hK_i; 8.3 nM, rat K_i: 15 nM).

Some of the compounds (**3**, **7**–**9**, **11**, **12**, **16**, **17** and **19**) were tested at human H_4R.[27,28] These studies revealed their moderate to weak affinities (hK$_i$: 118–1420 nM). The most potent was **7** (hK$_i$: 118 nM), also very active at human H_3R (hK$_i$: 4.7 nM). These chosen compounds (**3**, **7**–**9**, **11**, **12**, **16**, **17** and **19**) had some selectivity for the H_3R (from 9 to 25-fold) over the H_4R, in some cases even better than the reference compounds (Table 1).

In summary, we investigated a series of branched 3-(1*H*-imidazol-4-yl)propyl *N*-alkylcarbamates which were found to be potent human H_3R ligands. Additional pharmacological evaluation of nine selected compounds showed that these structures, as most imidazole-containing ligands, displayed also affinity for the H_4R. However, our present and unpublished results indicate that selectivity for the H_3R (high affinity) among imidazole-containing derivatives over the H_4R (weak or lack of affinity) is possible to achieve.

Acknowledgments

This work was supported by the Deutscher Akademischer Austauschdienst (D/06/25529), Germany, the Ministry of Scientific Research and Information Technology, Poland DAAD/55/2007 Program and by the 'LOEWE Lipid Signalling Forschungszentrum' (LiFF, Frankfurt/Main). D.L., M.W., T.K., L.W., R.S., H.S. and K.K.K. are affiliated with COST Action BM0806.

