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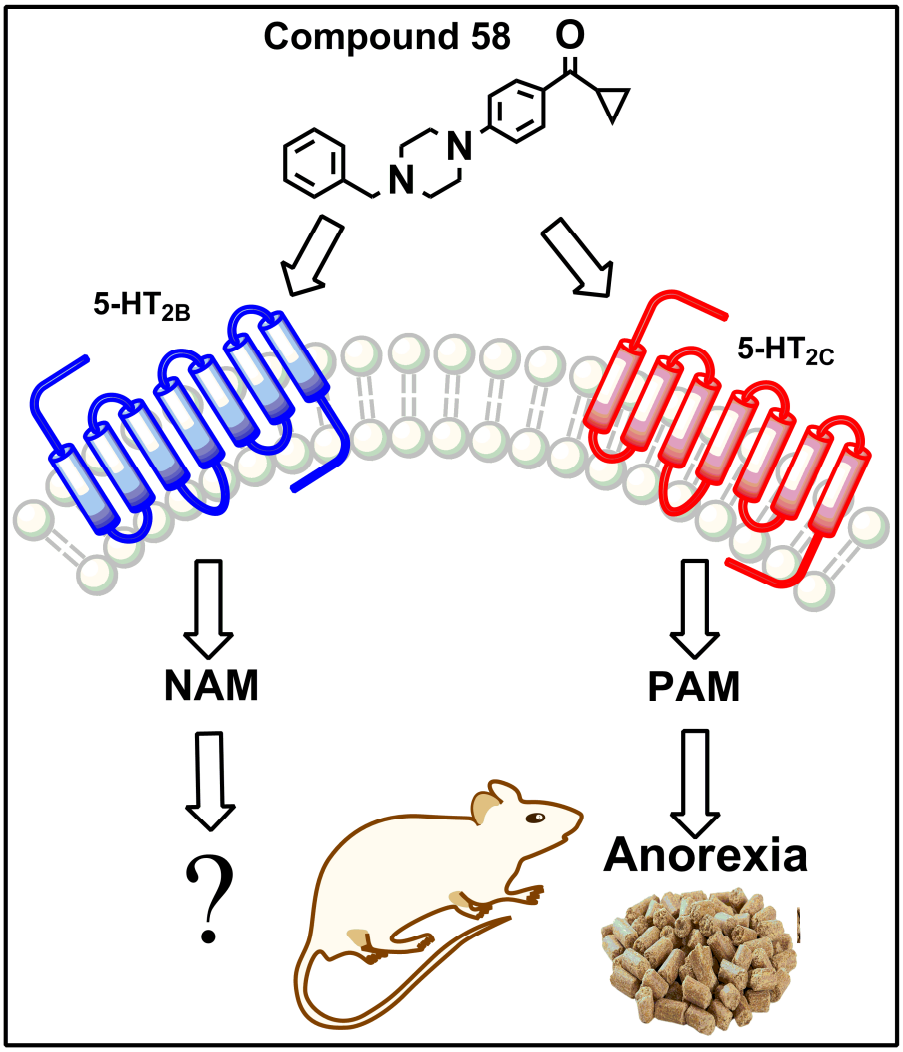

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Identification of Dual Role of Piperazine-Linked Phenyl Cyclopropyl Methanone as Positive Allosteric Modulator of 5-HT_{2C} and Negative Allosteric Modulator of 5-HT_{2B} Receptors

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Abstract

Allosteric modulators of G protein-coupled receptors have lately gained significant traction in drug discovery. Recent studies have shown that allosteric modulation of serotonin 2C receptor (5-HT_{2C}) as a viable strategy for the treatment of various central nervous system (CNS) disorders. Considering the critical role of 5-HT_{2C} in the modulation of appetite, a selective positive allosteric modulator (PAM) of 5-HT_{2C} offers a new opportunity for anti-obesity therapeutic development. In this study, phenyl cyclopropyl-linked *N*-heterocycles were synthesized and evaluated at 5-HT_{2C} for agonist and PAM activity. Our study shows that imidazole linked phenyl cyclopropyl methanones has PAM activity on both 5-HT_{2C} and serotonin 2B receptor (5-HT_{2B}). Interestingly, piperazine linked phenyl cyclopropyl methanones (**58**) was active as PAM of 5-HT_{2C} (increased the E_{max} of 5-HT to 139 %), and as negative allosteric modulator (NAM) of 5-HT_{2B} (decreases EC_{50} of 5-HT 10 times without affecting E_{max}). Similar effect of compound **58** was observed with synthetic orthosteric agonist lorcaserin on 5-HT_{2B}. Molecular docking study revealed that all active compounds were binding to the predicted allosteric site on 5-HT_{2C} and shared a common interacting residues**.** Finally, compound **58** suppressed food intake in Sprague Dawley (SD) rats similar to lorcaserin after i.c.v. administration. Therefore, these results suggest that piperazine moiety is essential for dual activity (PAM & NAM) of compounds **58,** and supports the hypothesis of 5-HT_{2C} PAM for the treatment of obesity similar to the full agonist.

