Functionalization of imidazo[2,1-*c*][1,2,4]triazine core and their evaluation in H2O2-induced oxidative stress

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1 – Background/ Purpose

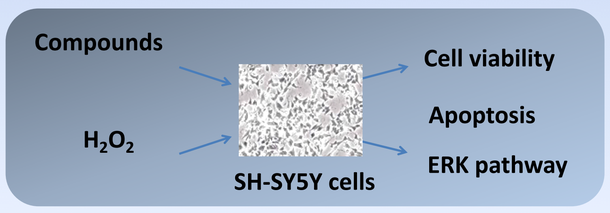
Neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, Huntington's disease and epilepsy are among the most serious health problems. The molecular pathogenesis of neurodegenerative disorders is associated with mitochondrial dysfunction, oxidative stress, and apoptosis. Apoptosis is a genetically regulated process of cell deletion and plays an essential role in the maintenance of tissue homeostasis.

❑**Aim/purpose:**

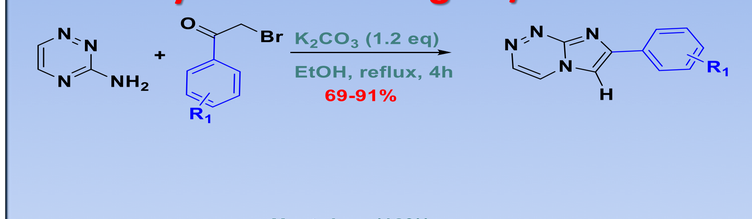
✓ Synthesize imidazo[2,1-c][1,2,4]triazines derivatives

✓ Evaluate their effects in H_2O_2-induced oxidative stress in human neuroblastoma cell line (SH-SY5Y cells).

Figure 1



2 - Synthetic strategies / Pharmacomodulations



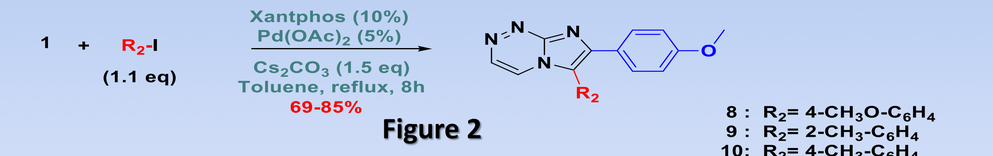


Figure 2

✓ Synthesis of various imidazo[2,1-*c*][1,2,4]triazine derivatives from common 3-amino-1,2,4-triazine.

✓ Various of electrophiles were regioselectively introduced in position C-6 giving access to a diversified library of disubstituted imidazotriazines in good overall yields.

3 - *In vitro* evaluation

❑ Quantification of **Bax/Bcl-2** (A) and **Bcl-2/Bax** (B) ratio in H_2O_2-treated SH-SY5Y cells.

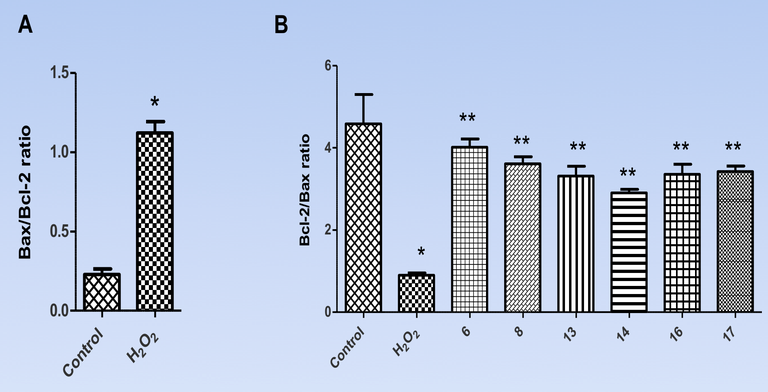
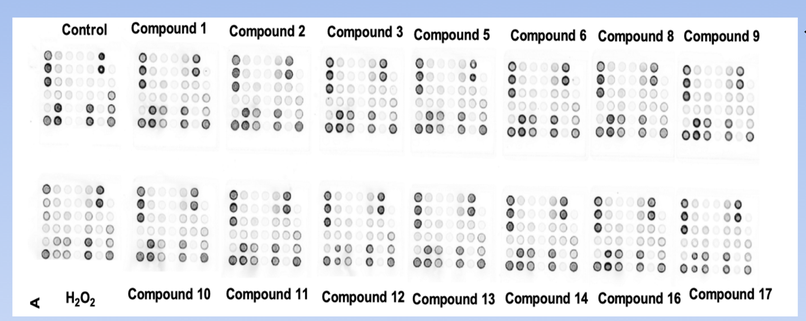


Figure 3

✓ Bcl-2/Bax ratio was significantly increased following compounds **6, 8, 13, 14, 16** and **17** treatments when compared to H_2O_2-treated cells.



