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Sulfonamides with the *N*-alkyl-*N*′-dialkylguanidine moiety as 5-HT$_7$ receptor ligands

Paweł Zajdel [a,*], Gilles Subra [b], Pascal Verdie [b], Ewa Gabzdyl [a], Andrzej J. Bojarski [c], Beata Duszyńska [c], Jean Martinez [b], Maciej Pawłowski [a]

[a] Department of Medicinal Chemistry, Jagiellonian University Medical College, 9 Medyczna Street, 30-688 Kraków, Poland
[b] Department of Amino Acids, Peptides and Proteins, Institut des Biomolécules Max Mousseron, UMR 5247, CNRS, University Montpellier I and II, 15 Charles Flahault, 34-093 Montpellier, France
[c] Department of Medicinal Chemistry, Institute of Pharmacology, Polish Academy of Sciences, 12 Smętna Street, 31-343 Kraków, Poland

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ABSTRACT

A series of arylsulfonamides containing guanidine incorporated in the structure of secondary amines (piperidine, piperazine) was synthesized on SynPhase Lanterns and evaluated for 5-HT$_{1A}$, 5-HT$_{2A}$, and 5-HT$_7$ receptors. The results demonstrated that *N*-alkyl-*N*′-dialkylguanidines displayed good 5-HT$_7$/5-HT$_{1A}$ selectivity and may be regarded as promising structural core for development of 5-HT$_7$ ligands.

The actions of 5-hydroxytryptamine (5-HT), one of the major modulatory neurotransmitters in the central nervous system (CNS), are mediated by a number of receptors grouped in seven families. Scientific interest has focused on the most recently identified 5-HT subtype—the 5-HT$_7$ receptor. On the basis of CNS localization (thalamus, hypothalamus, hippocampus, amygdala) and pre-clinical pharmacological investigation, it has been hypothesized that 5-HT$_7$ receptors may be involved in affective disorders and mood regulation connected with sleep and circadian rhythms.[1] It is also worth noting that several antipsychotic drugs exhibit a high affinity for 5-HT$_7$ receptors.[2]

The knowledge of the involvement of 5-HT$_7$ receptors in the pathomechanism of psychiatric disorders has been improved by the development of selective agonists and antagonists, as well as due to the findings of several in vivo investigations.[3] Those works have proven that model 5-HT$_7$ antagonists (e.g., SB-269970) are efficacious in animal models of depression and anxiety.[4,5] Based, among others, on this fact, it has recently been hypothesized that 5-HT$_7$ antagonists seem promising in the process of elaboration of novel antidepressants with improved efficacy and devoid of a long onset of action.[6]

5-HT$_7$ receptor antagonists, followed by many SAR studies, have been described in a few reviews.[7,8] Among this class of molecules, a variety of sulfonamide derivatives with different aliphatic and aromatic secondary amine fragments occupy a prominent position (Fig. 1). Our interest focused on guanidine moiety since it may be regarded as one of crucial components of medicinally interesting molecules acting on CNS.[9–11] In particular it was found to be an essential part in the structure of several 5-HT receptor ligands affecting affinity and/or selectivity.[12–15] Recently, a number of derivatives containing an amidino-urea fragment have been described as 5-HT$_7$ ligands (Fig. 2).[16]

Taking account of the above-mentioned findings, we designed a small library of compounds containing both the sulfonamide moiety and a guanidine motif incorporated in the secondary amine (e.g., piperidine or piperazine). Structural modifications also comprised diversification of the length (C_2–C_4) of an alkylene spacer between sulfonamide and a molecule's basic center, and finally the kind of an arylsulfonyl fragment to determine the effect of steric properties. To efficiently obtain the designed compounds, we took advantage of a solid-phase methodology and developed a robust, parallel synthetic route to sulfonamide derivatives of *N*-alkyl-

* Corresponding author. Tel.: +48 12 620 54 50; fax +48 12 657 02 62.
E-mail address: mfzajdel@cyf-kr.edu.pl (P. Zajdel).

