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One pot Click chemistry: A three component reaction for the synthesis of 2-mercaptobenzimidazole linked coumarinyl triazoles as anti-tubercular agents

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ABSTRACT

2-Propargylthiobenzimidazole **1**, 4-bromomethyl coumarins/1-aza-coumarins **2**/**3** and sodium azide have been reacted in one pot under Click chemistry conditions to give exclusively 1,4-disubstituted triazoles **5a**–**n**. Anti-tubercular assays against *M. tuberculosis* ($H_{37}Rv$) coupled with in silico molecular docking studies indicated that dimethyl substituents **5c** and **5d** showed promising activity with higher C-score values.

Designing drugs for the treatment of tuberculosis has been a challenging area in medicinal chemistry in view of the multi-drug resistance[1] and high mortality rate[2] associated with this disease. Emergence of resistance against new TB drugs is an alarming issue demanding new drug profiles. Clinically accepted drugs in chemotherapy like Isoniazid, Rifampicin, Pyrazinamide and Delamanid possess a nitrogen heterocycle viz pyridine, piperazine, piperidine and pyrazine ring systems with azomethine and aryloxy moieties which constitute their core structural features.

In recent years, 1,2,3-triazoles generated using Click chemistry[3] have gained multidimensional importance in view of their binding ability with various enzymes through hydrogen bonding.[4] Triazole skeleton possesses moderate dipolar character, rigidity and stability under in vivo conditions which qualifies them as lead frameworks in drug design.[5] Privileged structure of benzimidazole[6,7] has been found to be promising in chemotherapy of tuberculosis. Recently, 2-aryl-*N*-cinnamoyl benzimidazoles have been reported to be very effective against *M. tuberculosis* $H_{37}Rv$ strain.[8] Introduction of nitrile, azomethine and hydrazone moieties derived from 2-acetyl benzimidazoles have been found to have low MIC values in anti-tubercular screening. 2-Benzothiazinones were found to be potent inhibitors of the conversion of decaprenylphosphoryl-β-D-ribose 2′-oxidase (DprE1), which is involved in arabinogalactin synthesis[9] and further they are reported to be suicide substrates of the FAD-dependent DprE1, an enzyme involved in cell-wall biogenesis.[10,11]

2-Mercaptobenzothiazole-triazole-conjugates have been reported to be bactericidal and inhibited the growth of $H_{37}Rv$ strain at the concentration of 8 μg/mL.[12] Coumarin triazole hybrids with an aryloxy moiety have been reported from our laboratory as potential anti-tubercular agents[13] (Fig. 1). 1,2,3-Triazoles derived from 3-azido coumarin and 5-propargyloxy-2-aryl thiazoles have been found to be effective against *M. tuberculosis* Gyr B.[14]

The design concept of the present compounds is derived from the pharmacophoric moieties of the potent molecules indicated in Figure 1 which retain the sulfur content of benzothiazoles and introduces the amphoteric benzimidazole moiety. These new molecular entities with rotatable bonds having donor–acceptor sites can lead to structural and stereoelectronic optimization required for an effective interaction with the receptor sites.

Required regioselectivity in the azide-alkyne cycloaddition (AAC) is derived from Cu(I) catalysed reaction. The associated chemistry connected with the generation of the required synthons and one-pot Click chemistry approach is presented in Scheme 1.

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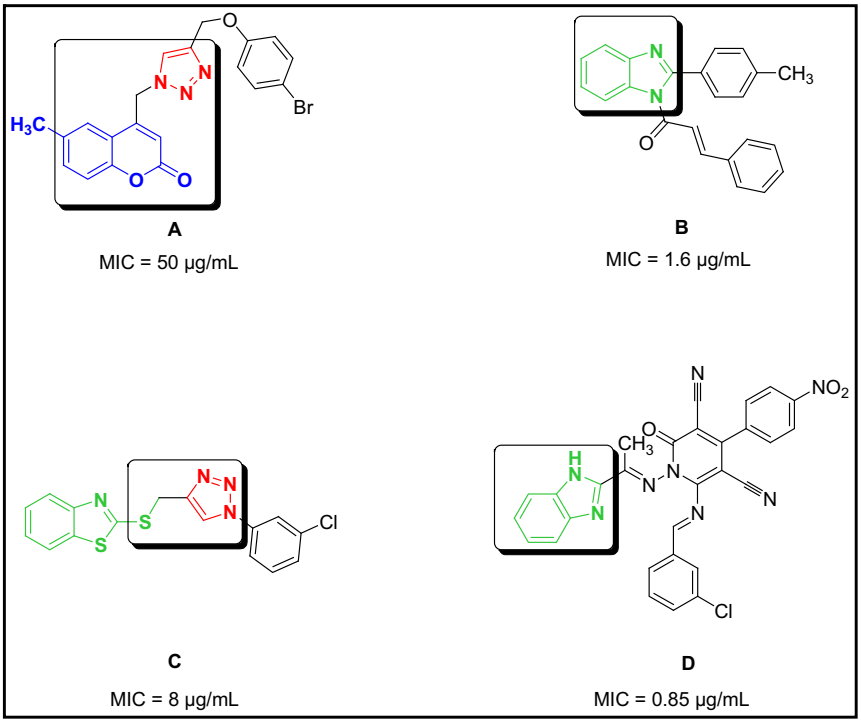
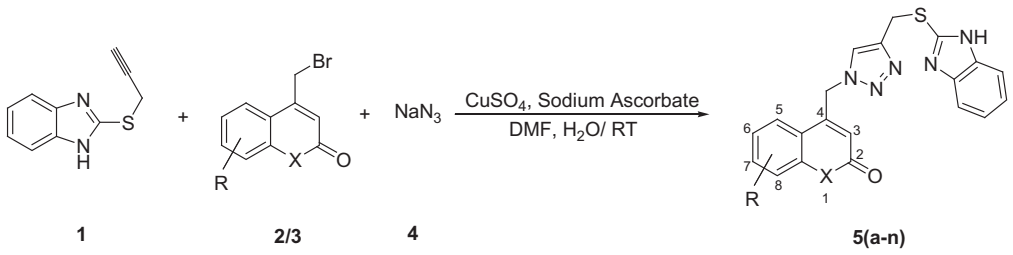