References and notes

1. de Luca, L. *Curr. Med. Chem.* **2006**, *13*, 1.
2. Celanire, S.; Wijtmans, M.; Talaga, P.; Leurs, R.; de Esch, I. J. P. *Drug Discovery Today* **2005**, *10*, 1613.
3. Esbenshade, T. A.; Fox, G. B.; Cowart, M. D. *Mol. Interventions* **2006**, *6*, 77.
4. Wijtmans, M.; Leurs, R.; de Esch, I. J. P. *Expert Opin. Investig. Drugs* **2007**, *16*, 967.
5. Berlin, M.; Boyce, C. W. *Expert Opin. Ther. Patents* **2007**, *17*, 675.
6. Sander, K.; Kottke, T.; Stark, H. *Biol. Pharm. Bull.* **2008**, *31*, 2163.
7. Celanire, S.; Lebon, F.; Stark, H. In *The Third Histamine H_3 Receptor: Selective Ligands as Potential Therapeutic Agents in CNS Disorders*; Vohora, D. S., Ed.; Taylor & Francis CRC Press: Boca Raton, Fla.; 2009; pp 103–165.
8. Stark, H.; Kathmann, M.; Schlicker, E.; Schunack, W.; Schlegel, B.; Sippl, W. *Mini-Rev. Med. Chem.* **2004**, *4*, 965.
9. Murray, M. *Drug Metab. Rev.* **1987**, *18*, 55.
10. Yang, R.; Hey, J.; Aslanian, R.; Rizzo, C. *Pharmacology* **2002**, *66*, 128.
11. Berlin, M.; Ting, P. C.; Vaccaro, W. D.; Aslanian, R.; McCormick, K. D.; Lee, J. F.; Albanese, M. M.; Mutahi, M. W.; Piwinski, J. J.; Shih, N.-Y.; Duguma, L.; Solomon, D. M.; Zhou, W.; Sher, R.; Favreau, L.; Bryant, M.; Korfmacher, W. A.; Nardo, C.; West, R. E., Jr.; Anthes, J. C.; Williams, S. M.; Wu, R.-L.; She, S. H.; Rivelli, M. A.; Corboz, M. R.; Hey, J. A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 989.
12. Chadha, H. S.; Abraham, M. H.; Mitchell, R. C. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2511.
13. Jablonowski, J. A.; Ly, K. S.; Bogenstaetter, M.; Dvorak, C. A.; Boggs, J. D.; Dvorak, L. K.; Lord, B.; Miller, K. L.; Mazur, C.; Wilson, S. J.; Lovenberg, T. W.; Carruthers, N. I. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 903.
14. Zampeli, E.; Tiligada, E. *Br. J. Pharmacol.* **2009**, *157*, 24.
15. de Esch, I. J. P.; Thurmond, R. L. J. A.; Jongejan, A.; Leurs, R. *Trends Pharmacol. Sci.* **2005**, *26*, 462.
16. Gbahou, F.; Vincent, L.; Humbert-Claude, M.; Tardivel-Lacombe, J.; Chabret, C.; Arrang, J. M. *Br. J. Pharmacol.* **2006**, *147*, 744.
17. Burns, S.; Hamley, P. Patent WO2005014579, Feb. 17, 2005.
18. Igel, P.; Schneider, E.; Schnell, D.; Elz, S.; Seifert, R.; Buschauer, A. *J. Med. Chem.* **2009**, *52*, 2623.
19. Igel, P.; Schnell, D.; Bernhardt, G.; Seifert, R.; Buschauer, A. *Chem. Med. Chem.* **2009**, *4*, 225.
20. Sasse, A.; Kieć-Kononowicz, K.; Stark, H.; Motyl, M.; Reidemeister, S.; Ganellin, C. R.; Ligneau, X.; Schwartz, J.-C.; Schunack, W. *J. Med. Chem.* **1999**, *42*, 593.
21. Kieć-Kononowicz, K.; Więcek, M.; Sasse, A.; Ligneau, X.; Elz, S.; Ganellin, C. R.; Schwartz, J. C.; Stark, H.; Schunack, W. *Pharmazie* **2000**, *55*, 349.
22. Compounds **2**–**12** and **14**–**20** were described previously.[20,21] Compounds **13**, **21** and **22** were prepared as described by Sasse et al.[20] The products were obtained as colorless oils and crystallized as hydrogen maleates in EtOH/Et_2O. (a) Compound **13**. Starting from 4-methylpentan-1-ol; *N*-(4-Methylpentyl)phthalimide, yellow oil (yield: 71%); 4-Methylpentanamine hydrochloride, white solid, Mp 197 °C; yield: 72%; 3-(1-*H*-Imidazol-4-yl)propyl *N*-(4-methylpentyl)carbamate hydrogen maleate, white solid; Mp 81–82 °C; yield: 15%. ^{1}H NMR [DMSO-d_6]: δ = 8.83 (s, 1H, Im-2-*H*), 7.37 (s, 1H, Im-5-*H*), 7.06 (t, J = 5.6 Hz, 1H, CONH), 6.04 (s, 2H, Mal), 