SUMMARY

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Introduction

Small molecules can be powerful tools in biology and medicine, functioning as therapeutics and as probes that can help to illuminate the macromolecules regulating biological processes. Certain classes of compounds that are highly represented in the overall bioactive compound population have demonstrated a wealth of biological activity in addition to sound 'drug like' properties. Yet, despite advances on many fronts, including the ability of synthetic chemists to prepare libraries containing thousands of compounds efficiently, the ability to make critical drug discoveries remains a slow and arguably, serendipitous one. For instance, the use of HTS, CADD and combinatorial chemistry and screening of compounds collected through phenotypic or biochemical assay often yields disappointing results in terms of useful compounds discovered, relative to the cost and time involved in them. Broadly it can be assumed that still we are unable to crack the mystery behind the factors necessary to create compound libraries that have potent and specific biochemical activity. Commercial compound libraries, for example, while readily available, suffer from low hit rates: this is in part because their members typically possess low structural diversity and poor physicochemical properties.

Consequently, solving the challenges of creating collections of unique, highly potent bioactive small molecules could dramatically accelerate the rate at which critical biochemical discoveries are made and ultimately enable diseases not only to be managed, but also to be eradicated. Here, we focus on one approach to overcome this problem: creating compound collections based on 'privileged scaffolds,' molecular

frameworks, as first coined by Evans in the late 1980s, seemingly capable of serving as ligands for a diverse array of receptors.

The proposed work has been divided in to three main sections depending upon the synthetic and pharmacological applications.

SECTION-I is focused on the chemistry of transition metal (Pd) and cross-coupling reactions.

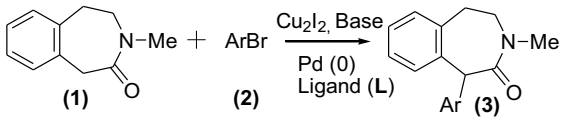
SECTION-II of the research work contains the design, synthesis and $5HT_{2C}$ receptor activity of benzazepine scaffold, useful for different neurological/neuro-metabolic disorders.

SECTION-III contains the developmental chemistry of cyclic guanidine molecules, useful for neurodegenerative disorders. Synthesis of different cyclic guanidine molecules by using ionic liquid is well explored and established. The biological activity section of **SECTION-III** is further divided into two sub parts; **Part-A** for anti-Alzheimer's activity and **Part-B** for anti-thrombotic activity.

SECTION-I: Palladium catalyzed cross-coupling reactions

The palladium-catalyzed process has been sufficiently explored as a mild catalytic method to form the C-C bond between an aryl ring and the α-position of a carbonyl compound. It has been shown that the palladium-catalyzed intermolecular coupling of halides and keto-enolates or ester-enolates is a useful method for synthesizing α-aryl ketones and α-aryl esters. α-Arylation of amides is not well explored. Amide requires a stronger base than the ketones and esters to generate the enolate, but the use of strong base has several significant drawbacks. To overcome these problems, reactions that occur with enolates that are less basic than alkali metal

enolates of amides need to be developed. Few methods have emphasized the use of zinc metal as milder basic functionality for α-arylation. On the other hand copper (I) as a co-catalyst with palladium has been extensively used for the coupling of sp and sp^2 C-C bond formation. Sonogashira, Tohda, and Hagihara discovered and reported a process of sp-sp^2 coupling that could be performed easily at room temperature using palladium as a catalyst source, combined with co-catalytic amounts of Cu(I) in an amine. Considering the reports of greater functional group tolerance of the coupling of aryl and alkyl zinc reagents than that of the aryl and alkyl magnesium, sodium or lithium reagents, and the successful use of copper as a co-catalyst in Sonogashira coupling, we anticipated that the use of copper as a co-catalyst with sp^3 carbon could work efficiently offering milder reaction conditions for the α-arylation of amide enolates. The coupling of copper enolates of amides could also address the problem of functional group tolerance under the given set of reaction conditions, additionally. We explored the *in situ* generation of copper (I) enolates of amides starting from the displacement of alkali metal enolates and their cross-coupling with aryl bromides by palladium catalysts. Here, we report the palladium catalyzed α-arylation of benzo-fused cyclic amide, 3-benzazepin-2-one with co-catalyst copper (I) iodide (**Scheme 1**).



