Depressive disorders generally associated with severe functional impairment and high health care costs have increasingly become a public health concern [Brown et al., 2004]. According to recent epidemiological surveys, the life time incidence of depression is escalated up to 10% to 15% [Lepine and Bliley 2011]. Major depressive disorder (MDD) has serious impacts on morbidity and mortality [Kessler et al., 2005; Schulz et al., 2002]. The classical antidepressants in recent times have been challenged for clinical limitations and adverse effects. Thus, it is particularly urgent to develop efficient and safe antidepressant drugs.

During last years, the therapeutic effect of natural products particularly fatty acids on depressive disorders has drawn great attention. Several research have suggested omega-3 fatty acids as potential augmenters of antidepressant drug effects, especially in the treatment of resistant depression [Fava et al., 2001, Nemets et al., 2002, Logan et al., 2003, Jazayeri et al., 2008]. A recent meta analysis of omega-3 fatty acid has found statistically significant antidepressant effects, but the clinical significance was limited secondary to publication bias and significant heterogeneity between studies [Lin et al., 2007]. A small number of placebo-controlled studies have failed to show antidepressant effects for omega-3 fatty acids [Rogers et al., 2008]. It has been also reported that omega-3 fatty acids were more efficacious than the placebo among those patients not suffering a full major depressive episode but had no efficacy for those patients with MDD [Rakofsky et al., 2009]. However, gamma linolenic acid, an essential polyunsaturated fatty acid has been reported to selectively inhibit tumor cells without harming normal cells [Reddy et al., 1998].

Heterocyclic compounds belonging to 1,2,4-triazole and pyrazoline nucleuses have been shown to have antidepressant and MAO inhibitory activities of [Kane et al., 1998, Palaska et al.,2001; Sarva et al., 2002, Chimenti et al., 2006]. Some triazole derivative drugs such as nefazodone (45) and etoperidone (46) are currently in clinical use to treat depression. Both have been reported to show their antidepressant action with relation to central seronergic system. During the last two decades, the chemistry of 1,2,4-triazole, 1,3,4-oxadiazole and their derivatives have received considerable attention owing to their anticancer activities [Padmavathi et al., 2009; Aboria et al., 2006; Holla et al., 2003].
(45). Nefazodone  

(46). Etoperidone

It was found that the lipophilic alkyl/alkenyl chain in combination with a heterocyclic moiety is expected to show promising biological properties [Sandra et al., 2003]. Based on the above observations, it was proposed to attach different heterocyclic moieties such as 1,3,4-oxadiazole, 1,2,4-triazole, and 1,3,4-thiadiazole to different fatty acids like gamma linolenic acid, linoleic acid, stearic acid and palmitic acid and to evaluate the antidepressant activity. Based on the economic constrains, it was decided to isolate gamma linolenic acid from the microalgae *Spirulina platensis*. As gamma linolenic acid has been found to possess anticancer activity, it was also decided to screen the cytotoxicity of GLA containing 1,3,4-oxadiazole/ 1,2,4-triazole derivatives.

The objectives of our work are as follows;

**Phase 1:** Literature review
A thorough literature review of the selected heterocyclic compounds and fatty acids

**Phase 2: Isolation of gamma linolenic acid methyl ester**
Collection of *Spirulina platensis* and isolation of gamma linolenic acid from *Spirulina platensis* in its ester form.

**Phase 3: In-silico docking studies**
- Preparation of compound libraries of fatty acids containing 1,3,4-oxadiazole/1,2,4-triazole 1,2,4- triazolo [3,4-b]1,3,4- thiadiazole derivatives
- *In silico* docking studies of designed compounds targeting the key enzyme h MAOB and evaluation of their ADMET studies.

**Phase 5: Synthesis of designed compounds and their characterization**
Synthesis of the compounds which have good glide scores and their spectral characterization.
Phase 6: Biological evaluation

a. Screening of antidepressant activity by
   - Forced Swim test
   - Elevated plus maze test
   - Photoactometer test

b. *In-vitro* cytotoxicity studies by Sulphorhodamine-B method on human lung carcinoma (A-549) cell lines
SCHEMES FOR THE SYNTHESIS OF THE NOVEL COMPOUNDS

Reagents and conditions. 

a) \( \text{NH}_2\text{NH}_2 \), reflux 8 h. 

b) \( \text{CS}_2 \), reflux 8-18 h, acidification with HCl upto pH 3 

c) \( \text{NH}_2\text{NH}_2 \), reflux 8 h acidification with HCl upto pH 3 

d) \( \text{Ar-CHO}, \text{K}_2\text{CO}_3 \), reflux, 5 h, neutralization with 1:1 HCl 

e) \( \text{Ar-COOH}, \text{POCl}_3 \), reflux 5 h, neutralization with NaHCO_3
Scope and plan of the work

Scheme 2

Reagents and conditions. a) $\text{NH}_2\text{NH}_2$, reflux 8 h.  b) $\text{POCl}_3$, $\text{C}_{17}\text{H}_{35}\text{COOH}$, reflux, 8 h, neutralization with NaOH. e) $\text{NH}_2\text{NH}_2$, reflux, 8 h, acidification with HCl up to pH 3. d) CS$_2$/ Aq. KOH/C$_2$H$_5$OH, stirring 10 h. e) $\text{NH}_2\text{NH}_2$ reflux, 3 h, acidification with HCl. f) $\text{POCl}_3$, $\text{C}_{17}\text{H}_{35}\text{COOH}$, reflux, 8 h, neutralization with NaOH.
STEPWISE MECHANISM FOR THE SCHEMES

Formation of fatty acid hydride (47)

Formation of fatty acid moiety substituted 1,3,4-oxadiazole-2-thiol (SA-1, PA-1, LA-1, GLA-1)
Scope and plan of the work

Formation of fatty acid moiety substituted 4-amino - 1,2,4-triazole thiol (SA-2, SA-5, PA-2, LA-2, GLA-2)

Formation of fatty acid moiety substituted (1,2,4)-triazolo(3,4-b)(1,3,4)-thiadiazole (SA-3, PA-3)

Formation of fatty acid moiety substituted 5-aryl- 1,3,4-oxadiazole (SA-4, SA-7, PA-4 & PA-5)

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Formation of potassium dithiocarbazinate (52)

\[
\begin{align*}
R\text{NH}_2\text{NH}_2 + S\text{S} &\xrightarrow{\text{K}^+\text{OH}^- \text{methanol}} R\text{NH}_2\text{NH}_2\text{SSH}^+ + \text{H}^+\text{O}^-
\end{align*}
\]

Formation of 4-amino-5 substituted-1,2,4-triazole thiol (53)

\[
\begin{align*}
\text{O}^\cdot \text{N} \text{H} \text{H} \text{N} \text{H} \text{S} \text{S}^\cdot &\xrightarrow{\text{K}^+\text{OH}^-} \text{O}^\cdot \text{N} \text{H} \text{H} \text{N} \text{H} \text{S} \text{S}^\cdot \text{O}^\cdot \text{H}^+
\end{align*}
\]

Formation of fatty acid moiety substituted (1,2,4)-triazolo (3,4-b) (1,3,4)-thiadiazole (SA-6)

\[
\begin{align*}
\text{N} \text{N} \text{N} \text{NH}_2 \text{R} \text{S} \text{C} \text{O} \text{O} \text{H} &\xrightarrow{\text{C}_{17}\text{H}_{35}\text{COOH}} \text{N} \text{N} \text{N} \text{NH}_2 \text{R} \text{S} \text{C} \text{O} \text{O} \text{H} \text{C}_{17}\text{H}_{35}
\end{align*}
\]