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Design, synthesis of novel furan appended benzothiazepine derivatives and *in vitro* biological evaluation as potent VRV-PL-8a and H^+/K^+ ATPase inhibitors

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ABSTRACT

A series of new of furan derivatised [1,4] benzothiazepine analogues were synthesized starting from 1-(furan-2-yl)ethanone. 1-(Furan-2-yl)ethanone was converted into chalcones by its reaction with various aromatic aldehydes, then were reacted with 2-aminobenzenethiol in acidic conditions to obtain the title compounds in good yields. The synthesized new compounds were characterized by ^{1}H NMR, ^{13}C NMR, Mass spectral studies and elemental analyses. All the new compounds were evaluated for their *in vitro* VRV-PL-8a and H^+/K^+ ATPase inhibitor properties. Preliminary studies revealed that, some molecules amongst the designed series showed promising VRV-PL-8a and H^+/K^+ ATPase inhibitor properties. Further, rigid body docking studies were performed to understand possible docking sites of the molecules on the target proteins and the mode of binding. This finding presents a promising series of lead molecules that can serve as prototypes for the treatment of inflammatory related disorder that can mitigate the ulcer inducing side effect shown by other NSAIDs.

The heterocyclic nucleus of thiazepine is present in a number of bioactive molecules, and is recognized as a key building block for the synthesis of small-molecules with potential pharmaceutical activities.[1] The broad spectrum of clinical applications and commercial success associated with benzothiazepine derivatives have placed them as important molecules in the field of medicinal chemistry.[2] Various protocols have been developed for the synthesis of benzothiazepines in literature. To mention two representative examples: the reaction of acid amides with phosphoryl chloride furnishes 2,3-dihydro-l,4-benzothiazepine[3] and the one-pot reaction between 2-aminobenzo[*d*]isothiazol-3-one and alkyl propiolates in the presence of triphenylphosphine produces 1,4-benzothiazepines.[4]

Further, molecules possessing benzothiazepine skeleton have exhibited high biological profiles.[5] These classes of compounds have been known to show anti-arrhythmic, angiogenic, central nervous system activities,[6] antimicrobial,[7] antioxidant,[8] anti-inflammatory, analgesics, antitumor, and anticonvulsant properties.[9] 1,4-Benzothiazepine derivatives also show interesting neuroprotective activity in addition to their demonstrated blockade of the mitochondrial sodium/calcium exchanger.[10] The chemical modification of heterocyclic systems by devising a new protocol for design of new compounds with high pharmacological profile is always a challenge for the medicinal chemist. We herein report the synthesis of functionalized 1,4-benzothiazepine derivatives and *in vitro* screening results for their VRV-PL-8a and H^+/K^+ ATPase inhibitor properties.

The strategy adopted for the synthesis of the target compounds, **3**(**a**–**h**), is depicted in Fig. 1. The intermediate chalcones, **3**(**a**–**h**), were synthesized by the Claisen-Schmidt condensation reaction of 1-(furan-2-yl)ethanone, **1**, and aromatic aldehydes, **2**(**a**–**h**), in the presence of potassium hydroxide in methyl alcohol. Then, the chalcones, **3**(**a**–**h**), were transformed into target molecules **5**(**a**–**h**) by their reaction with 2-aminobenzenethiol, **4,** and concentrated hydrochloric acid (4–6 drops) in methyl alcohol under reflux conditions.

The resultant structures of the synthesized compounds **3**(**a**–**h**) and **5**(**a**–**h**) were confirmed by ^{1}H NMR, ^{13}C NMR, Mass spectral studies and CHN analyses. In ^{1}H NMR spectrum, compound **3b**

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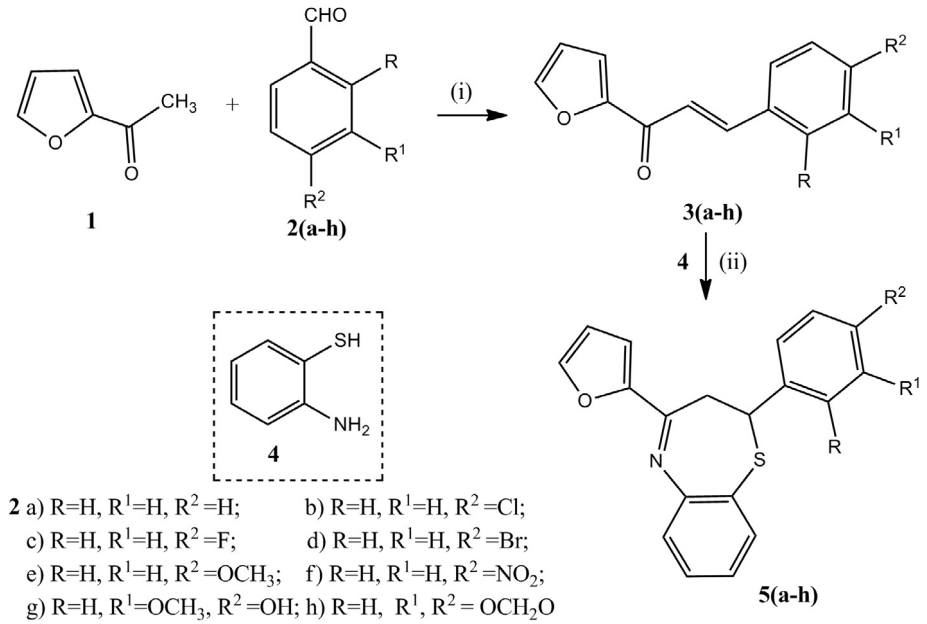

