SYNTHESIS OF INDOLE-TRIAZOLE CONJUGATES AS POTENTIAL ANTIBACTERIAL COMPOUNDS

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Abstract **:**A simple strategy for the synthesis of densely functionalized small molecules having indole and triazole units has been developed. The adopted approach highly modular employs simple building blocks and involves three addition events in a sequence. We have used pTSA as a simple catalyst for the C2 and C3 alkylation of indole nucleus.

Key word:**Antibaterial,Indole Nucleus**

I INTRODUCTION

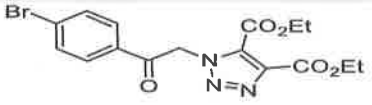
It is indisputable that advances in the central disciplines of chemistry are essential in amalgamating chemistry, biology, material science and medicine to contribute to human progress. Organic synthesis is definitely an indispensable tool to develop the molecules with the properties desired. The continuing evolution of organic synthesis depends heavily on the design/discovery of reactions and the development of concise strategies that would allow the synthesis of small molecules of varying complexity. The combinatorial chemical approach for molecular libraries synthesis conceptualized in the early 90's of last century and practiced until recently has been recognized as a versatile handle to populate the chemical space. However, despite the rapid speed of synthesis, no combinatorial magic bullet was delivered. Although, the reasons for this apparent lack of productivity remain unclear, it has been attributed in part to the molecular simplicity and to too much similarity within the library. This shifted the field slowly from the numbers game to focused, biologically relevant libraries, admitting the complexity and diversity in nature's small-molecules. Several efforts to identify planning concepts for syntheses of small-molecules, inspired by structural complexity, have been reported recently. These strategies include, among others, diversity oriented synthesis (DOS, Schreiber), biology oriented synthesis (BIOS Waldmann), "molecular editing" or "diverted total synthesis" (DTS, Danishefsky), and "libraries-from-libraries" (Houghten).[1]

Amongst the all, the DOS combines the concepts of Target Oriented Synthesis and combinatorial technologies. It moves in the forward direction by identifying a set of complexity generating reactions and selection of substrates in such a way that products of each step will be the reactants for the next reaction. Moreover, the structural complexity, the function of natural products and, more importantly, the biological target have minimal role in the design of DOS libraries.

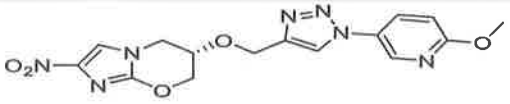
II. OBJECTIVE

The objective of this work is to develop strategies funded upon the concepts of DOS and the utilization of the resulting small molecules to identify the leads for developing new drugs for the Tuberculosis (TB) treatment. TB is a disease which is a major threat for the developing and the tropical countries and has been a neglected target in majority of the Pharmaceutical industries. Hence the first disease target taken up is Tuberculosis (TB). Tuberculosis is caused due to bacteria called "Mycobacterium Tuberculosis". These are aerobic, non-motile, non-capsulated, non-sporing and resistant to chemical disinfectant.[3] TB is a highly contagious air borne infection which has its main target, the respiratory system, though it affects other organs as well. TB is the most common opportunistic infection affecting people living with HIV worldwide. TB is one of the leading causes of fatality in the developing nations. TB is a global infection and ranks second only to HIV as the leading killer infectious disease of adults worldwide. As per WHO report, one-third of the world's population is currently infected with the TB of which 80% are from the 22 high-burden countries alone.

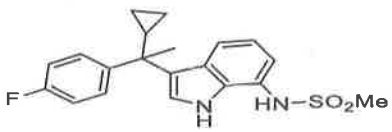
The present drugs available for the treatment of tuberculosis such as Isoniazide-isonicotinylhydrazide (INH), is orally highly active with low MIC (0.02 to 0.06μg/mL) and exhibits bacteriostatic effects on bacillus but is highly toxic. Hence efforts are being made to develop new INH derivatives with greater activity, lower toxicity, and fewer side effects than INH. Sutherland and Ponnuswamy groups have recently synthesized a series of 1,2,3-triazoles with promising MIC values.[4,5] In 2007 Michael G. Bell and co-workers have reported the identification of 3-aryl indoles (**C**, Figure 1) as potential mineralocorticoid receptor (MR) antagonists.[6]



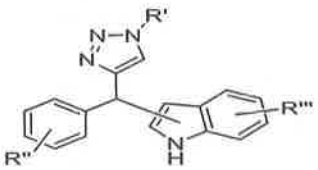
A (MIC 1.56 μg)



B (MIC 0.44 μg)