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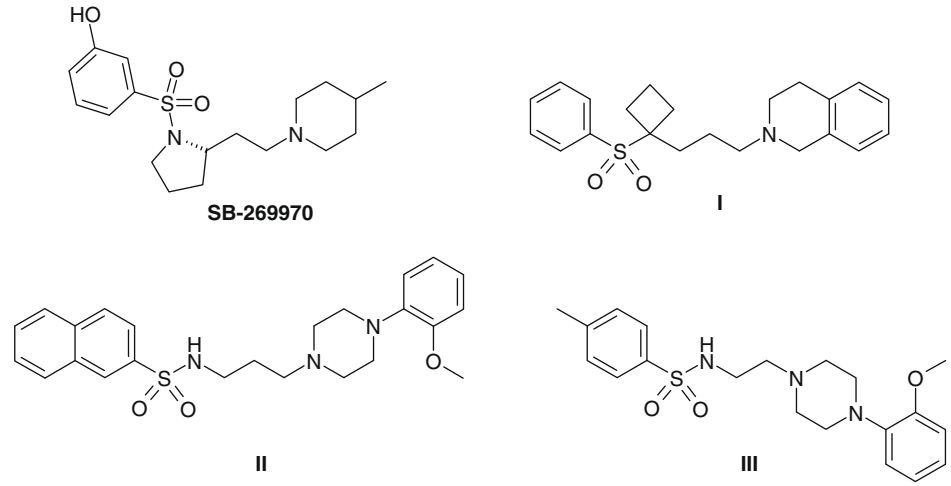


Figure 1.

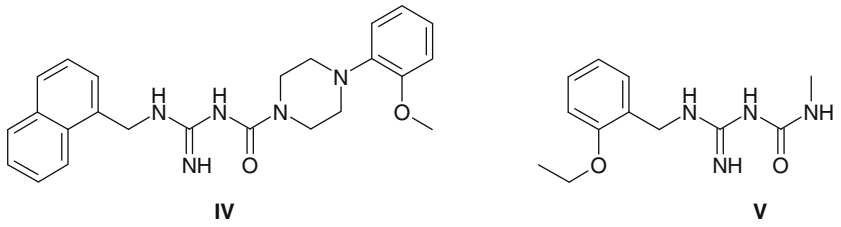


Figure 2.