Introduction

5-HT_{2C} is a G_q coupled G protein-coupled receptor (GPCR) widely known for its important role in central nervous system (CNS) disorders, including obesity, anxiety, Parkinson's disease, schizophrenia, and drug addiction [1-3]. Compounds like *meta*-chlorophenylpiperazine (*m*-CPP) (**1**) and related are known to be the earliest tool compounds used in pharmacological studies for understanding the pharmacology and biology of the 5-HT_{2C} (**Fig. 1**) [4, 5]. Apart from these compounds, recent finding suggests 2-phenylcyclopropylmethylamine (**2**) scaffold as 5-HT_{2C} agonist with drug like properties in rodent models of schizophrenia [6, 7]. Vabicaserin (**3**), which is a high-affinity full agonist of 5-HT_{2C} and 5-HT_{2B} was tested in clinical trials for the treatment of schizophrenia and depression but failed to meet the primary endpoints (ClinicalTrials.gov Identifier: NCT00563706) [8]. Fenfluramine which was approved as an appetite suppressant, but later on discontinued due to $5HT_{2B}$ mediated cardiac valvulopathy, which underlines the importance of 5-HT_{2C} selectivity over 5-HT_{2B} [9]. Lorcaserin (Belviq®, **4**) is the first FDA approved drug targeting 5-HT_{2C} receptor with 100-fold selectivity for 5-HT_{2C} over 5-HT_{2B} [10-13]. So the major challenge in designing 5-HT_{2C} specific agonist is to develop selectivity over 5-HT_{2A} and 5-HT_{2B}, which result in significant CNS (5-HT_{2A}) and cardiovascular (5-HT_{2B}) adverse effects.

Given the highly conserved orthosteric site across all 5-HT receptors, designing of receptor-specific positive allosteric modulators (enhances the binding affinity or efficacy, PAMs) or negative allosteric modulators (decreases the binding affinity and/or efficacy, NAMs) appears to be more appropriate approach to develop drug candidates targeting 5-HT receptor. The first known PAM of 5-HT_{2C} is PNU-69176E **5a** with high receptor subtype selectivity profile (Pharmacia, Pfizer), but exhibit response in high micro molar range [14]. Furthermore, a recent report showed that *N*-[(1-benzyl-1*H*-indol-3-yl) methyl]pyridin-3-amine (VA012, **5b**) exhibit selective PAM activity at 5-HT_{2C}, induces significant anorexia and weight loss without causing CNS-related malaise [15]. Thus, PAMs and NAMs provide a unique and advantageous way of inducing selectivity and reducing side effects of not so selective 5-HT_{2C} agonist [16]. In this study, we synthesized compounds containing piperazine[17] and *N*-heteroaryl-phenyl cyclopropyl methanone with an objective of designing selective agonist for 5-HT_{2C}.

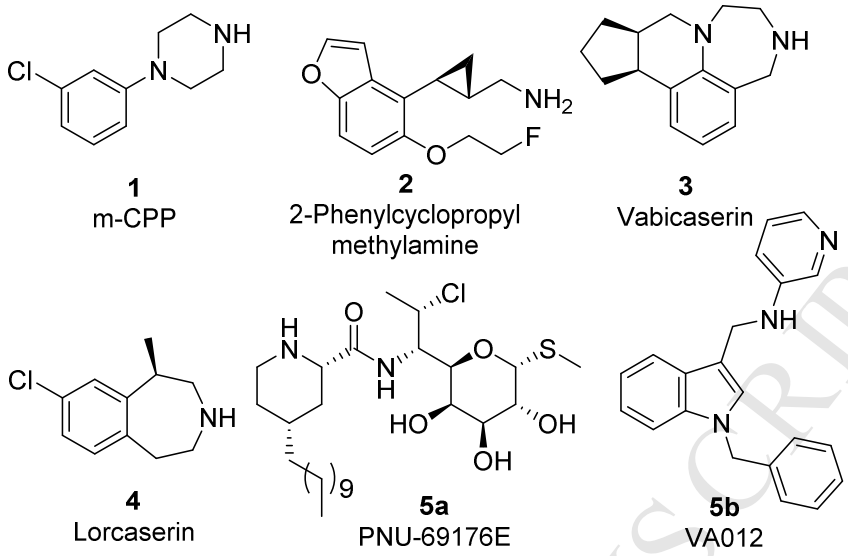

Fig. 1. 5-HT_{2C} agonist (**1**-**4**) and PAM (**5a&b)**

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Result and Discussion

N-linked heteroaryl, arylpiperazine (e.g., m-CPP **1**) and 2-Phenylcyclopropylmethylamine **2** containing scaffolds are known to act as an agonist on the 5-HT_{2C} [1, 18-23]. Moreover, cyclopropyl ring containing scaffold in drugs have shown enhanced potency, pharmacokinetic properties, aqueous solubility and increase in blood-brain barrier (BBB) permeability [24-28] In continuation of our endeavor to develop new chemical entities (NCE) as CNS active agents [29], we embarked upon a new series of compounds consisting of piperazine, *N*-heteroaryl, and cyclopropyl scaffolds were evaluated for agonist and PAM activity on 5-HT_{2C} (**Fig. 2**).