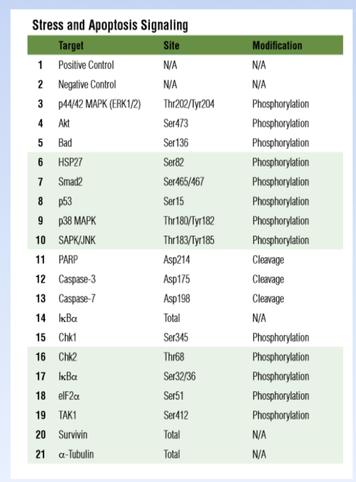


Figure 4

✓ Stress and apoptosis were evaluated by using PathScan® Stress and Apoptosis Signaling Antibody Array kit to evaluate the potential regulatory role of selected compounds in Akt signaling and ERK pathway while fighting against oxidative stress.

✓ Numbers on the target map correspond to the numbered targets shown on the right. The expression levels of α-tubulin were used to normalize the signals between various samples.

❑ The changes in cleavage of caspase-7, caspase-3 and PARP in SH-SY5Y cells treated with selected compounds against H_2O_2-induced oxidative stress.

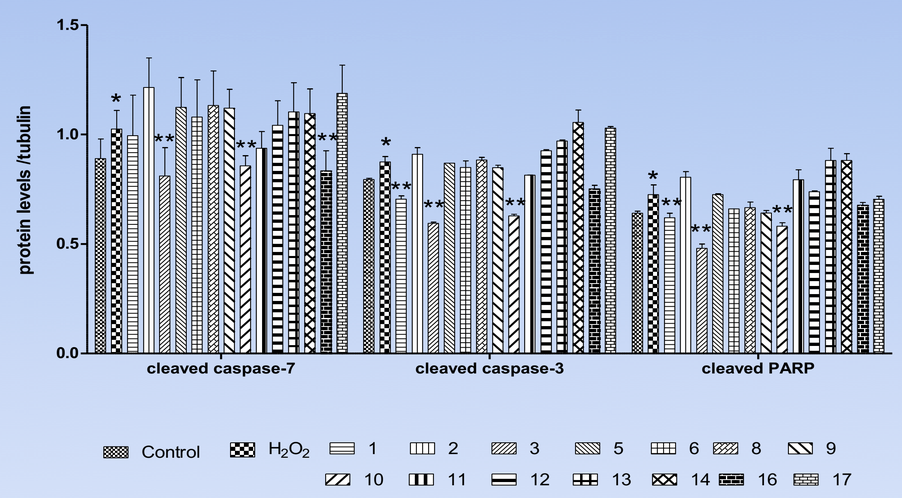


Figure 5

✓ H_2O_2-induced toxicity increased **cleaved caspase-7, cleaved caspase-3** and **cleaved PARP** levels which indicates the induction of apoptosis at molecular level.

✓ Our findings indicate that particularly compound 1,3 and 10 and 16 prevent H_2O_2-induced apoptosis through the inactivation of caspase cascades in SH-SY5Y cells.

❑ **Anti-apoptotic proteins analysis**

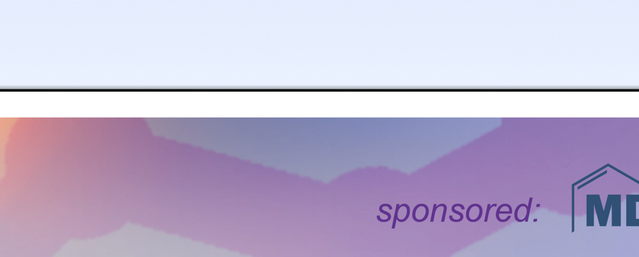


Figure 6

✓ The significant elevation in phosphorylated p44/42 MAPK levels was observed following compound 1, 3, 8, 9, 10, and 16 treatments when compared to H_2O_2-treated group indicating that the inhibition of **ERK signalling** can be achieved by indicated compounds and thus the induction of apoptosis can be inhibited.

❑ The changes in phosphorylated p44/42 MAPK (ERK1/2) in SH-SY5Y cells treated with selected compounds against H_2O_2-induced oxidative stress.

4 – Conclusion

In the present study, the neuroprotective properties of novel imidazo[2,1-c][1,2,4]triazine have been explored. $H_2O_2$was used to generate oxidative stress conditions in human neuroblastoma cell line, SH-SY5Y . Our results suggest that both activation of PI3K/Akt cascade and inhibition of ERK signaling are involved in neuroprotection by four compounds 1, 3, 10 and 16 in H_2O_2-induced toxicity in SH-SY5Y cells and further investigations are needed to reveal their potential in specific disease models where oxidative stress is involved in.

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