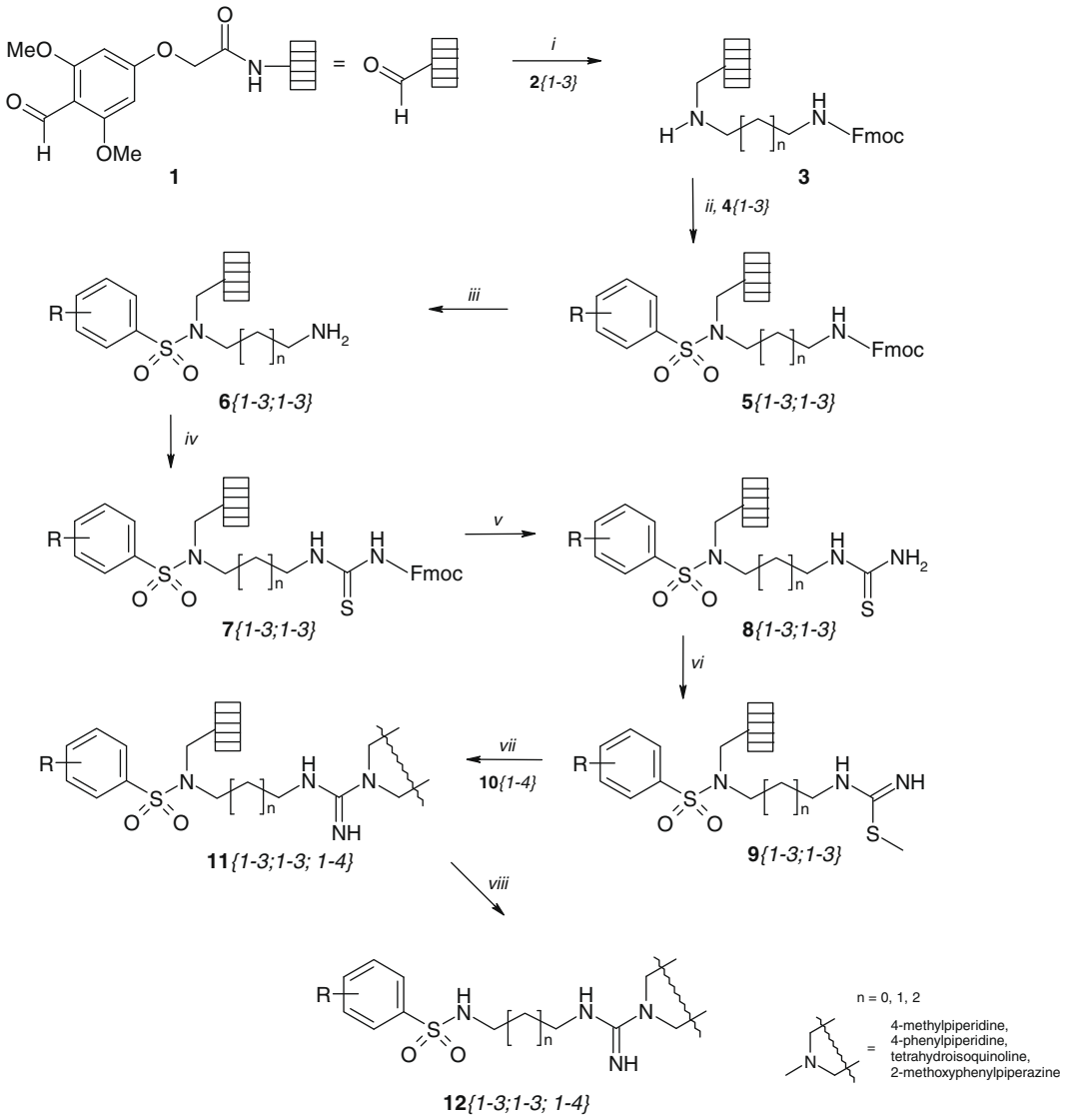
N′-dialkylguanidines (**12**, Scheme 1). The affinity of the selected library members was preliminarily tested for 5-HT_{1A}, 5-HT_{2A}, and 5-HT_7 receptors.

The general synthetic approach to the guanidine derivatives is presented in Scheme 1. The key starting Fmoc-protected diaminoalkanes (Fig. 3), prepared from corresponding diamines, were loaded to BAL Lanterns in an optimized one-pot reductive amination, involving $NaBH_3CN$ in a 10% solution of AcOH in a mixture of DMF/MeOH (50:50, v/v), the reaction taking place at a room temperature for 24 h. The subsequent coupling of secondary amines (**3**) with sulfonyl chlorides (diversity reagents 4; Fig. 4) in the presence of TEA in DCM yielded resin-bound sulfonamides **5**. Typically, the preparation of guanidines involves a reaction of amines with electrophilic amidine derivatives, protected by Boc groups.[17,18] Since such a protection was not orthogonal with our BAL linkage strategy, we treated deprotected primary amines (**6**) with Fmoc-isothiocyanate and obtained thiourea derivative **7**. Next, after Fmoc removal, the intermediate product (**8**) was submitted to double treatment with a MeI solution in DMF at a room temperature for 1 h to yield *S*-methyl derivative **9**. *N*-Alkyl-*N*′-alkylguanidines (**11**) were achieved via replacement of the methylthio group of **9** with representatives of diverse secondary amines (Fig. 5), the reaction taking place in an anhydrous DMSO at 80 °C for 24 h. The final products (**12**) were obtained upon treatment with a mixture of TFA/DCM 95:5 (v/v) for 2.5 h.