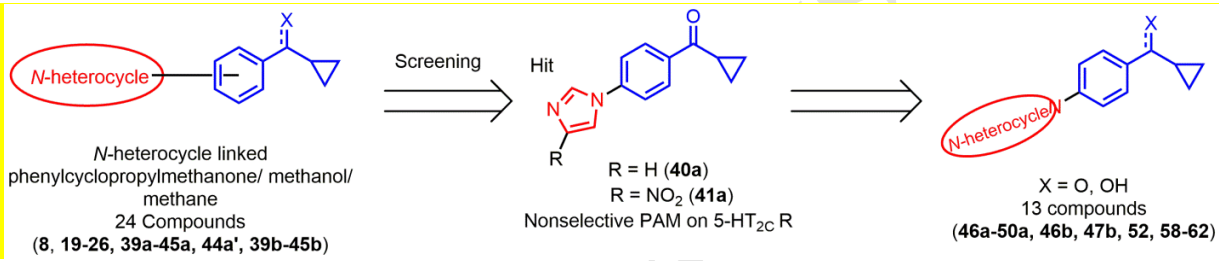
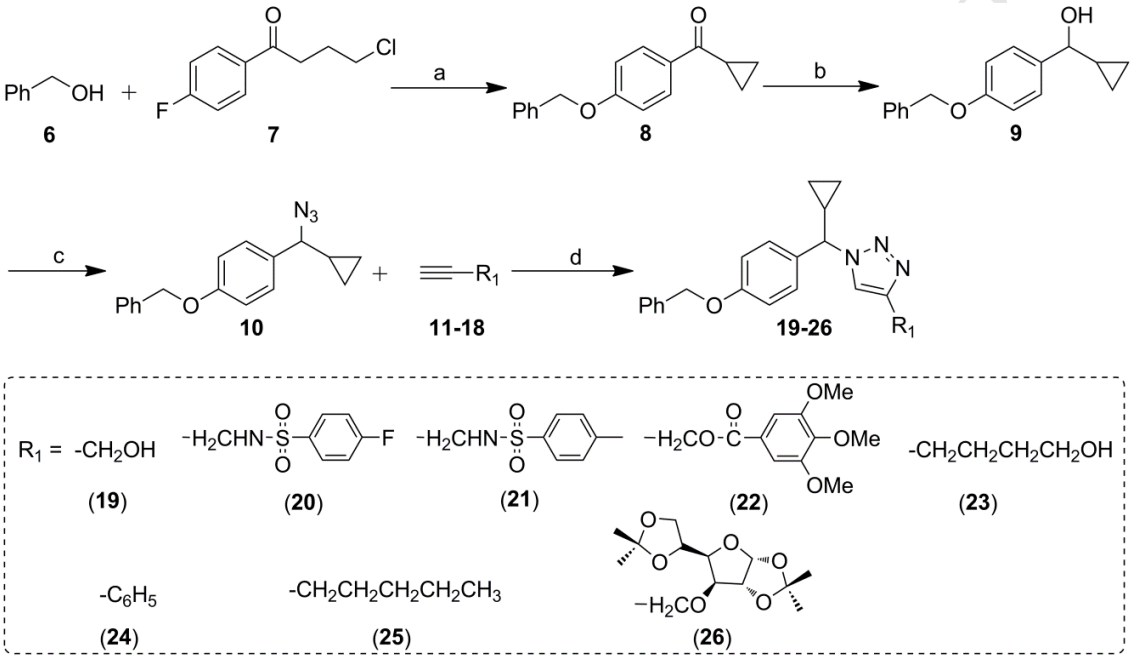


Fig. 2 Screening of *N*-heterocycle linked phenyl cyclopropyl derivatives allowed to identify hit compound **40a** and **41a**, which entered in the further modification on heterocycle unit for the search of PAM of the 5-HT_{2C} Receptor.

Chemistry

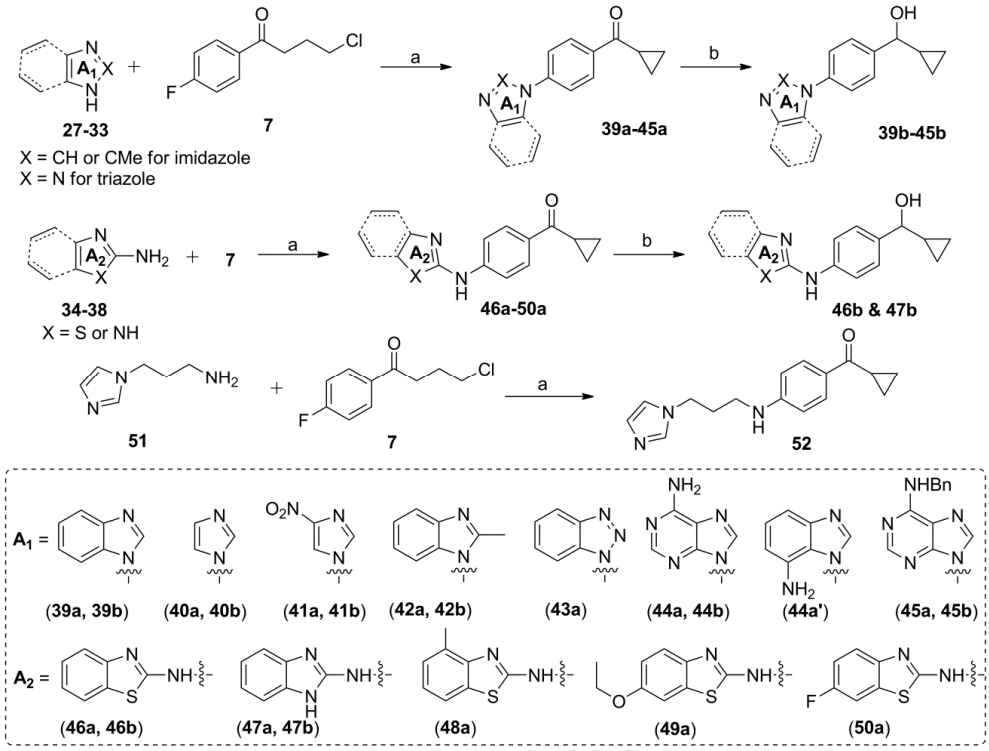
The synthesis of cyclopropyl methane/methanone derivatives were achieved by employing similar methods reported by us previously, starting from the commercially available 4-chloro-4-fluorobutyrophenone **7** [30, 31]. Two series of phenyl cyclopropyl-linked *N*-heterocycle derivatives were synthesized. The first series of compounds **19-26** (Scheme 1) were synthesized by CuAAC reactions with phenyl cyclopropyl methyl azide **10**. Azide intermediate **10** was synthesized from pre-synthesized phenylcyclopropylmethanol **9** using sodium azide in acidic condition [32]. Different alkyne derivatives were used during synthesis that are commercially available (**19, 23, 24** and **25**), or pre-synthesized sulfonamide (**20**, **21**), ester (**22**) and sugar derivative (**26**). Having the azide derivative 1-[azido(cyclopropyl)methyl]-4-(benzyloxy)benzene