Scheme 1. α-Arylation of 3-benzazepin-2-one

A rapid and high yielding convenient process for α-arylation of 3-benzazepin-2-one has been developed with introduction of Cu(I) as a co-catalyst and microwaves as

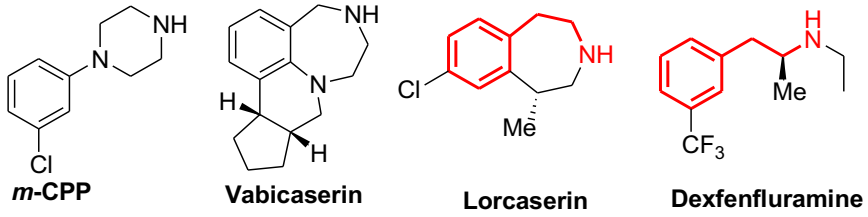
energy source. The process offers good to high yields of the α-arylated products using different type of aryl bromides. A plausible mechanism has also been proposed.

SECTION–II: 3-Benzazepine derivatives

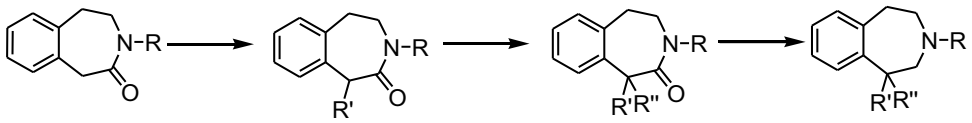
The neurotransmitter serotonin (5-HT) mediates its effects through at least 14 different receptor subtypes that have been classified into seven major families, 5-HT_{1-7}. 5-HT_{2C} receptor agonists have become attractive drug targets that have potential use in the treatment of a number of conditions including obesity, schizophrenia, sexual dysfunction, depression, anxiety and urinary incontinence. For these indications, selectivity over agonism at the 5-HT_{2A} and 5-HT_{2B} receptors would be a key objective because 5-HT_{2A} agonists can potentially be hallucinogenic and have cardiovascular (CV) effects, whereas 5-HT_{2B} agonism has been associated with heart valvulopathy and pulmonary hypertension. The nonselective 5-HT_{2C} receptor agonist *meta*-chlorophenylpiperazine (*m*CPP) has been shown to cause weight loss by reduction of food intake in humans and rodents. Nor-dexfenfluramine, a circulating metabolite of the weight loss drug dexfenfluramine, is a nonselective 5-HT_{2C} receptor agonist, and the anorectic effects of dexfenfluramine and nor-dexfenfluramine are blocked by the selective 5-HT_{2C} receptor antagonist, SB-242084. The search for potent and selective 5-HT_{2C} agonists has identified lorcaserin (APD-356; Arena) for the treatment of obesity and vabicaserin (SCA-136; Wyeth) a novel antipsychotic and anorectic agent. Recently FDA panel voted to recommend lorcaserin with certain restrictions and patient monitoring.

Since 3-benzazepine system contains phenethylamine skeleton which is common in dexfenfluramine and lorcaserin, it is of great interest from medicinal

chemistry viewpoint. As part of our research efforts to identify potential new 5-HT_{2C} agonist drug candidates, we adopted a strategy of exploring multiple chemical templa-



-tes containing 3-benzazepine ring in common. For the synthesis of substituted 3-benzazepine scaffold different alkyl halides were used for selective alkylation in the presence of BuLi/NaH (**Scheme 2**).



Scheme 2. Synthesis of substituted 3-benzazepines

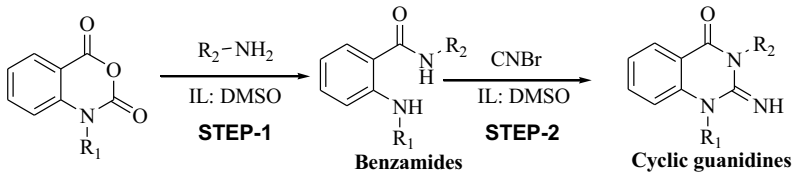
The synthesized compounds were screened on different *in vitro* and *in vivo* protocols to establish the potential for their activity on 5-HT_{2C} receptors. The functional activity of the compounds for the 5-HT_{2C}, 5-HT_{2A} and 5-HT_{2B} receptors was found to be dependent on the substitution pattern on 3-benzazepine ring. Compound (**2a**), our first C-1 substituted compound in this series, demonstrated 5-HT_{2A} antagonistic activity and was eliminated from the study. Simultaneously compounds (**3a** and **3c**) have shown $5HT_{2B}$ agonistic activity and were also eliminated from the study but compound (**3b**) with more lipophilic and bulkier aryl substituents at C-1 and N-3 has shown no activity for $5HT_{2A}$ and $5HT_{2B}$ and compounds (**4a**, **4b** and **4c**) also showed no interactions with $5HT_{2A}$ and $5HT_{2B}$. With these results in