Based on initially optimized conditions, a library containing 36 derivatives was synthesized in a parallel manner by a split-and-pool approach on Syn-Phase Lanterns.[19] The Lanterns were equipped with colored cogs and spindles. The isolated products were found to be of moderate-to-high purity. Surprisingly, under optimized conditions, the obtained representatives containing an ethylene spacer showed low purity (16–52%). For other library members: the overall yields, calculated on the basis of the initial loading of the Lanterns, were between 24% and 48%, the purity values ranging from 73% to 99% (Table 1). Finally, eight library members were purified using a reverse-phase preparative LC/MS ESI automated system (Waters Micromass). The yielded compounds were submitted to biological assays. Selected library representatives were tested in competition binding experiments for native 5-HT_{1A} (rat hippocampus), 5-HT_{2A} (rat cortex), and cloned human 5-HT_7 (stably expressed in HEK-293 cells) receptors, according to the previously published procedures.[20,21]

Interestingly enough, the investigated compounds showed good affinity for 5-HT_7 receptors, which ranged from 140 to 339 nM, and very low activity at 5-HT_{1A} receptors (K_i = 1.09–17.59 μM). Considering 5-HT_{2A} receptor affinity, the reported compounds displayed good-to-low affinities ranging from 148 to 1251 nM (Table 2). In the series of investigated compounds neither the linker length nor the kind of arylsulfonyl fragment significantly influenced affinity for 5-HT receptors.

As part of ongoing efforts towards identification of selective 5-HT_7 receptor ligands several research groups focused on arylsulfonamides connected by an alkylene spacer with diverse secondary amine fragments (e.g., alkyl/aryl-piperidines or piperazines). It was demonstrated that the affinity of sulfonamide derivatives for 5-HT_7 receptors was often accompanied with high affinity for 5-HT_{1A} subtypes.[25,26] From the comparison between biological activity of the new derivatives and their close analogs without guanidine moiety (**12**{*2,3,4*} and **12**{*1,2,4*} vs **II** and **III,** Fig. 6) it comes out that the introduction of delocalized positive charge in the ionic center of molecule generally attenuated affinity for the tested 5-HT receptors. Interestingly, the relatively small decrease in activity was observed for 5-HT_{2A} and 5-HT_7 receptors, and at the same time all the



Scheme 1. Solid phase synthesis routes for sulfonamide **12**: (i) Diversity reagent **2**{*1–3*}, $NaBH_3CN$, DMF/MeOH/AcOH 45:45:10 (v/v/v), rt, 24 h; (ii) Diversity reagents **4**{*1–3*}, DMF, TEA, rt, 2 × 2.5 h; (iii, v) 20% piperidine/DMF; (iv) FmocNSC, DCM, rt, 2 × 1 h; (vi) MeI, DMF, 2 × 1 h; (vii) Diversity reagent **10**{*1–4*}, DMSO, 80 °C, 24 h; (viii) TFA, 2.5 h.

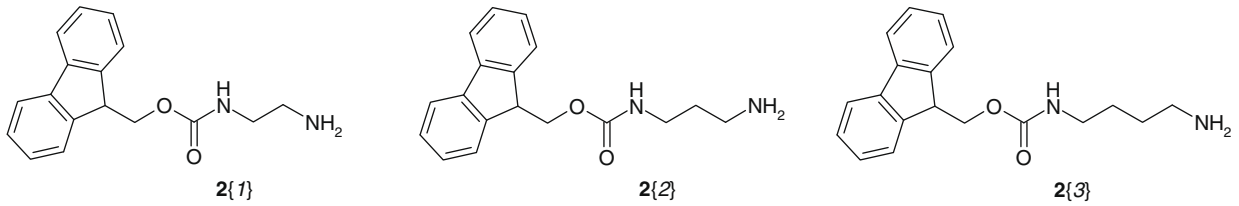


Figure 3. Protected aliphatic diamines, **2**{*1–3*}.