10 and alkynes derivatives, the CuAAC reactions were performed in *t*-BuOH/H_2O (1:1) using equimolar quantities of the reactants, $CuSO_4.5H_2O$ (10 mol%) and sodium ascorbate (20 mol%) at ambient temperature that lead to synthesis of 1-(cyclopropyl(phenyl)methyl)-1H-1,2,3-triazole derivatives in excellent yield 88-93 % (**Scheme 1**).



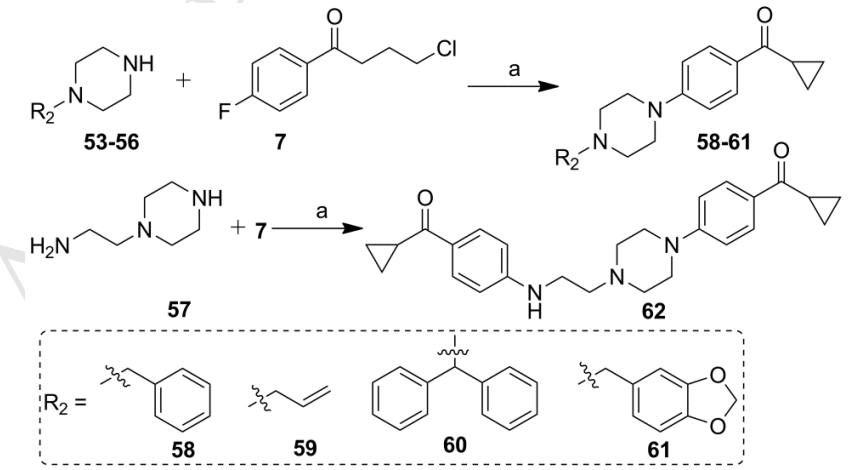
Scheme 1 Synthesis of phenyl cyclopropyl triazolyl methanes (**19-26**). Reagents and conditions: (a) NaH, THF, TBAB, 0 °C- rt, 6 h (b) $NaBH_4$, MeOH, 0 °C - rt, 4 h (c) NaN_3, 56% H_2SO_4-$CHCl_3$ (1:1), 0 °C- rt, 5 h (d) $CuSO_4$ (10 mol%), sodium ascorbate (20 mol%), tert-BuOH-H_2O (1:1), 30 °C, 3-4h.

In scheme 2, 4-chloro-4-fluorobutyrophenone **7** was used to synthesize phenyl cyclopropyl methanone-linked *N*-heterocyclic compounds (**39a-50a** and **58-62**). Different *N*-heteroaryls were fused with 4-chloro-4-fluorobutyrophenone in the presence of K_2CO_3 in DMSO at 140 °C. The reaction proceeded through intramolecular cyclization, followed by SNAr substitution reactions (**39a-50a**, Scheme 2). *N*-heterocycles linked cyclopropyl phenyl methanols (**39b-47b**) were synthesized by carrying out the reduction of the cyclopropyl phenyl methanones with $NaBH_4$ at ambient temperature (**Scheme 2**).



Scheme 2 Synthesis of 4-heterocycle substituted phenyl cyclopropyl methanones and methanols compounds. Reagents and conditions: (a) K_2CO_3, DMSO, 140 °C, 14-16 h (b) $NaBH_4$, MeOH, 0 °C - r.t., 4-5 h.

Further, we use different piperazines to synthesized piperazine-linked phenyl cyclopropyl methanones (**58-62**) in same reaction conditions as described above (**Scheme 3**).



Scheme 3 Synthesis of 4-piperazinyl phenyl cyclopropyl methanones compounds **58-62**. Reagents and conditions: (a) K_2CO_3, DMSO, 140 °C, 12-14h.