3.96 (t, J = 6.5 Hz, 2H Im···CH_2–O), 2.93 (q, J = 6.4 Hz, 2H, N-CH_2), 2.66 (t, J = 7.6 Hz, 2H, Im–CH_2), 1.87 (m, 2H, Im–CH_2–CH_2), 1.51(m, 1H, –CH(CH_3)$_2$), 1.38 (m, 2H, –CH_2–CH_2–CH(CH_3)$_2$), 1.12 (m, 2H, –CH_2–CH(CH_3)$_2$), 0.84 (d, J = 6.6 Hz, 6H, (CH_3)$_2$); IR (KBr) (cm^{-1}): 1694s (ν [C=O]); MS m/z (%) 253 ([M$^+$], 8), 109 ([Im–(CH$_2$)$_3^+$], 32), 108 (100), 107 (38), 95 ([Im–(CH$_2$)$_2^+$], 67), 82 (22), 81 ([Im–CH$_2^+$], 35), 80 (11), 54 (16), 41 (18). Anal. Calcd for $C_{13}H_{23}N_3O_2{\cdot}C_4H_4O_4{\cdot}0.5H_2O$ (M_r: 378.30): C, 53.98; H, 7.46; N, 11.11. Found: C, 54.23; H, 7.10; N, 11.13.(b) Compound **21**: Starting from (*R*)-(−)-octan-2-amine (Lancaster). White solid, Mp 105–107 °C; yield: 30%; [α]$_D$: −2.77 (*c* 1.0, EtOH); ^{1}H NMR [DMSO-d_6]: δ = 8.90 (s, 1H, Im-2-*H*), 7.40 (s, 1H, Im-5-*H*), 6.96 (d, J = 8.3 Hz, 1H, CON*H*), 6.06 (s, 2H, Mal), 3.96 (t, J = 6.6 Hz, 2H Im···CH_2–O), 3.70–3.38 (br s, 1H, N–CH + H_2O), 2.69 (t, J = 7.4 Hz, 2H, Im–CH_2), 1.90 (t, J = 7.4 Hz, 2H, Im–CH_2–CH_2), 1.34–1.24 (m, 10H, –(CH_2)$_5$), 1.02 (d, J = 6.6 Hz, 3H, –CH–CH_3), 0.82 (t, J = 6.3 Hz, 3H, CH_2–CH_3); IR (KBr) (cm^{-1}): 1689s (ν [C=O]); MS m/z (%) 281 ([M$^+$], 4), 113 (46), 109 ([Im–(CH$_2$)$_3^+$], 37), 108 (74), 107 (23), 95 ([Im–(CH$_2$)$_2^+$], 70), 82 (24), 81 ([Im–CH$_2^+$], 53), 70 (100), 55 (37), 44 (48). Anal. Calcd for $C_{15}H_{27}N_3O_2{\cdot}C_4H_4O_4{\cdot}0.75H_2O$ (M_r: 410.98): C, 55.53; H, 7.58; N, 10.38. Found: C, 55.48; H, 7.97; N, 10.22.(c) Compound **22**: Starting from (*R*)-(−)-octan-2-ol (Aldrich); *N*-(*S*)-(+)-2-octylphthalimide, colorless oil; yield: 79%; [α]$_D$: +29.48 (*c* 3.0, EtOH); (*S*)-(+)-octan-2-amine hydrochloride, white solid, Mp 85–86 °C; yield: 36%; [α]$_D$: −4.42 (*c* 1.5, MeOH); 3-(1-*H*-Imidazol-4-yl)propyl) *N*-[(*S*)-(+)-2-octyl]carbamate hydrogen maleate, white solid; Mp 108–110 °C; yield: 7%; [α]$_D$: +2.93 (*c* 1.0, EtOH); ^{1}H NMR [DMSO-d_6]: δ = 8.85 (s, 1H, Im-2-*H*), 7.40 (s, 1H, Im-5-*H*), 6.91 (d, J = 8.3 Hz, 1H, CON*H*), 6.02 (s, 2H, Mal), 3.93 (t, J = 6.6 Hz, 2H Im···CH_2–O), 3.42–3.30 (br s, 1H, N–CH + H_2O), 2.65 (t, J = 7.4 Hz, 2H, Im–CH_2), 1.86 (qu, J = 7.4 Hz, 2H, Im–CH_2–CH_2), 1.31–1.16 (m, 10H, –(CH_2)$_5$), 0.98 (d, J = 6.6 Hz, 3H, –CH–CH_3), 0.82 (t, J = 6.1 Hz, 3H, CH_2–CH_3); IR (KBr) (cm^{-1}): 1689s (ν [C=O]); MS m/z (%) 281 ([M$^+$], 12), 109 ([Im–(CH$_2$)$_3^+$], 34), 108 (100), 107 (22), 95 ([Im–(CH$_2$)$_2^+$], 56), 82 (23), 81 ([Im–CH$_2^+$], 41), 72 (14), 54 (17), 45 (16). Anal. Calcd for $C_{15}H_{27}N_3O_2{\cdot}C_4H_4O_4{\cdot}0.5H_2O$ (M_r: 406.48): C, 56.14; H, 7.94; N, 10.34. Found: C, 56.27; H, 7.89; N, 10.13.
23. Kieć-Kononowicz, K.; Zejc, A. *Polish J. Chem.* **1984**, *58*, 761.
24. Mitsunobu, O. *Synthesis* **1981**, 1.
25. Garbarg, M.; Arrang, J. M.; Rouleau, A.; Ligneau, X.; Trung Tong, M. D.; Schwartz, J. C.; Ganellin, C. R. *J. Pharmacol. Exp. Ther.* **1992**, *263*, 304.
26. Ligneau, X.; Morisset, S.; Tardivel-Lacombe, J.; Gbahou, F.; Ganellin, C. R.; Stark, H.; Schunack, W.; Schwartz, J.-C.; Arrang, J.-M. *Br. J. Pharmacol.* **2000**, *131*, 1247.
27. Schneider, E. H.; Schnell, D.; Papa, D.; Seifert, R. *Biochemistry* **2009**, *48*, 1424.
28. Tanrikulu, Y.; Proschak, E.; Werner, T.; Geppert, T.; Todoroff, N.; Klenner, A.; Kottke, T.; Sander, K.; Schneider, E.; Seifert, R.; Stark, H.; Clark, T.; Schneider, G. *Med. Chem. Med.* **2009**, *4*, 820.