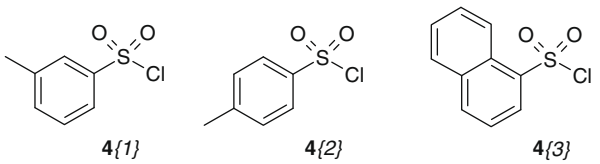
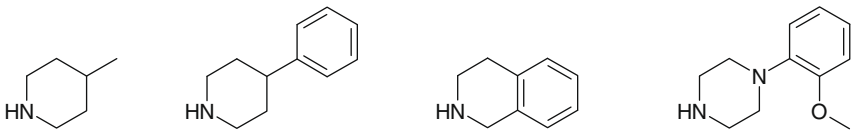


Figure 4. Diverse sulfonyl chlorides, **4**{*1–3*}.

compounds (except **12**{*1,1,1*} and **12**{*3,3,3*}) were practically inactive for 5-HT_{1A} receptors. In this way selectivity of the new compounds significantly increased over 5-HT_{1A} receptors (from 6 to 80-fold). This finding seems to be of special value since classic long-chain arylpiperazines, especially those containing *ortho*-methoxyphenyl fragment, were classified as highly active 5-HT_{1A} receptor ligands[26,27] or dual 5-HT_{1A} and 5-HT_7 receptor li-



10{*1*} **10**{*2*} **10**{*3*} **10**{*4*}

Figure 5. Diverse secondary amines, **10**{*1–4*}.

Table 1
Analytical data for library

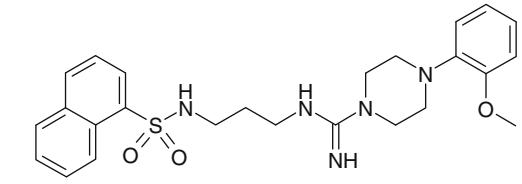
Compd[a]	Purity[b] (%)	MW calcd	$[M+H]^+$ found
12{*1,1,1*}	33	338.18	339.22
12{*1,1,2*}	17	400.19	421.21
12{*1,1,3*}	17	372.26	373.22
12{*1,1,4*}	19	431.2	432.3
12{*1,2,1*}	11	338.18	339.22
12{*1,2,2*}	21	400.19	401.27
12{*1,2,3*}	31	372.16	373.22
12{*1,2,4*}	18	431.2	432.31
12{*1,3,1*}	52	374.18	375.18
12{*1,3,2*}	42	436.19	437.25
12{*1,3,3*}	35	408.19	409.3
12{*1,3,4*}	30	467.2	468.27
12{*2,1,1*}	91	352.2	353.27
12{*2,1,2*}	100	414.21	415.27
12{*2,1,3*}	73	386.51	387.21
12{*2,1,4*}	91	445.21	446.24
12{*2,2,1*}	88	352.19	353.27
12{*2,2,2*}	90	414.21	415.27
12{*2,2,3*}	95	386.51	387.21
12{*2,2,4*}	93	445.21	446.24
12{*2,3,1*}	91	388.19	389.24
12{*2,3,2*}	89	450.21	451.25
12{*2,3,3*}	96	422.18	423.25
12{*2,3,4*}	78	481.21	482.22
12{*3,1,1*}	88	366.21	367.27
12{*3,1,2*}	96	428.22	429.33
12{*3,1,3*}	88	400.19	401.27
12{*3,1,4*}	83	459.23	460.3
12{*3,2,1*}	87	366.2	366.4
12{*3,2,2*}	97	428.22	429.27
12{*3,2,3*}	97	400.19	401.27
12{*3,2,4*}	87	459.23	460.3
12{*3,3,1*}	87	402.21	403.32
12{*3,3,2*}	81	464.22	465.31
12{*3,3,3*}	87	436.57	437.25
12{*3,3,4*}	91	495.23	496.28

[a] Library members encoded as **12**{*Diversity reagent 2, Diversity reagent 4, Diversity reagent 10*}.
[b] Determined by integration of the peak area at $\lambda = 214$ nm.