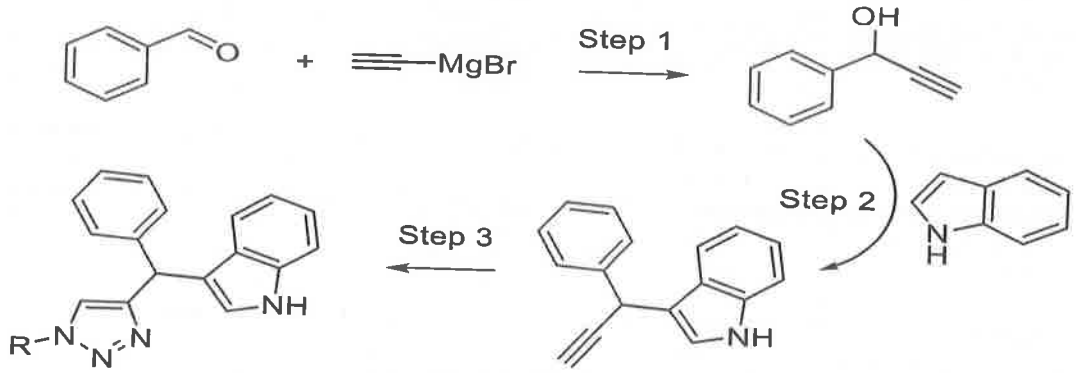
Selective nonsteroidal MR Antagonist (**C**)



Newly designed Targets (**D**)

Figure 1: Structures of some trizoles with potential anti-TB activity (A & B), of MR antagonist (C) and the newly designed scaffold integrating triazoles with C

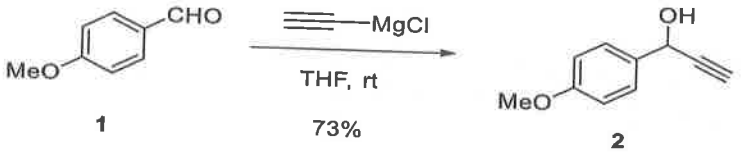
Funded upon the structural elements present in A – C, we have designed a new scaffold D that integrates three structural units namely a) triazole; b) indole; and a functionalize aryl ring being all the units pendant on a single carbon. The proposed strategy for the synthesis of compounds of type D has its own origins from the concepts of diversity oriented synthesis. As mentioned above, a DOS route will be highly effective if it involves the coupling of different structural units in sequence without involving any intermediate functionalization. Basically, this requires the products of each step should be the starting precursor for the next reaction. As shown in Scheme 1, our basic strategy comprises three steps and utilizes four different building blocks which are simple and commercially available. The first step is the addition of an alkyl anion to an aldehyde. The –OH in the resulting propargyl alcohol will be used as a handle for a Friedel–Crafts type alkylation at C2 or C3 of the indole.[7] In the third step, the intact alkyne will be subjected for a Cu-catalyzed [3 + 2] cycloaddition with an azide (Click Reaction).[8] Overall, in three steps, two of each new C – C and one C – N bond will be made.



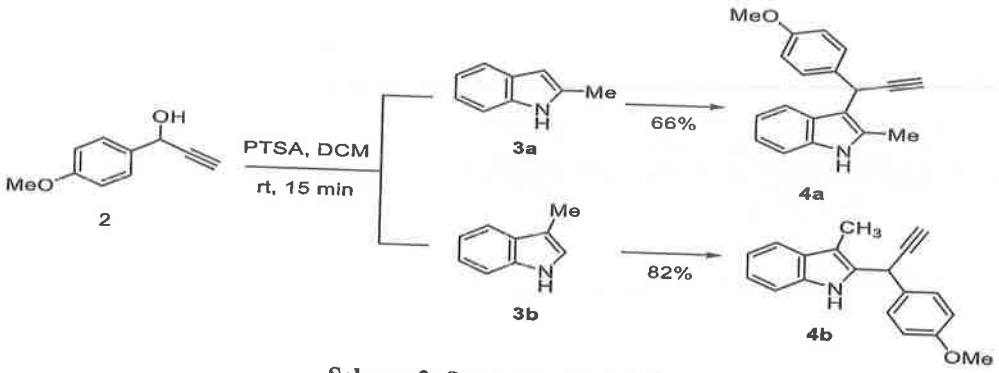
Scheme 1: ***Converging bi-molecular couplings/additions in sequence***

III. RESULTS AND DISCUSSION

Our journey in this context started with selecting the preparation of alkynol**2**, by using 4-methoxybenzaldehyde. The acetylene Grignard reaction was performed and Grignard was generated in situ by passing the acetylene gas into a solution of n-BuMgCl in THF (Scheme 2).



