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Antidepressant Potential of 5-HT$_3$ Receptor Antagonist, *N*-n- propyl-3-ethoxyquinoxaline-2-carboxamide (6n)

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ABSTRACT

The present study was designed to evaluate the antidepressant potential of 5-HT3 receptor antagonist *N*-n-propyl-3-ethoxyquinoxaline-2-carboxamide (6n). The compound '6n' with optimum log P and pA_2 value identified from a series of compounds synthesized in our laboratory was subjected to forced Swim Test (FST) (1, 2, and 4 mg/kg, i.p) and Tail Suspension Test (TST) (1, 2, and 4 mg/kg, i.p.). The compound '6n' significantly reduced the duration of immobility in mice without affecting the baseline locomotion. Moreover, '6n' (2 mg/kg, i.p.) potentiated the 5-hydroxytryptophan (5-HTP)-induced head twitch responses in mice and '6n' at tested dose (1 and 2 mg/kg, i.p.) reversed the reserpine-induced hypothermia in rats. In interaction studies of '6n' with various standard drugs/ligands using FST, '6n' (1 mg/kg, i.p.) potentiated the antidepressant effect of venlafaxine (4 and 8 mg/kg, i.p.) and fluoxetine (10 and 20 mg/kg, i.p.). Additionally, '6n' (1 and 2 mg/kg, i.p.) influenced the effect of harmane (5 mg/ kg, i.p.) as well as reversed the effect of parthenolide (1 mg/kg, i.p.) by reducing the duration of immobility in FST. Furthermore, '6n' (1 mg/kg, i.p.) potentiated the effect of bupropion (10 and 20 mg/kg, i.p.) in TST. Chronic '6n' (1 and 2 mg/kg, i.p.) treatment attenuated the behavioral abnormalities in olfactory bulbectomized rats. In conclusion, these various findings reiterated the antidepressant-like effects of '6n' in behavioral models of depression.

Key words: 5-HT$_3$ receptor antagonists, forced swim test, head twitch, reserpine, tail suspension test

INTRODUCTION

Depression is a chronic, recurring, and potentially life- threatening illness that affects up to 20% of the population across the globe.[1-4] It is one of the top ten causes of morbidity and mortality worldwide, based on a survey by the World Health Organization. Despite a steady increase in the number of antidepressants over the years, the prevalence of the disorder remains stable which may be due to unclear pathophysiology or the inconsistent efficacy of currently available antidepressants with undesirable side effects. However, there is a direct correlation between the catecholaminergic neuronal systems and depression. Serotonin is the major neurotransmitter involved in the depression. Till now, seven superfamilies of serotonin receptors are identified; in that, serotonin type 3 (5-HT$_3$) receptors are pentameric ligand-gated ion channels belonging to the superfamily of Cys-loop receptors. 5-HT$_3$ receptors are known to be expressed in the central nervous system in regions

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involved in the vomiting reflex, processing of pain, the reward system, cognition, depression and anxiety control. The abundance of 5-HT_3 receptors in the chemoreceptor triggering zone has qualified them as primary targets for anti-emetic agents. Selective 5-HT_3 receptor antagonists, such as; ondansetron (OND) and tropisetron are now recognized as drugs of choice in managing cancer chemotherapy- induced and postoperative nausea and vomiting.[5,6] The motivating outcomes from preliminary behavioral tests on 5-HT_3 receptor antagonists, their good safety profile, and the complementary effectual regional distribution of 5-HT_3 receptors in the central nervous system have urged further research to establish their potential usage in a range of central nervous system disorders. Studies on human beings using selective 5-HT_3 receptor antagonists discovered heterogeneous distribution throughout the brain within the brainstem, e.g., nucleus tractus solitarius, area postrema, and spinal trigeminal nucleus as well as the forebrain, e.g., hippocampus, amygdala, nucleus accumbens, putamen, caudate.[7,8]

The role of 5-HT_3 receptors in anxiety is confirmed by studies of 5-HT_{3A} knockout mice which revealed that 5-HT_{3A} receptor subtypes regulate depression- and anxiety-related behaviors.[9] Evidence for the relevance of 5-HT_3 receptor antagonists in the treatment of depression stems from clinical trials in which patients suffering from complex disorders such as fibromyalgia and bulimia showed improvement of the comorbid depression.[10,11]

