Section-II

Chapter-5

DISCUSSION

5. DICUSSION

Selective serotonin reuptake inhibitors (SSRIs) expand levels of synaptic serotonin, which acts at the diverse serotonin (5-HT) receptor subtypes (upwards of 14 separate receptors). The antidepressant activities of SSRIs are likely intervened by one or a greater number of these receptors, yet it is impossible that every one of the 14 subtpes assume a basic role. Also, the unwanted adverse effects of SSRIs are likely intervened by activation of one or a greater amount of these receptors, which may be unique from those that intercedes antidepressant activity. In addition, because of key regulation by 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} receptors, constant organization of SSRIs is important to control increase in serotonin levels [143, 144]. Therefore, the onset of action can be improved by particularly targeting a postsynaptic serotonin receptor. One competitor 5-HT receptor upholds by preclinical reports, as ahead of schedule as the 1990s, for mediating the antidepressant-like effect of SSRIs is the 5-HT_{2C} receptor. 5-HT_{2C} receptor agonists illustrate antidepressant-like activity in numerous animal models (both acute and chronic) of depression. For example, 5-HT_{2C} receptor agonist reduces immobility time and enhances swimming time in the FST in rats in a way similar to SSRIs [145]. The therapeutic effects of the 5-HT_{2C} receptor agonists and SSRIs in the rat FST are antagonized by the 5-HT_{2C} antagonists [145]. This report further supports the role of 5-HT_{2C} receptors in mediating antidepressant-like activity of SSRIs and 5-HT_{2C} receptor agonists. Other studies with 5-HT_{2C} receptor agonists have demonstrated that they are efficient in multiple models of antidepressant effect with the chronic mild stress model and the BULB model [146, 147], the resident–intruder model and the DRL-72 (differential reinforcement of low rate) model [148, 149].

According to previous reports, WAY-163909 (a 5-HT_{2C} agonist) significantly reduced immobility in the FST in both WKY and SD rats. In the SD rats, WAY-163909 augmented swimming and had no result on climbing, seen with SSRIs. The diminishments in immobility produced by WAY-163909 in the WKY rats were completely reversed by the 5-$HT_{2C/2B}$ receptor antagonist SB 206553, demonstrative of a function for 5-HT_{2C} and/ or 5-HT_{2B} receptors in mediating this behavioral effect. Past studies have demonstrated that structurally diverse 5-HT_{2C} receptor agonists such as WAY-161503 or Ro 60-0175 also reduce immobility and enhance swimming [145]. In another report, WAY-163909 was surveyed in a new model [150] of antidepressant-induced sexual dysfunction. In this model, male rats that had a past overnight sexual experience are put in a room with responsive females that provide auditory, visual and olfactory prompts. Under these conditions, there is an enhancement in the number of spontaneous penile erections.

The wide exhibit of behavioral changes connected with 5-HT_{2C} receptor agonism is truly intriguing. In this respect, WAY-163909 produces antipsychotic-like effects, anorectic effects, and antidepressant-like effects [151, 152]. The capability of 5-HT_{2C} receptor antagonists to obstruct the effects of WAY-163909 over these various areas is consistent with WAY-163909 producing its effects via activation of the 5-HT_{2C} receptor. 5-HT_{2C} receptors are extensively expressed in brain and that may, to some degree, clarify the assorted qualities of 5-HT_{2C} receptors. As it has long been realized that 5-HT has a wide variety of utilitarian exercises, the widespread dissemination of the 5-HT_{2C} receptor, may permit activation of this receptor to imitate huge number of effects of 5-HT.

5-HT_2 receptor family comprises of three subunits: 5-HT_{2A}, 5-HT_{2B} and 5-$HT_{2C.}$ They exhibit 46-50% overall sequence identity due to their homologous nature. 5-HT_{2C} receptors play a pivotal role in regulation of anxiety, depression, food intake, penile erection etc. This puts great emphasis on finding of potent and selective 5-HT_{2C} receptor modulators devoid of the hallucinogenic and cardiac side effects associated with 5-HT_{2A} and 5-HT_{2B} receptors respectively. Recent evidences of vabicaserine [153] and lorcaserin [154] support the above argument.