Scheme 2: Synthesis of the alkynol 2



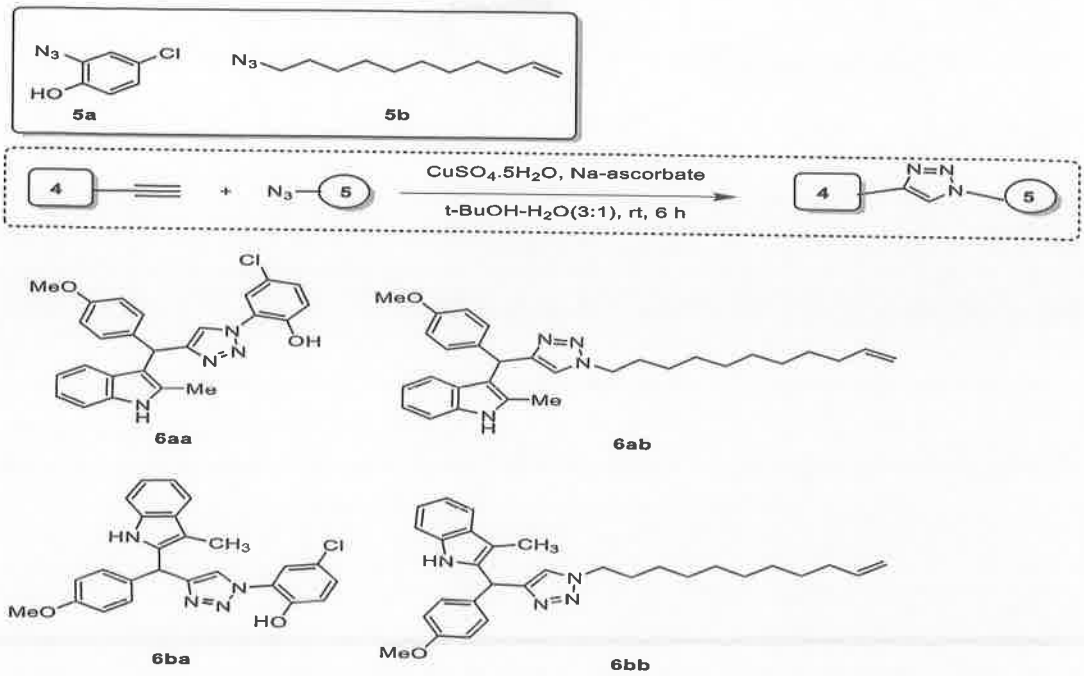
Scheme 3: Synthesis of indolyl alkynes 4a and 4b

The structure of alkynol2 was determined with the help of spectroscopic data. In the ^{1}H NMR spectrum of compound 2, the alkyne – H was resonated at upfield as a doublet with a coupling constant of $J = 2.3$ Hz. The benzylic – H was resonated as a doublet of doublet with coupling constants $J = 5.8$ and 2.2 Hz. The second coupling was due to the pendant –OH group (resonated at 3.66 ppm as a double with J – 1.77 Hz). The methoxy group appeared as singlet at 3.82 ppm.

After having the alkynol**2** in hand, next we proceeded for the Friedel–Crafts reaction with 2-methyl (**3a**) and 3-methyl indole (**3b**). Amongst various acid catalysts screened, with *p*-TSA the requisite reaction proceeded smoothly at rt in dichloromethane as a solvent (Scheme 3). Thus the reaction of **2** with **3a** gave **4a** (66% yield) and that with **3b** gave **4b** (82% yield). The compounds **4a** and **4b** have been characterized by ^{1}H and ^{13}C NMR data. The presence of the indole unit in compounds **4a** and **4b** is evident from the appearance of the 2-3-methyl groups around δ 2.25 ppm.

After having the two penultimate intermediate alkynes **4a** and **4b**, next we proceeded further for the final (3+2) cycloaddition by employing two representative azides**5a** (2-azido-4-chlorophenol) and **5b** (undec-10-enyl azide). The (3+2) cycloaddition reaction of 4a with 5a was carried out in t-BuOH-H_2O (3:1) in the presence of Na-ascorbate and $CuSO_4.5H_2O$ to get the expected triazoles**6aa** and **6bb**

respectively. [9] Similarly, 2 more triazoles**6ab** and **6ba** were synthesized by using alkyne **4b**. All the triazoles have been characterized by ^{1}H and ^{13}C NMR spectral data. All the four compounds have been submitted for CSIR – IICT for the anti-bacterial screenings.



Scheme 4: The synthesis of the proposed triazole compounds 6aa – 6bb

IV. CONCLUSION

To conclude, a simple strategy for the synthesis of densely functionalized small molecules having indolecandtriazole units has been developed. The adopted approach highly modular employs simple building blocks and involves three addition events in a sequence. We have used p-TSA as a simple catalyst for the C2 and C3 alkylation of indole nucleus. Currently, the extension of this approach by employing a wide range of aldehydes, indoles and azides is under progress.

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[10] General Procedure for Click Reaction: To a solution of alkyne**4a** (100 mg, 0.3636mol) in t-BuOH-H_2O (6mL+2mL, 3:1) 2-azido-4-chlorophenol (**5a**) (61.818mg, 0.3636mol), Na-ascorbate (68.393 mg, 0.34542mol) and $CuSO_4.5H_2O$ (18.107 mg, 0.07272 mol) were added sequentially and the reaction was stirred for 6 h at rt. Then reaction mixture was extracted with EtOAc and dried with Na_2SO_4. The solvent was removed on low pressure and purified by column chromatography to afford **6aa** (120 mg, 74.17%) as a brown solid.