Fig. 1. Schematic diagram for the synthesis of benzothiazepines, **5**(**a**–**h**).

showed two doublets for one proton each at δ 6.285 ppm and δ 6.793 ppm which were due to olefinic CH=C and C=CH protons, respectively. An array of signals observed as multiplet for seven protons at δ 7.244–8.201 ppm were due to aromatic protons. Two methylene (C-3) protons of the newly formed benzothiazepine ring in compound **5b**, exhibit typical ABX spin system, and are diastereotopic appearing as two doublet of doublets. C_3-H_a resonates with both C_3-H_b and C_2-H appearing as doublet of doublet at δ 2.923–2.985 (*J = 12.4, 24.8 Hz*) ppm and C_3-H_b resonates with both C_3-H_a and C_2-H appearing as doublet of doublet at δ 3.214–3.259 (*J = 8.0, 18.0Hz*) ppm. C_2-H coupled with both C_3-H_a and C_3-H_b and appeared as doublet of doublet at δ 5.045–5.086 (*J = 6.8, 16.4 Hz*) ppm. An array of signals appearing as multiplets for eleven protons at δ 6.587–8.182 ppm were due to aromatic protons.

In ^{13}C NMR spectrum, compound **3b** showed signals at δ 121.41, 144.63 and 170.44 ppm due to olefinic CH=, =CH, and C=O carbons, respectively. Aromatic carbons showed the signals in the region δ 112.10–153.86 ppm. For compound **5b**, the signals due to C-2, C-3 and C-4 carbons of the newly formed thiazepine ring appeared at δ 34.54, 25.76 and 158.32 ppm, respectively. Aromatic carbons showed the signals in the region δ 110.32–153.09 ppm. Para substitution effect caused the two carbons, each at *ortho* and *meta* positions of chlorophenyl ring, to abosrb at δ 128.76 and 129.54 ppm, respectively. The NMR data of the synthesized series of compounds **3**(**a**–**h**) and **5**(**a**–**h**) are tabulated in Table 1.

In mass spectra, compounds **3g** and **5g** showed base peaks at *m*/*z* 244.09 and 351.03 respectively, corresponding to their molecular massess. Except, the compounds with chloro and bromo substitutions, all compounds amongest the series **3**(**a**–**h**) and **5**(**a**–**h**) showed the base peaks corresponding to their molecular masses. Compounds **3b** and **5b,** having chloro substitutions, and **3d** and **5d**, having bromo substitutions, showed base peaks at their respective molecular masses and M+2 peaks due to isotopes ^{37}Cl, ^{81}Br with relative abundances of 34%, 34%, 98%, 97.2% respectively. All compounds showed satisfactory elemental analyses data.

Inflammation is a complex immunological cascade driven by several different factors and can be initiated by manifold cues including, but not limited to, pathogen invasion, tissue damage due to oxidative challenge etc. COX-2 is an important player in bringing about inflammation. Primarily during tissue damage, the first enzyme to get activated is sPLA2, which drives the substrate for COX-2. Inhibition of sPLA2 will result in substrate depletion for COX-2, thereby bringing down the inflammation, as there will be no pro-inflammatory and inflammatory Prostaglandins (PG). In this context, we assessed the inhibitory potential of the newly synthesized benzothiazepines to inhibit sPLA2, rather than COX-2.[11]

As a prototype to test our findings, $sPLA_2$ (VRV-PL-8a) from *V. russelli* venom was employed instead of the human homologue. The protein was purified to homogeneity by reported procedure,[12] and estimated by Lowry's method.[13] *In vitro* inhibition of $sPLA_2$ (VRV-PL-8a) by the synthesized benzothiazepine derivatives, **5**(**a**–**h**) was assayed according to reported procedure.[14] Further, indirect hemolytic activity of the synthesized benzothiazepine derivatives, **5**(**a**–**h**), was assayed by reported method.[15] The series of benzothiazepine derivatives **5(a–h)** were assessed for $sPLA_2$ inhibition studies and the results are tabulated in Table 2.

Furthermore, the H^+/K^+-ATPase (pig stomach mucosal membrane) inhibition activity of the synthesized benzothiazepine derivatives, **5**(**a**–**h**) was also determined as described by W B Im.[16] The gastric H^+/K^+-ATPase, together with Na^+/K^+-ATPase and Ca^{2+}-ATPase, is a member of the P-type ATPase. The ion pump is an essential electrogenic pump maintaining potential difference across the intracellular and extracellular compartments in a cellular matrix by retaining low sodium and high potassium intracellularly. These proteins engage in a common catalytic cycle with ion translocation coupled to phosphorylation and dephosphorylation of a conserved aspartate residue.[17] Some of them belong to the Haloacid dehalogenase family of enzyme with a conserved DXDXV/T motif, with the second aspartate in the motif critical for the formation of the phosphoenzyme intermediate.[18] The assay was carried out by initiating the ATPase reaction by the addition of the substrate (ATP), carried out at 37 °C for 15 min and stopped with 1.0 mL ice cold 20 % TCA. The liberated inorganic phosphate from ATP was estimated by Fiske Subbarow's method.[19] The assessed H+/K+ ATPase activity is reported in Table 2.