Novel 5-HT$_{1A}$-receptor agonists: F11440, MKC242 and BAYx3702

Selective 5-HT reuptake inhibitors

The second-generation antidepressant drugs, the selective serotonin (5-HT) reuptake inhibitors (SSRIs) fluoxetine (Prozac) and paroxetine (Seroxat), are among the most profitable synthetic drugs ever marketed. Increasingly, these drugs are not only prescribed for depression, but also for treating anxiety and certain phobia disorders. The SSRIs potently and selectively inhibit the presynaptic 5-HT transporter, thereby increasing 5-HT availability at the synapse.

At the last count, 15 separate subtypes of 5-HT receptors have been identified by molecular cloning techniques to be distinct genetic entities. SSRIs will therefore cause inhibition of 5-HT uptake by all 5-HT-responsive neurones, many of which will have other physiological properties. Depression and related affective and anxiety disorders involve suboptimal activity of the post-synaptic 5-HT$_{1A}$ receptor subtype [Stahl, S.M. *J. Clin. Psychiatry* (1997) 58 (Suppl. 8), 20–26]. Non-selective serotonergic activation following SSRI treatment might explain the slow onset of their antidepressant effects in humans, and could be involved in some of their undesired side-effects, notably loss of libido [Waldinger, M.D. *et al. Int. Clin. Psychopharmacol.* (1988) 13 (Suppl. 6), S27–S33; Labbate, L.A. *et al. Biol. Psychiatry* (1998) 43, 904–907]. Selective 5-HT$_{1A}$ receptor agonists could therefore be attractive alternatives to the present prosperous SSRIs.

Role of 5-HT1A receptors in depression and anxiety

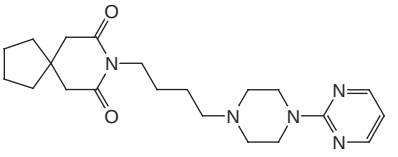
Several recent studies further imply diminished 5-HT$_{1A}$-receptor action in depression and anxiety. Reduced 5-HT$_{1A}$ activity results in inhibition of the superficial cells of the entorhinal cortex (EC), the main input to the hippocampus. Activation of EC 5-HT$_{1A}$ receptors removes such inhibition [Schmitz, D. *et al. J. Neurophysiol.* (1998) 80, 1116–1121]. In accord, long-term SSRI treatment resulted in tonic activation of forebrain 5-HT$_{1A}$ receptors [Haddjeri, N.J. *et al. Neuroscience* (1998) 18, 10150–10156]. Rats exposed to chronic stress, as well as suicide victims, express reduced 5-HT$_{1A}$ mRNA and receptor binding levels in their hippocampus [Lopez, J.F. *et al. Biol. Psychiatry* (1998) 43, 547–573]. Moreover, 5-HT$_{1A}$-knockout mice were shown to behave similarly to humans with an anxiety-related disorder [Ramboz, S. *et al. Proc. Natl. Acad. Sci. U. S. A.* (1998) 95, 14476–14481].

5-HT receptor agonists for treatment of Alzheimer's disease

Subtype-selective 5-HT receptor agonists might also have a potential for treating Alzheimer's disease (AD). Large reductions of 5-HT levels in cerebrospinal fluid [Tohgi, H. *et al. Neurosci. Lett.* (1992) 141, 9–12] and in blood platelets [Kumar, A.M. *et al. Neuropsychobiology* (1995) 32, 9–12] have been observed in AD. Although no drug trials with 5-HT agonists have been reported for AD, SSRIs were beneficial for treating anxiety symptoms in Down's syndrome, which shares certain aspects with AD [Geldmacher, D.S. *et al. J. Geriatr. Psychiatry Neurol.* (1997) 10, 99–104].

Drug companies are thus keen on developing novel selective 5-HT$_{1A}$ receptor agonists as third-generation antidepressants and anxiolytics. Some presently available 5-HT$_{1A}$ receptor agonists have limited value because of interactions with other receptors, such as anti-dopaminergic activity (buspirone, **1**) or anti-histaminergic activity (flosinoxan, **2**).