Pharmacology

Identification of novel 5-HT_{2C} PAM

The phenyl cyclopropyl methane/methanone derivates (**8**, **19-26**, **39a-45a**, **44a' 39b-45b**) were evaluated on human 5-HT_{2C} for agonist and PAM activity using NFAT-RE luciferase assay in HEK293-T cells. For a compound to be active as an agonist, it should have more than 2-fold stimulation above the baseline. None of the triazole-linked phenyl cyclopropyl methane derivatives (**19-26**) and phenyl cyclopropyl methanone and methanol derivatives (**8**, **39a-45a**, **39b-45b**) were active as an agonist on the 5-HT_{2C} (**Fig. 3A**). We further evaluated these compounds for PAM activity on the 5-HT_{2C}. For a compound to be active as a PAM, the compound should either increase maximum efficacy (E_{max}) of serotonin by 2 fold or decrease the EC_{50} value of serotonin on 5-HT_{2C}. Interestingly, we identified three active molecules (**40a**, **41a** and **22**), out of these two imidazoles derived phenyl cyclopropyl methanones (**40a**, **41a**) were found consistently active as PAM on the 5-HT_{2C} (**Fig. 3B, C**). Compound **22** was discarded due to inconsistency in the PAM activity. We also evaluated these two active compounds on 5-HT_{2B} to determine selectivity (**Fig. 4A-D**), which shows that **40a** and **41a** were non-selective and exhibited 5-HT_{2B} PAM response similar to 5-HT_{2C} (**Fig 4A-D**). Further, reduction of the active cyclopropyl methanone derivatives to respective methanol derivatives (**40b**, **41b**), which did not exhibit any PAM activity at 5-HT_{2C}.

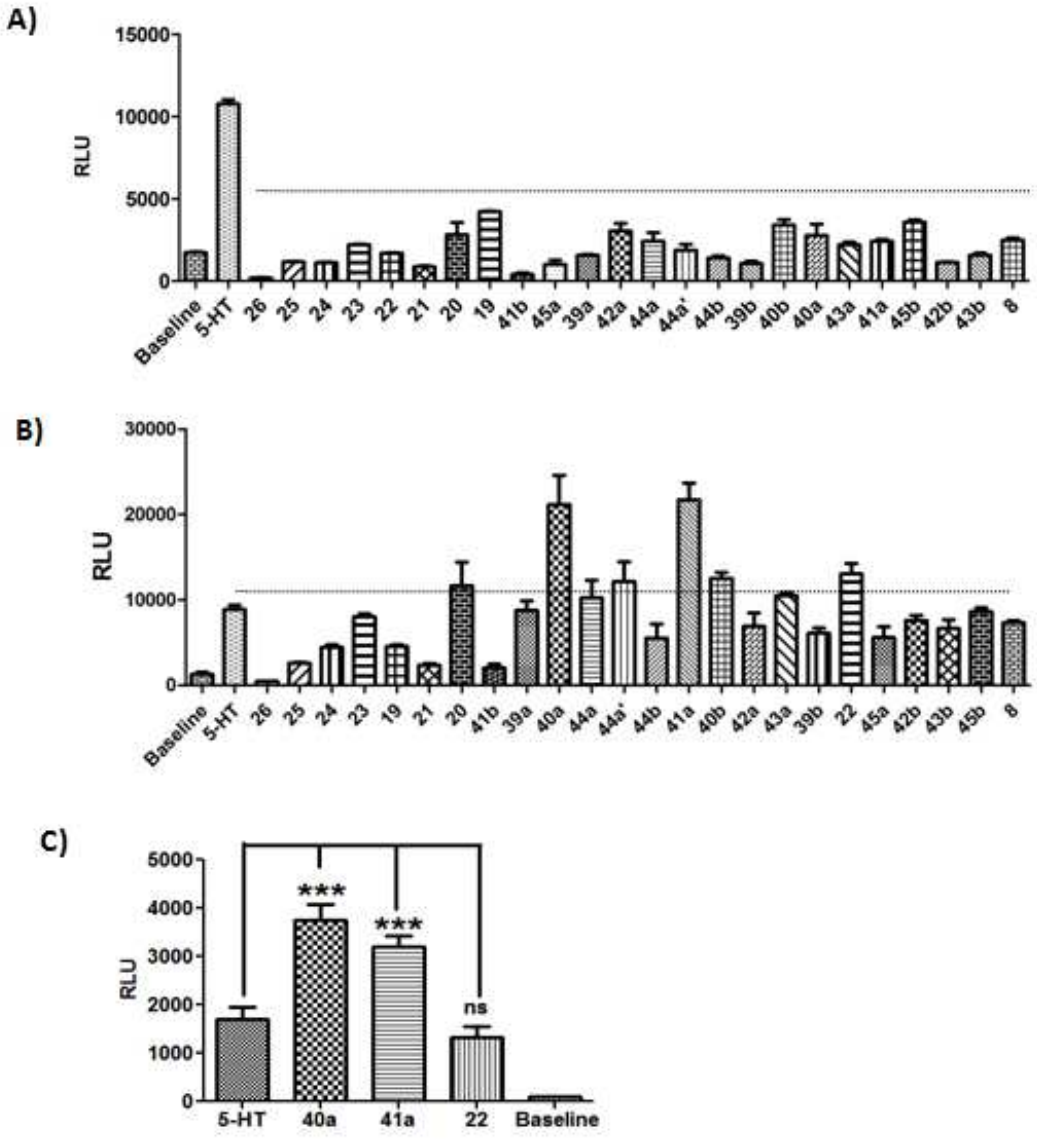


Fig. 3A) Representative bar graph shows 5-HT_{2C} dependent increase in relative luminescence units (RLU) after treatment with test compounds (**8**, **19-26**, **39a-45a**, **39b-45b**) at10 µM for 6 hrs for agonist activity at 5-HT_{2C}. Serotonin (5-HT, 1µM) was used as positive control. Dashed lines represent half of the E_{max}. **B**) Representative bar graph shows stimulation of 5-HT_{2C} as measured of increase of RLU after treatment with test compounds (**8**, **19-26**, **39a-45a**, **39b-45b**) at 10 µM along with 5-HT (1µM for PAM activity at 5-HT_{2C}. Dashed lines represents E_{max} of 5-HT. **C**) Representative bar graph shows RLU of active compounds (**40a, 41a** and **22) at** 10 µM + serotonin (1µM for PAM activity at 5-HT_{2C}).

