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Synthesis and SAR study of new halogenated analogues of SSRI

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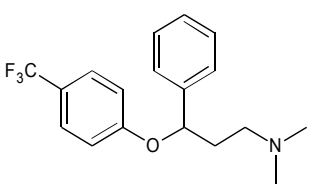
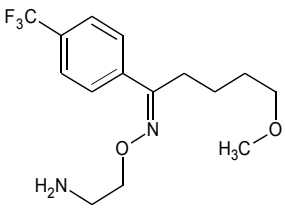
Selective serotonin reuptake inhibitors (SSRI) acting through blockade of serotonin transporter (SERT) are frequently prescribed therapeutic agents in various affective disorders. The SSRIs are therapeutically useful in the treatment of panic disorder, posttraumatic stress disorder, social anxiety disorder, obsessive-compulsive disorder, premenstrual dysphoric disorder, and anorexia.[1] Since the first blockbuster SSRI, Fluoxetine (Prozac), arrived on the scene in 1988, SSRIs have dominated the market of antidepressants, because they typically have fewer adverse effects than other types of medicaments with the same effectiveness. To this day, seven drugs in the SSRI class have been approved by FDA (fluoxetine, paroxetine, citalopram, escitalopram, sertraline, fluvoxamine and vilazodone).[2] Although generally well tolerated with numerous advantages over other antidepressants, SSRIs are not devoid of adverse effects, such as anxiety, anticholinergic effects, gastrointestinal and sexual dysfunction. In general, variations in side-effect profiles are attributed to mechanistic differences of SSRI and the difference in patient profiles, ranging from genetic polymorphisms to personality dimensions.[3] Therefore, the discovery of new SSRIs may increase the pool of available drugs and improve the currently available therapies.

As a part of our study on the SERT, novel series of halogenated fluoxetine/fluvoxamine analogues has been designed and synthesized.



Fluoxetine



Fluvoxamine

The SERT affinities for all the synthesized compounds were assessed in radioligand binding experiments. The structure-affinity relationships and the results of molecular modelling experiments are discussed.

[1] Spinks, D. et al. (2002). Current medicinal chemistry. 9(8):799-810
[2] www.fda.gov; [3] Cascade E.et al. (2009). Psychiatry (Edgmont). 6(2):16-18

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