A large trial with zalospirone, a cyclic imide with partial 5-HT$_{1A}$-agonist activity, failed because it caused severe dizziness and nausea in almost half the study participants [Rickels, K. *et al. J. Clin. Psychopharmacol.* (1996) 16, 212–217].



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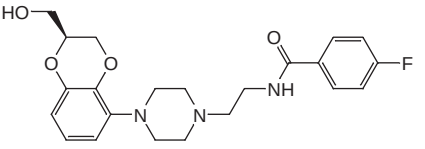

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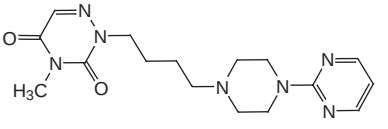
Recent 5-HT$_{1A}$ receptor agonists

Some newly introduced 5-HT$_{1A}$ receptor agonists seem to be devoid of the undesired activities described above. For example, F11440 (4-methyl-2-{4-[4-(pyrimidin-2-yl)-piperazino]-butyl}-2*H*,4*H*-1,2,4-triazin-3,5-dione, **3**) was recently introduced as such a selective novel drug [Koek, W. *et al. J. Pharmacol. Exp. Ther.* (1998) 287, 266–283].



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This compound exhibited a nanomolar affinity towards the 5-HT$_{1A}$ receptor, and in animal models produced anxiolytic- and antidepressant-like effects that were more substantial than those of the 'older' 5-HT$_{1A}$ agonists buspirone, ipsapirone and flesinoxan.

Another promising drug is the novel benzodioxan derivative, 5-(3-{[(2*S*)-1,4-benzodioxan-2-ylmethyl]amino}propoxy)-1,3-benzodioxole HCl (MKC242,**4**), which showed anxiolytic-like and antidepressant-like effects in several animal models [Abe, M. *et al. J. Pharmacol. Exp. Ther.* (1996) 278, 898–905].

Yet another unique 5-HT$_{1A}$ receptor agonist drug candidate, recently intro-

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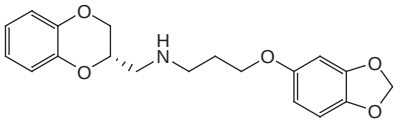

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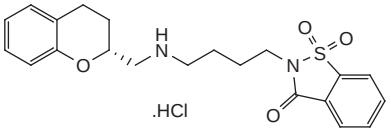
duced by Bayer, is the aminomethylchroman derivative {*R*-(−)-2-4-[(chroman-2-ylmethyl)-amino]-butyl-1,1 dioxobenzo(d) isothizolone HCl, BAYx3702, **5**}.



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In addition to its anxiolytic and antidepressant effects in animal models, this compound exhibited neuroprotection, which may reflect its ability to inhibit ischemia-induced excessive glutamate release [De Vry, J. and Jentzsch, K.R. *Eur. J. Pharmacol.* (1998) 357, 1–8]. Treatment of rats with BAYx3702 within 4 h of occlusion of the middle cerebral artery reduced the volume of the subsequent cortical infarct by ~50% [Semkova, I. *et al. Eur. J. Pharmacol.* (1998) 359, 251–260].

Such promising drug leads will certainly add zest and excitement to the competitive antidepressants and anxiolytics drug scene.

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In short…

GumTech International (Phoenix, AZ, USA; a manufacturer of specialty chewing gum products designed to provide health benefits to consumers) and **Gel Tech** (a company specializing in the use of nasal gels for delivering health- care products) enter into joint venture. GumTech has signed a letter of intent with Gel Tech to form a Limited Liability Corporation to market and distribute ZICAM™, a homeopathic cold remedy. ZICAM is a homeopathic nasal gel containing an ionic emulsification formula called Zinullose™ (patent pending). Early clinical research indicates that ZICAM significantly reduces the duration of the common cold.

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