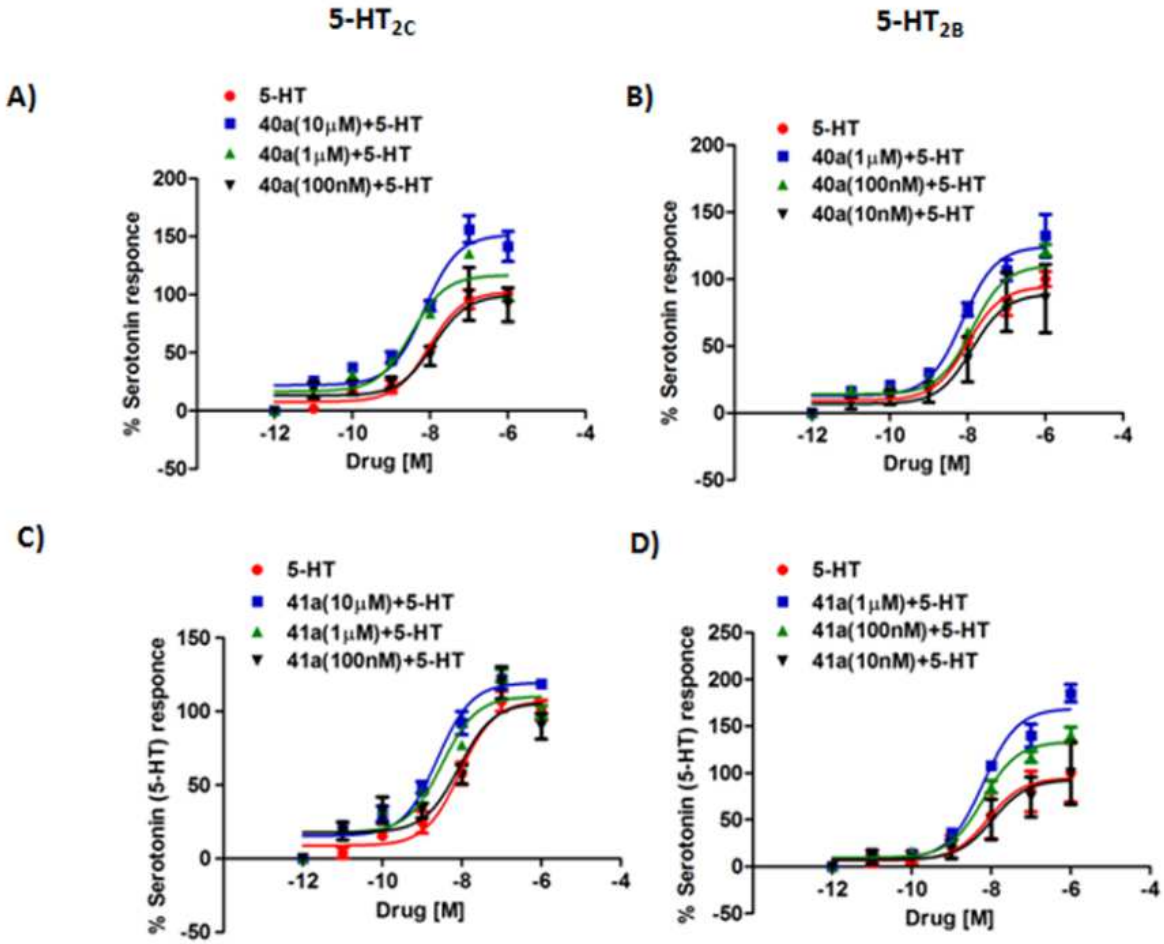


Fig. 4. Concentration response curve of **40a +** 5-HT (**A** and **B**) and **41a** + 5-HT (**C** and **D**) with at 5-HT_{2C} (**A** and **C**) and 5-HT_{2B} (**B** and **D**) for PAM activity in transiently transfected HEK293T cells with NFAT-RE luciferase along with either 5-HT_{2C} or 5-HT_{2B}.