hand, a small set of compounds based on 3-benzazepine was designed to explore the effects of substitution at the C-1 and N-3 positions. At the C-1 position, di-substitutions of the bulkier benzyl group resulted into good $5HT_{2C}$ potency. Compound (**13a**) with no substitution at N-3 position and no oxo- at C-2 position demonstrated highest agonist potency for $5HT_{2C}$ receptor. Compounds (**2a, 3a, 3c, 9a** and **10a**) with oxo- at C-2 position and less lipophilic substituents or no substituents at C-1 and N-3 positions resulted in high potencies towards $5HT_{2A}$ and $5HT_{2B}$ receptors. Compounds (**4c** and **12c**) with no oxo- at C-2 and bulkier substituents at C-1 and N-3 positions exhibited good $5HT_{2C}$ potencies and selectivities. At the C-1 and N-3 positions, replacing the benzyl with methyl, ethyl or allyl groups showed a trend towards decreasing the potency at the $5HT_{2C}$ receptor with decreasing bulk size of the substituent. In summary, bulkier substituents at C-1 and N-3 positions and no substituent at C-2 position showed good $5HT_{2C}$ potencies while oxo substitution at C-2 position and small alkyl groups at C-1 and N-3 positions showed decreased activity towards $5HT_{2C}$ and increased activity for $5HT_{2A}$ and $5HT_{2B}$ receptors.

SECTION-III: Cyclic Guanidine and Benzamide derivatives

The use of room temperature ionic liquids (RTILs) as solvents or catalysts for chemical reactions offers several advantages from the environmental perspective. Therefore, RTILs are attracting academic and industrial attention worldwide, as these can be used to replace the organic solvents in catalysis, synthesis and separations. The unique properties of RTILs enable their use as alternative solvents and may speed up the introduction of potentially 'green' solvents in sustainable industrial processes. The synthetic protocols used in our research work involve the use of RTILs in DMSO as

solvent at room temperature. The method is appealing especially for synthesis of benzamides and cyclic guanidines as it involves very mild conditions in contrast to the reported methods. (**Scheme 3**)



Scheme 3. Synthesis of benzamides and cyclic guanidines

Part-A: Anti-Alzheimer's activity of cyclic guanidines

Alzheimer's disease is a progressive brain disorder that damages and eventually destroys brain cells, leading to loss of memory, thinking and other brain functions. It usually develops slowly and gradually gets worse as more brain cells shrivel and die. Ultimately, Alzheimer's is fatal, and currently, there is no cure. Alzheimer's disease (AD) is characterized as a progressive, neurodegenerative disorder that affects the cholinergic regions of the central nervous system (CNS), associate with cognitive function and spatial awareness. Alzheimer's is not a normal part of aging, although the greatest known risk factor is increasing age, and the majority of people with Alzheimer's are elderly populations. Most often, AD is diagnosed in people over 65 years of age, although the less-prevalent early-onset Alzheimer's can occur much earlier. In 2006, there were 26.6 million sufferers worldwide. Alzheimer's is predicted to affect 1 in 85 people globally by 2050. Alzheimer's disease (AD) is classified as a progressive, neurodegenerative disease that affects the cholinergic regions of the central nervous system (CNS) that associates with cognitive function and spatial awareness. The hallmark characteristics of AD include the rapid loss of cholinergic

neurotransmission, accelerated aggregation of amyloid-β (Aβ) peptides and formation of neurofibrillary tangles (NFTs) of hyperphosphorylated tau protein. These characteristics establish the basis for the cholinergic, amyloid and tau hypotheses for AD pathology, respectively.

