ABSTRACT

New drug candidates have remained under consideration by the pharmaceutical industries to cure new arising diseases. To fulfill the requirement of new drug candidates, synthetic chemistry has added much in this regard. A large number of bioactive compounds have been synthesized by different fields of Chemistry which emphasize the significance of synthetic chemistry in the field of pharmacy. The presented work is also about the synthesis of some new bioactive molecules by coupling different bioactive functionalities. The valuable biological activities of derivatives of thaizole, 1,2,4-triazole and 1,3,4-oxadiazole prompted us to synthesize some new compounds comprising amalgamation of these functionalities; and to demonstrate their enzyme inhibitory potentials supported by kinetic studies and computational docking simulations and also find out their % hemolytic activities.

The presented work has been extended into different seven (7) schemes. In the first scheme the starting compound, ethyl 2-(2-amino-1,3-thiazol-4-yl)acetate (**1**) synthesis was geared up by refluxing compound **1** with methanol and hydrazine hydrate to get its acetohydrazide (**2**). The **2** was further refluxed with phenyl isothiocyante in methanol to obtain the solid intermediate hydrazinecarbothioamide (**4**) which was further cyclized to get 5-[(2-amino-1,3-thiazol-4-yl)methyl]-4-phenyl-4*H*-1,2,4-triazole-3-thiol (**5**). The nucleophile **5** was dissolved in DMF and one pinch (0.02 g) of LiH was added the mixture was stirred for 15 - 20 min to activate its mercapto position. Finally, the nucleophilic substitution reaction was carried out with equimolar amounts of different aralkyl halides (**6a-i**, one in each reaction) to achieve the targeted derivatives, 4-({5-[(aralkyl)sulfanyl]-4-phenyl-4*H*-1,2,4-triazol-3-yl}methyl)-1,3-thiazol-2-amines, **7a-i** (Scheme-1)

Eleven compounds were synthesized as 2-({5-[(2-amino-1,3-thiazol-4-yl)methyl]-4-phenyl-4*H*-1,2,4-triazol-3-yl}sulfanyl)-*N*-(substituted-phenyl/benzyl/phenethyl)acetamides (**11a-k**, Scheme-2) by the cyclized compound (**5**). The electrophiles (**10a-k**) were synthesized by reacting 2-bromoacetyl bromide (**9**) with un/substituted amine (**8a-k**) in complementary set of reaction. Finally nucleophile **5** was dissolved in DMF and activated by adding a pinch of LiH and then reacted with equimolar quantity of electrophiles, **10a-k** (one in each reaction) to yield **11a-k** molecules.

The precipitates of **2** were refluxed with ethyl isothiocyante (**12**) in methanol to obtain an intermediary compound, 2-[2-(2-amino-1,3-thiazol-4-yl)acetyl]-*N*-ethyl-1-hydrazinecarbothioamide (**13**) which was cyclized to obtain a solid nucleophile, 5-[(2-amino-1,3-thiazol-4-yl)methyl]-4-ethyl-4*H*-1,2,4-triazole-3-thiol (**14**). This bi-heterocyclic nucleophile (**14**) was then treated with equimolar amounts of various aralkyl halides (**6c, 6e, 6f-i**), acting as electrophiles, to acquire the targeted hybrid molecules 4-({4-ethyl-5-[(aralkyl)sulfanyl]-4*H*-1,2,4-triazol-3-yl}methyl)-1,3-thiazol-2-amines (**15a-f**, Scheme-3).

Twelve ethylated bi-heterocyclic acetamides, 2-({5-[(2-amino-1,3-thiazol-4-yl)methyl]-4-ethyl-4*H*-1,2,4-triazol-3-yl}sulfanyl)-*N*-(un/substituted-phenyl)acetamides, **16a-l** were designed by coupling compound **14** with different electrophiles, **10a, 10d, 10e, 10g-I, 10l-q**, in DMF using LiH as an activator and outlined in **Scheme-4**.

In Scheme 5, the cyclization of hydrazide **2** was carried out by refluxing it with carbon disulfide and KOH using ethanol as solvent to get the solid bi-heterocyclic core, 5-[(2-amino-1,3-thiazol-4-yl)methyl]-1,3,4-oxadiazole-2-thiol **17**. The nucleophile **17** was further reacted with the equimolar amounts of newly synthesized electrophiles, *N*-(aryl)-3-(chloromethyl)bezamides **19a-m** (one in each reaction) to achieve the targeted hybrid molecules, 3-[({5-[(2-amino-1,3-thiazol-4-yl)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)methyl]-*N*-(aryl)benzamides, **20a-m**

The designed multi-functional benzamides 4-[({5-[(2-amino-1,3-thiazol-4-yl)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)methyl]-*N*-(aryl)benzamides, (**23a-k**) were produced by several steps through a convergent approach as designated in Scheme-6. The cyclized compound (**17**) was reacted with the equimolar amounts of newly synthesized electrophiles *N*-(aryl)-4-(chloromethyl)bezamides (**22a-k**, one in each reaction) to achieve the targeted hybrid compounds, **23a-k**.

2-Aminothiazole and oxadiazole bi-heterocyclic core along with a butanamide moiety were produced in several steps as designated in Scheme-7. The cyclized product (**17**) were reacted with different electrophiles, *N*-(aryl)-4-chlorobutanamides (**25a-d**) with equimolar amounts to synthesied derivatives, 4-({5-[(2-amino-1,3-thiazol-4-yl)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)-*N*-(aryl)butanamides, **26a-d**.

The structural characterization has been well supported by spectral data of IR (Infra Red), ^{1}H-NMR (Proton Nuclear Magnetic Resonance), ^{13}C-NMR (Carbon-13 Nuclear Magnetic

Resonance), HMBC (Heteronuclear Multiple Bond Correlation), HMQC (Heteronuclear Multiple Quantum Coherence) and EIMS (Electron Impact Mass Spectrometry). Some of the ^{1}H-NMR, ^{13}C-NMR, EIMS and IR spectra of synthesized compounds are also presented for the obvious perceptive of signals. The physical data of all the compounds is also provided which included color, state, yield, melting points (in case of solids), molecular formula and molecular mass.

The enzyme inhibitory activity of these synthesized compounds against tyrosinase or elastase was determined along with their kinetic studies to find out the mode of action of inhibitors and inhibition constant. The enzyme inhibition data are also explicated in detail through molecular docking studies and finally found out their % hemolytic activity. The reference standards used were kojic acid for tyrosinase, oleanolic acid for elastase and triton X-100 for % hemolytic evaluation.

All the compounds were found active and showed excellent or good results. The biological activity data in comparison of each scheme with the reference standard drugs are presented in results and discussion section.