After identification of the imidazole linked phenyl cyclopropyl methanone scaffold important for PAM activity, we synthesized more azole-linked phenyl cyclopropyl methanones (**46a-50a**) and also replaced the imidazole unit with piperazine unit (**58-62**). These compounds were also evaluated for agonist activity and PAM activity on 5-HT_{2C} (**Fig. 5A**).Surprisingly, none of these compounds were active as agonist on 5-HT_{2C}. Interestingly however, compound **58** (piperazine-linked phenyl cyclopropyl methanone) was found active as PAM of 5-HT2C and increased the maximum efficacy (E_{max}) of 5-HT from 100% to 149 % at 10 μM and 139 % at 1μM but was inactive at other concentrations **(Fig. 5B**, **D**). PAM activity of compound **58** was also confirmed by using another functional assay in which we measured intracellular calcium flux (iCa^{++}) in

HEK293T cells transiently expressing 5-HT_{2C} in response to 5-HT either alone or combination of compound **58**. Indeed, we observed the increase of 5-HT activity by compound **58** at 1 μM (E_{max} from 100 to 123.94, **Fig. 5E**).Compound **58** on Upon further evaluation of receptor subtype selectivity of compound **58,** we found that this compound exhibit NAM activity at 5-HT_{2B} as it decreased serotonin EC_{50} by 10 fold. Moreover, the NAM effect of compound **58** was found to be concentration dependent as shown in **Fig. 5C**. Further change of **58** to allylpiperazine derivative **59** resulted in the loss of PAM activity. The activity of these compounds was also sensitive to steric bulk, as piperazine derivative with biphenyl (**60**) and piperonyl unit (**61**) were inactive at this receptor. In this series, none of the phenyl cyclopropyl methyl triazole derivatives were active as PAM or agonist on 5-HT_{2C}. In case of the phenyl cyclopropyl methanone-linked azoles, only imidazoles derivatives (**40a**, **41a**) were active as PAM at 5-HT_{2C} and 5-HT_{2B}, while the bicyclic imidazoles and other azoles (**39a, 42a-50a**) derivatives were inactive. Since **40a** were active as 5-HT_{2C} PAM, we sought to evaluate the activity of imidazole linked phenyl cyclopropyl methanone with propyl linker **52,** and observed that this modification lead to loss of the PAM activity in 52. These results suggest that imidazole should be directly linked to the phenyl cyclopropyl methanone scaffold for PAM activity at 5-HT_{2C} (**Fig. 6**).