In contrast, the amyloid hypothesis suggests that the progression of AD is attributed to the accelerated accumulation of toxic forms of self-induced and/or AChE-promoted toxic aggregates of Aβ peptides. In this regard, recent studies indicate a link between the cholinergic and amyloid hypotheses. These multiple factors in AD pathology mandate the need to develop small molecule therapies that exhibit dual ChE inhibition as well as reduce the formation of neurotoxic Aβ-aggregates. Research into the cholinergic hypothesis has led to the development of several fused and non-fused amine containing ring systems as ChE inhibitors as well as some cyclic guanidines examined for their ability to inhibit the aggregation of Aβ plaques.

Synthesized compounds were screened for their activity. The screening data demonstrated that the ring size of cyclic guanidine motif was the most important factor for the activity of guanidine derivatives. Among the three scaffolds only the six-membered (2-iminoquinazolin-4-one) was found to provide active compounds. Increasing or decreasing the ring size of cyclic guanidine motif resulted in overall decrease in activity and this result is supported by molecular docking studies also, as six membered ligands fitted deeply into the catalyatic active site (CAS) of ChE crystal structure. Structure–activity relationship (SAR) studies indicated that the cholinesterase inhibition and selectivity were sensitive to steric and electronic parameters at N-1 and N-3 positions of the central quinazolinone ring. The most active

compound (**3bk**) for AChEI activity had cyclopropyl substituent at N-3 position and ethyl substituent at N-1 position. In general, compounds with ethyl substituent at N-1 position (**3bg, 3bh, 3bi, 3bk, 3bl, 3bm, 3bo** and **3bs**) acquired good activity for AChEI. At N-3 position, compounds having cyclopropyl substituent (**3bk** and **3ek**) demonstrated very good activity for AChEI. The observation matched with docking studies as cyclopropyl ring appeared at peripheral anionic site (PAS). The isopropyl substituent at N-3 position (**3al, 3bi** and **3ei**) also demonstrated good AChEI activity except for compound (**3ci**). Increasing the chain length at N-3 position from propyl to butyl (**3bh, 3ch** and **3eh**) caused the AChEI activity to slightly decrease. Introducing the aromaticity at N-3 position (**3am**, **3an**, **3bo, 3cn, 3dn, 3en** and **3es**) in general slightly decreased the AChEI activity but in compounds (**3bm** and **3bs**) the activity did not decrease because of ethyl substituent at N-1 position. Apart from other substituents, allyl and benzyl substituents at N-1 position did not made any significant change in AChEI activity of the compounds. On the other hand substituents with aromatic character made significant changes in BuChEI activity of compounds; activity was increased in general especially in the case of *p*-methoxybenzyl substituents (**3an, 3cn, 3dn** and **3en**). Docking studies also suggested that the methoxyphenyl ring had good hydrophobic interactions with the active sites of *h*BuChE. The most active compound (**3an**) for BuChEI activity had a methoxybenzyl substituent at N-3 position and methyl substituent at N-1 position. It was also observed that the compounds which are more active towards BuChEI activity demonstrated very high selectivity (**3an** and **3bg**). As it has been previously mentioned that during the initial stages of AD the prevalence and role of AChE is highly dominating but at advanced stage or in later days of AD the prevalence and

activity of BuChE increases significantly, as a result Aβ-aggregation increases. Keeping these facts in mind the designing of NCEs could be directed in that way i. e. in the initial stage of AD treatment targeting AChE and BuChE should be given and at a later stage more selective treatment BuChEI should be used. The active compounds obtained at the end of this study could be used in both stages; compound (**3bk**) in the initial stage and compound (**3an**) in the advanced stage of AD.

Part-B: Anti-thrombotic activity of benzamides

The discovery of orally active, small molecule competitive fXa inhibitors in preclinical animal thrombosis models in recent years has spurred the process for discovery of such molecules as anti-thrombotic drugs. Survey of literature revealed carboxamides and anthranilamides to possess either fXa inhibitory activity or anti-platelet aggregating activity. Betrixaban, an anthranilamide derivative, is a proven orally active fXa inhibitor useful in prevention of thromboembolic events. Taking betrixaban as the lead it was planned to substitute both the nitrogens with various alkyl/aryl substituents to provide benzamides and to evaluate the synthesized compounds for their antithrombotic efficacy (**Scheme 3, STEP-1**). As fXa is responsible for thrombotic activity ultimately, it was thought of studying the binding interactions of the active compounds using crystallographic 3D structure of fXa and docking studies have been performed with fXa to establish a prospective mechanism of action of the synthesized compounds as potential inhibitors of fXa.