Figure 1. Pharmacophores derived from structurally related anti-tubercular agents.



X=O, R= (5a) 6-CH_3, (5b) 7-CH_3, (5c) 5,7 Di-CH_3, (5d) 7,8 Di-CH_3, (5e) benzo[*f*], (5f) benzo[*h*], (5g) 7-Cl, (5h) 7-OH, (5i) 6-OCH_3, (5j)7-OCH_3

X=NH, (5k) R= H, (5l) 6-Cl, (5m) 8-CH_3, (5n) 7-Cl

Scheme 1. Three component one pot synthesis of 1,4-substituted triazoles **5**(**a**–**n**).

Acetylenic dipolarophile **1** was synthesized by the reaction of 2-mercaptobenzimidazole with 3-bromoprop-1-yne employing sodium acetate with few drops of acetic acid in acetone.[15] 4-(Bromomethyl)-2*H*-chromen-2-ones **4**(**a**–**j**) were synthesized via Pechmann cyclisation.[16] Further, substituted bromomethyl-1-*aza* coumarins were synthesized according to literature method.[17]

Three component one pot in situ azide-alkyne cycloaddition of 2-propargylthiobenzimidazole **1** with **2**/**3** in presence of sodium azide **4** were carried out using copper ascorbate in DMF/water at room temperature to obtain exclusively the 1,4 substituted-1,2,3-triazole hybrids **5**(**a**–**n**) (Scheme 1)

Structures of the compounds were confirmed using spectroscopic data. In the case of compound **5a**, (X = O, R = 6-CH_3) IR spectrum showed a band at 1719 cm^{-1} due to the lactone stretching. Compounds were further confirmed by the ^{1}H NMR wherein –NH of the mercaptobenzimidazole moiety resonated at 12.50 ppm as a singlet. A singlet at 8.21 ppm corresponded to the proton (C_5-H′) of the triazole ring. C_5-H of coumarin appeared as a singlet at 7.63 ppm. Singlets observed at 5.92 ppm, 5.72 ppm and 4.64 ppm were attributed to -NCH_2, C_3-H (coumarin) and -SCH_2 respectively. Methyl protons resonated at 2.34 ppm as a singlet. Aromatic protons appeared as multiplet between 7.10–7.53 ppm.

In 1D-NOE, irradiation of signal at 8.2 ppm (C_5-H′ of the triazole ring) showed an increase in the intensity of the signal at 7.6 ppm (C_5-H of coumarin), 5.9 ppm (–NCH_2), 5.7 ppm (C_3-H) and 4.6 ppm (–SCH_2 respectively). On the other hand, irradiation of signal at 4.6 ppm (–SCH_2) showed an increase in the intensity of the signal at 8.2 (C_5-H′ of the triazole ring) and 12.5 ppm (–NH) whereas irradiation of signal at 5.9 ppm (–NCH_2) showed an increase in the intensity of the signal at 8.2 ppm (C_5–H′ of the triazole ring), 7.6 ppm (C_5-H of coumarin) as well as 5.7 ppm (C_3-H) which confirmed the ^{1}H NMR interpretation of the two methylene groups in compound (Fig. 2). Long range heteronuclear correlation has been investigated using Heteronuclear Multi Bond Correlation (HMBC) experiments (Supplementary Information) which further supported our proposed structure and spectral interpretations. In ^{1}H ^{1}H COSY experiment (Supplementary Information), the proton at 8.2 ppm (C_5-H′ of the triazole ring) showed a correlation with