Present study deals with the pharmacological evaluation of some novel synthesized compounds as 5-HT_{2C} agonists. Test compounds **(7, 10-14, 18-20, 23, 26-29, 32-41, 45, 46, 48, 51, 57 and 58)** which were found to be inactive on 5-HT_{2A} and 5-HT_{2B} receptors in the *in vitro* studies suggesting their lack of selectivity towards these two receptors. Thus it was assumed that these compounds could be either inactive or might be selective 5-HT_{2C} receptor modulators. The proposed hypothesis was checked using different *in vivo* rodent models. The compounds were first checked using the TST in mice, a model for the assessment of the depression. From the above listed compounds, only **7, 19** and **28** showed significant decrease in the immobility time as compared to the saline control (p<0.001) which could be due to their 5-HT_{2C} receptor activity. Thus these compounds (**7, 19** and **28**) have shown antidepressant response similar to the standard, i.e. fluoxetine. There is a controversial effect of 5-HT_{2C} receptor agonists on the depression. Rajkumar et al have demostrated the ability of *m*-CPP to induce depressogenic behaviour in rodents [155] while Moreau et al have revealed the antidepressant effect of RO-600175 and RO-600332 [146].

Further, the compounds (**7, 19** and **28**) were evaluated for the anxiety model. Elevated plus maze test was adopted to assess anxiety like condition. These test compounds significantly reduced the exploration as well as time spent in open arm (p<0.001) showing anxiogenic like response similar to *m*-CPP. Anxiety is mainly regulated by amygdala region

of the brain with high level of 5-HT_{2C} receptor expression. Previous reports have demonstrated that activation of amygdala by 5-HT_{2C} receptor agonist is strongly associated with anxiety state [156]. So, antagonism of 5-HT_{2C} receptor might be beneficial for the treatment of anxiety [157, 158]. Similar to this context the compounds (**7**, **19** and **28**) showed anxiogenic response which was significantly reversed by **SB-206553** (a 5-HT_{2C} antagonist). This shows that the compounds (**7, 19** and **28**) are 5-HT_{2C} agonists.

Compounds (**7, 19** and **28**) were further assessed for the 5-HT_{2C} receptor mediated hypophagic response. They significantly attenuated the food intake which was reversed by **SB-206553**, a selective 5-HT_{2C} receptor antagonist, confirming their selectivity. Tecott et al have demonstrated that 5-HT_{2C} receptor knockout mice develop obesity and are hyperphagic throughout their life [159]. Pro-opiomelanocortin (POMC) neurons predominantly express 5-HT_{2C} receptor mRNA where its agonism lead to increased production of α-msh (melanocyte stimulating hormone) which ultimately enhances MC_4 receptor signalling [160-162], resulting in reduced food intake. 5-HT_{2C} receptor agonists are also able to increase satiety resulting in reduced food intake [161, 163].

Compounds (**7, 19** and **28**) were also evaluated for the 5-HT_{2C} receptor mediated penile erection along with **SB-206553**. *m*-CPP induces penile erection and excessive grooming with increased level of oxytocin, prolactin and corticosterones. Paraventricular nucleus is believed to control these behavioural and neuroendocrine responses [164]. **RO 60-0175**, a selective 5-HT_{2C} receptor agonist, mimics *m*-CPP induced penile erection [165]. **SB-200646** and **SB-206553**, which behave as potent antagonists at 5-HT_{2C} receptors [166, 167], reversed the effect. 5-HT_{2C} receptors at the lumbosacral level are strongly associated with the supraspinal serotonergic control of erection [168]. In accordance with previous reports, the compounds (**7**, **19** and **28**) showed significant penile erections which were reversed by **SB-206553** (a 5-HT_{2C} antagonist).

Previous studies revealed that 5-HT_{2C} receptors have influence on the firing of monoamine neurotransmitters. They negatively regulate firing of DA and 5-HT neurons in the dorsal raphe nucleus (DRN) and ventral tegmental area (VTA), respectively [169-172]. Present study revealed that the test compounds significantly decreased the DA and 5-HT levels in the rat brain similar to that of *m*-CPP [173]. This supports the above finding showing that 5-HT_{2C} receptor agonists decrease DA and 5-HT levels. These results indicated that the compounds (**7**, **19** and **28**) are potential 5-HT_{2C} agonists that can be evaluated further pre-clinically.