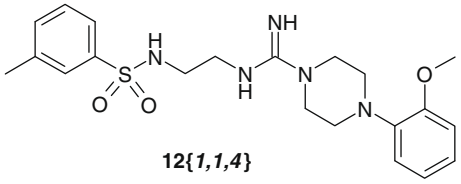
Table 2
Affinity data for 5-HT_{1A}, 5-HT_{2A}, and 5-HT_7 receptors for library representatives

Compd	K_i [nM][a]		
	5-HT_{1A}	5-HT_{2A}	5-HT_7
SB-269970[b]	>10,000	>10,000	1.2
I[c]	35	65	8
II[d]	4.6	85	20
III[e]	—	—	75
IV[f]	520	150	6
V[f]	>4000	400	49
12{*1,1,1*}	1098	148	177
12{*1,1,2*}	4555	160	161
12{*1,1,4*}	10,420	1146	339
12{*2,1,2*}	17,590	1251	276
12{*2,3,4*}	9860	940	195
12{*3,1,2*}	12,050	770	150
12{*3,2,4*}	10,200	340	140
12{*3,3,3*}	2080	195	198

[a] The estimated K_i values (see Ref. 20) were calculated from three independent binding experiments with SEM ⩽22%.
[b] Data taken from Ref. 22.
[c] Data taken from Ref. 23.
[d] Data taken from Ref. 24.
[e] Data taken from Ref. 25.
[f] Data taken form Ref. 16.



12{*2,3,4*}



12{*1,1,4*}

Figure 6.

gands.[24,28–30] Introduction of guanidine moiety into the structure of 5-HT ligands may now be considered as a method for designing more selective 5-HT_7 receptor agents.

Summing up, the synthesis and preliminary 5-HT_7, 5-HT_{1A}, and 5-HT_{2A} receptor activities of the series of guanidines incorporated in the structure of diverse well-known secondary amines with a potential application to CNS disorders have been described. We identified compounds possessing good affinity for 5-HT_7 and 5-HT_{2A} receptor, displaying selectivity over 5-HT_{1A} receptors. Further studies aimed at improvement of 5-HT_7 receptor binding will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.06.038.

References and notes

1. Hedlung, P. B.; Sutcliffe, J. G. *Trends Pharmacol. Sci.* **2004**, *25*, 481.
2. Roth, B. L.; Caragio, S. C.; Choudhary, M. S.; Uluer, A.; Monsma, F. J.; Meltzer, H. Y.; Sibley, D. R. *J. Pharmacol. Exp. Ther.* **1994**, *268*, 1403.
3. Guscott, M.; Bristol, L. J.; Hadingham, K.; Rosahl, T. W.; Beer, M. S.; Stanton, J. A.; Bromodge, F.; Owens, A. P.; Huscroft, I.; Myers, J.; Rupiak, N. M.; Patel, S.; Whiting, P. J.; Hutson, P. H.; Fone, K. C.; Biello, S. M.; Kulagowski, J. J.; McAllister, G. *Neuropharmacology* **2005**, *48*, 492.

