Synthesis and evaluation of antipsychotic activity of 11-(4′-(N-aryl carboxamido/N-aryl-α-phenyl-acetamido)piperazinyl)-dibenzo[b,f][1,4]-oxazepine derivatives

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Abstract In the present study, a series of new substituted N-11-(4′-N-aryl carboxamido/N-aryl-α-phenyl-acetamido)piperazinyl)-dibenzo[b,f][1,4]-oxazepine derivatives were designed on a revised structural model, length and nature of linker and introduced ary1 group. All the compounds (M1-M12) were synthesized by economical route and confirmed by IR, 1H NMR, and mass spectral analysis. The antipsychotic potentiometry of the synthesized derivatives were evaluated in mice by catalepsy and foot sore induced aggression. The present study demonstrates significant antipsychotic activity for most of the compounds from series. Compounds M1-M4 were found to be potent antipsychotic compounds of the series at 5 mg/kg dose level when compared with the reference drug clozapine.

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1. Introduction

Schizophrenia is one of the most widespread psychiatric disorders and approximately 1.5-2% of the world’s population suffers from severe symptoms occupied more than half of the bed in psychiatric clinic (The World Health Report, 2001). Currently many drugs are available for the treatment of psychosis. Ever since antipsychotics were introduced it has been observed that patients are liable to suffer from drug-induced extrapyramidal symptoms such as Parkinsonism, acute dystonic reactions, akathisia, tardive dyskinesia and tardive dystonia (Chakrabarti et al., 1980; Work group on schizophrenia, 1997). The introduction of the dibenzodiazepine antipsychotic agent clozapine ([3-chloro-1H-1,2,4-triazepine]-5H-dibenzo[b,f][1,4]-diazepine) was an important development in the pharmacotherapy of schizophrenia (Burki et al., 1975; Sayers et al., 1975). Preclinical and clinical investigations have shown that clozapine has properties different from those of classic neuroleptic agents, as well as a substantial therapeutic advantage (Kane et al., 1981; Lieberman et al., 1986; Lieberman et al., 1989). Clozapine was found to be one of the better choices for the treatment of refractory schizophrenia. Unlike classic neuroleptic agents, clozapine did not cause Parkinsonism, dystonia, or tardive dystonia,