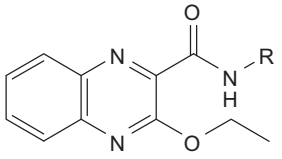
According to proposed hypothesis by Rajkumar and Mahesh (2010), postsynaptic 5-HT_3 receptor antagonism in serotonergic neurons can facilitate specific binding of 5-HT to other postsynaptic receptors such as 5-HT_{1B}, 5-HT_{2A}, and 5-HT_{2C}, thereby aiding in serotonergic transmission.[12] Thus, the paucity of evidence on the direct influence of 5-HT_3 receptor antagonist treatment on rodent depression-like behavior triggered the present study with objectives of which are (i) to screen the molecule '6n', preclinically in various behavioral and mechanistic rodent models of depression (ii) to conduct drug interaction studies with conventional antidepressants/ligands in order to propose the plausible mechanism underlying the above effect.

Using the three-component pharmacophore mode,[13] a series of 5-HT_3 receptor antagonists were designed, synthesized, and screened for their 5-HT_3 antagonist potential [Table 1]. The compounds were tested for their ability to inhibit the 5-HT_3 receptor in isolated guinea pig ileum, and the pA_2values were determined against 2-methyl- 5-hydroxytryptamine with OND as the reference drug.[6,14]

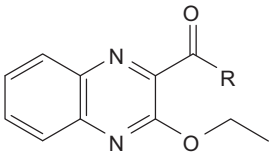
Preclinical screening of new chemical entity (NCE) in depression have been utilized vigorously to evaluate the novel compounds.[15] These tests neglect the aspect of face validity but have a strong predictive validity to aid in the identification of efficient antidepressant molecules.[16] Hence, a battery of behavioral tests were adopted for the study which included acute models like Forced Swim Test (FST),[17] Tail Suspension Test (TST),[18,19] mechanistic models like 5-hydroxytryptophan (5-HTP)-induced head twitch response in mice, and reserpine-induced hypothermia (RIH).[20] Evaluation of chronic effect of the compound was studied on olfactory bulbectomized (OBX) rats[21,22] to provide significant information on antidepressant activity of 6n, which was identified for this study based on pA_2 and log *P* values.

In the present study, compound *N*-n-propyl-3-ethoxyquinoxaline-2-carboxamide (6n) which exhibited an optimum log P and pA_2 values (pA_2-7.6) greater than the standard 5-HT_3 receptor antagonist, OND (p*A2* -6.9),[23,24] was selected for the preliminary antidepressant screening in the standard rodent models of depression as mentioned above.

Table 1: Log *P* and p*A2* values of series of 3-ethoxyquinoxali-2-carboxamides



6a-6q



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Compound	R	Log P[a]	pA_2[b]
6a	C_6H_5-	3.36	7.8
6b	4-Me-C_6H_4-	3.85	5.7
6c	4-MeO-C_6H_4-	3.23	6.1
6d	C_6H_5-CH_2-	3.43	6.2
6e	C_6H_5-NH-	2.88	5.8
6f	3-Ac-C_6H_4-	2.67	6.1
6n	3-Cl-C_6H_4-	3.92	5.4
6h	4-NO_2-C_6H_4-	3.36	5.5
6i	2-pyridinyl-	2.74	6.2
6j	3-Cl-2-CH_3-C_6H_3-	4.41	7.4
6k	Benzothiazol-2-yl-	4.56	6.8
6l	4-Benzamido-phenyl-	4.17	5.3
6m	2-Benzamido-phenyl-	4.17	6.2
6n	CH3CH2CH2-	2.52	7.6
6o	$CH_3CH_2CH_2CH_2$-	2.94	7.6
7	Pyrrolidinyl	2.25	4.9
6p	Cyclopentyl-	2.83	4.8
6q	Cyclohexyl-	3.25	7.8
-	Ondansetron	1.7	6. 9

[a]log*P* values were calculated using ChemBioDraw Ultra 11 (Cambridge Software)
[b]pA_2 values are the means of two separate experiments. SE was less than 10% of the mean