4. Wesołowska, W.; Nikiforuk, A.; Stachowicz, K.; Tatarczyńska, E. *Neuropharmacology* **2006**, *51*, 578.
5. Wesołowska, A.; Nikiforuk, A.; Stachowicz, K. *Eur. J. Pharmacol.* **2006**, *553*, 185.
6. Mnie-Filali, O.; Lambas-Senas, L.; Zimmer, L.; Haddjeri, N. *Drug News Perspect.* **2007**, *20*, 613.
7. Leopoldo, M. *Curr. Med. Chem.* **2004**, *11*, 629.
8. Pittala, V.; Salerno, L.; Modica, M.; Siracusa, M. A.; Romeo, G. *Mini Rev. Med. Chem.* **2007**, *7*, 945.
9. Kolar, D.; Keller, A.; Golfinopoulos, M.; Cumyn, L.; Syer, C.; Hechtman, L. *Neuropsychiatr. Dis. Treat.* **2008**, *4*, 107.
10. Robertson, M. M. *Eur. Child Adolesc. Psychiatry* **2006**, *15*, 1.
11. Kemme, M. J.; vd Post, J. P.; Schoemaker, R. C.; Straub, M.; Cohen, A. F.; van Gerven, J. M. *Br. J. Clin. Pharmacol.* **2003**, *55*, 518.
12. Dukat, M.; Choi, Y.; Teitler, M.; Du Pre, A.; Herrick-Davis, K.; Smith, C.; Glennon, R. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1599; Dukat, M.; Wesolowska, A.; Young, R.; Glennon, R. A. *Pharmacol. Bichem. Behav.* **2007**, *87*, 203.
13. Beattie, D. T.; Smith, J. A.; Marquess, D.; Vickery, R. G.; Armstrong, S. R.; Pulido-Rios, T.; McCullough, J. L.; Sandlund, C.; Richardson, C.; Mai, N.; Humphrey, P. P. *Br. J. Pharmacol.* **2004**, *143*, 549.
14. Greenhouse, R.; New Harris III, R.; Jaime-Figueroa, S.; Kress J. M.; Repke, D. B.; Stabler, R. S. Patent Application Publication US 20060167255, 2006.
15. New Harris III, R.; Kress, J. M.; Repke, D. B.; Stabler, R. S. Patent Application Publication US 7531577, 2009.
16. Hong, Y.; Kuki, A.; Tompkins, E. V.; Peng, Z.; Luthin, D. R. Patent Application Publication US 20040044037, 2004.
17. Dodd, D. S.; Wallace, O. B. *Tetrahedron Lett.* **1998**, *39*, 5701.
18. Powell, D. A.; Ramsden, P. D.; Batey, R. A. *J. Org. Chem.* **2003**, *68*, 2300.
19. <http://www.mimotopes.com> (last accessed March, 2009).
20. Zajdel, P.; Subra, G.; Bojarski, A. J.; Duszyńska, B.; Pawłowski, M.; Martinez, J. *J. Comb. Chem.* **2004**, *6*, 761.
21. Zajdel, P.; Subra, G.; Bojarski, A. J.; Duszyńska, B.; Pawłowski, M.; Martinez, J. *Bioorg. Med. Chem.* **2005**, *13*, 3029.
22. Lovel, P. J.; Bromidge, S. M.; Dabbs, S.; Duckworth, D. M.; Forbes, I. T.; Jennings, A. J.; King, F. K.; Middlemiss, D. N.; Rahman, S. K.; Saunders, D. V.; Collin, L. L.; Hagan, J. J.; Riley, G. J.; Thomas, D. R. *J. Med. Chem.* **2000**, *43*, 342.
23. Raubo, R.; Beer, M. S.; Hunt, P. A.; Huscroft, I. T.; London, C.; Stanton, J. A.; Kulagowski, J. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1255.
24. Yoon, J.; Yoo, E. A.; Pae, A. N.; Rhim, H.; Park, W. K.; Kong, J. Y.; Park Choo, H. Y. *Bioorg. Med. Chem.* **2008**, *16*, 5405.
25. Vermeulen, E. S.; van Smeden, M.; Schmidt, A. W.; Sprouse, J. S.; Wikstrom, H. V.; Grol, C. J. *J. Med. Chem.* **2004**, *47*, 5451.
26. Becker, O. M.; Dhanoa, D. S.; Marantz, Y.; Chen, D.; Shacham, S.; Cheruku, S.; Heifetz, A.; Mohanty, P.; Fichman, M.; Sharadendu, A.; Nudelman, R.; Kauffman, M.; Noiman, S. *J. Med. Chem.* **2006**, *49*, 3116.
27. Caliendo, G.; Santagada, V.; Perissutti, E.; Fiorino, F. *Curr. Med. Chem.* **2005**, *12*, 1721.
28. Perrone, R.; Berardi, F.; Colabufo, N. A.; Lacivita, E.; Leopoldo, M.; Tortorella, V. *J. Med. Chem.* **2003**, *46*, 646.
29. Bojarski, A. J.; Duszyńska, B.; Kołaczkowski, M.; Kowalski, P.; Kowalska, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5863.
30. Volk, B.; Barkoczy, J.; Hegedus, E.; Udvari, Sz.; Gacsalyi, I.; Mezei, T.; Pallagi, K.; Kompagne, H.; Levay, G.; Egyed, A.; Harsing, L. G., Jr.; Spedding, M.; Simig, G. *J. Med. Chem.* **2009**, *51*, 2522.