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Figure 5

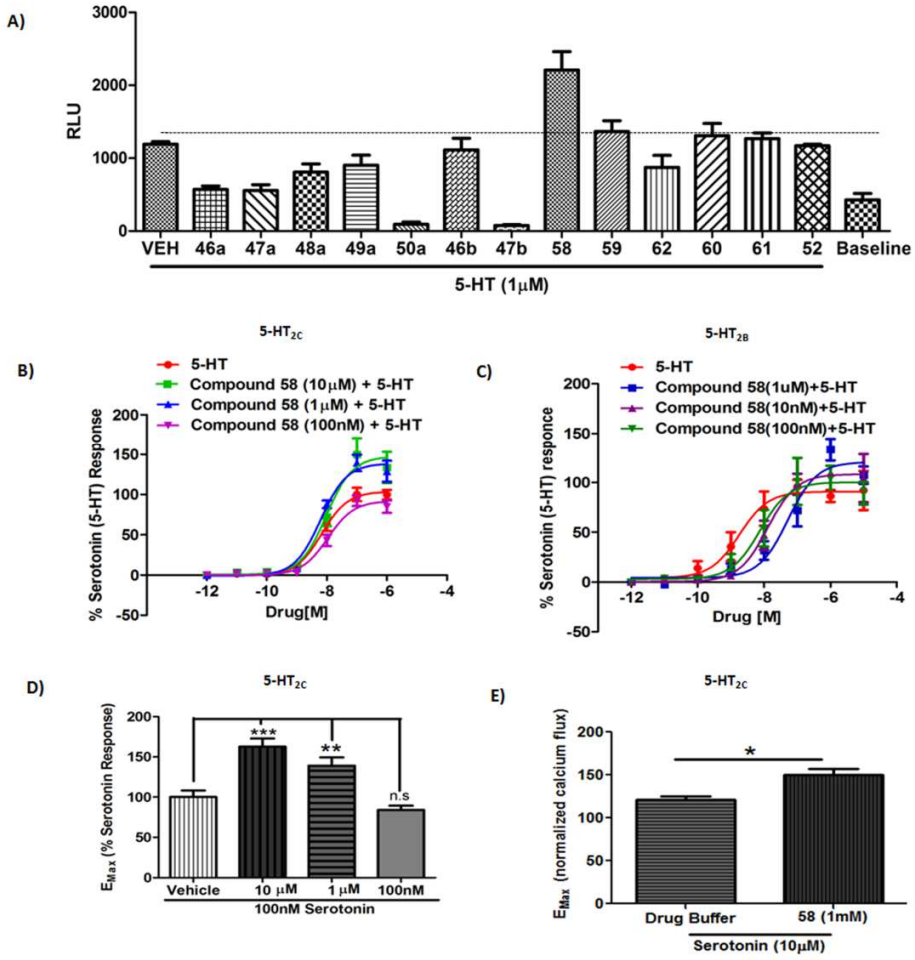

Fig. 5. Evaluation of phenyl cyclopropyl methanone derivatives on 5-HT$_{2C}$ for PAM activity using NFAT-RE luciferase assay. A) Representative bar graph showing change in relative luminescence units after addition of vehicle or compounds (**8**, **19-26**, **39a-45a**, **3b-45b)** at 10 μM followed by serotonin (5-HT, 1μM). The compound 58 showed about 2 fold stimulation over 5-HT alone. **B)** Representative concentration response curve of 5-HT (E_{max} =100% and log EC_{50} -8.01± 0.09) shows increased efficacy with 10 μM (E_{max} =149%, log EC_{50} = -8.1± 0.16), and 1 μM of compound **58** (E_{max} =139% and log EC_{50} = -8.21± 0.09). Data were plotted as mean ± SEM (n=3-4). **C)** Representative concentration response curve of 5-HT at 5-HT$_{2B}$ showing log EC_{50} -8.75 ± 0.17 were as 5-HT + **58** (1μM) shows affinity of log EC_{50} -7.28 ± 0.10, 5-HT+ **58** (100 nM) shows affinity of log EC_{50} -8.12 ± 0.15 and 5-HT+ **58** (10 nM) shows affinity of log EC_{50} -7.89 ± 0.13 did on 5-HT$_{2B}$ receptor. Data were plotted as mean ± SEM (n=3). **D)** Bar graph shows increase in E_{max} of 5-HT (100 nM) in the presence of compound **58** at various concentrations Data were plotted as mean ± SEM (n=3-4). **p<0.001, one way ANOVA Newman Keuls multiple comparisons *post hoc* test. **E)** Representative bar graph showing significant increase in E_{max} of intracellular calcium flux [iCa^{++}] in HEK293T cells transfected with 5-HT$_{2C}$ upon prior stimulation with compound **58** (1 μM). The E_{max} were plotted as mean ± SEM. *p<0.05, unpaired t-test. (n=4).

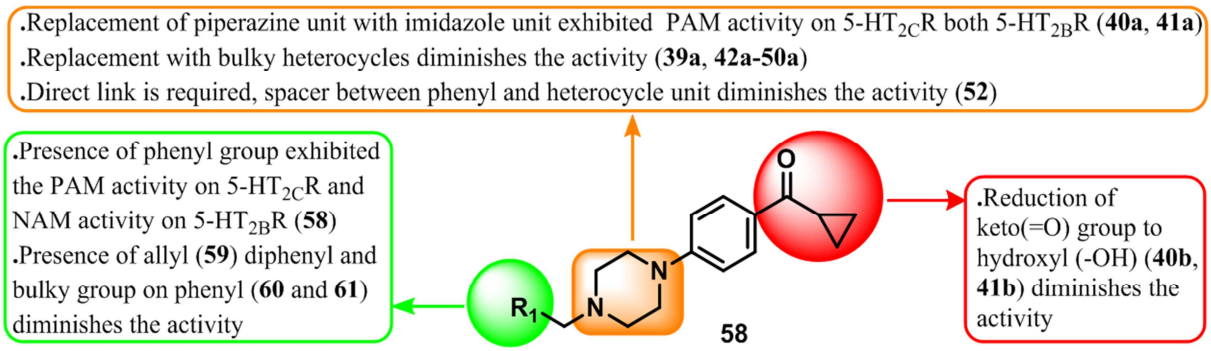

Fig. 6. SAR analysis of all synthesized *N*-heterocycle-linked phenyl cyclopropyl methanones.

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Selectivity of phenyl cyclopropyl methanones on 5-HT_{2A} and 5-HT_{2B} receptors

Since activation of 5-HT_{2C} analogous receptors 5-HT_{2A} and 5-HT_{2B} are widely known to induce severe adverse effects such as hallucination/psychosis (5-HT_{2A}) and cardiac valvulopathy (5-HT_{2B}), we determined the activity of compound **58** at 5-HT_{2A} and 5-HT_{2B} receptors. Our result showed that PAM activity of piperazine-linked phenyl cyclopropyl methanone derivative **58** (1 µM) and imidazole-linked phenyl cyclopropyl methanones **40a** and **41a** (1 µM) showed equal increase in the efficacy (100% to 140%) of 5-HT without affecting EC_{50} (**Table 1**) at 5-HT_{2C} (**Fig. 7C**). As the compound **58** was found active at 1 µM on the 5-HT_{2C}, we used this concentration for selectivity profile for all active compounds. All three active compounds (**58**, **40a** and **41a**) were inactive at 5-HT_{2A} receptor as an agonist (**Supp. Fig. 1**) or as PAM (**Fig. 7A**, **Table 1**). However, our initial screening showed that phenyl cyclopropyl methanone-linked imidazoles (**40a**, **41a**) exhibited non-selective PAM activity at 5-HT_{2B} receptor without affecting EC_{50} of 5-HT (**Fig. 7B, Fig. 4C, D, Table 1**). Interestingly, phenyl cyclopropyl methanone-linked piperazine derivative **58** showed NAM activity and decreased the EC_{50} of 5-HT 10 times at 5-HT_{2B} (**Fig7B, and Table 1**). These data reveal that the presence of benzylpiperazine moiety on phenyl cyclopropyl methanone scaffold is essential for dual activity of negative allosterism on 5-HT_{2B} and positive allosterism at 5-HT_{2C}. We also wanted to determine if compound **58** via NAM activity at 5-HT_{2B} receptor can increase selectivity of another orthosteric agonist such as lorcaserin. Lorcaserin has been reported to be 100 fold selective compared to 5-HT on 5-HT_{2B} [10]. We observed that compound **58** (1 µM) shifted EC_{50} of lorcaserin about 10 times at 5-HT_{2B} receptor (LogEC_{50} from -6.33 to -5.1, **Fig. 8**) which overall increases 1000 fold selectivity with respect to 5-HT (5-HT log EC_{50} -8.54 and compound **58** + lorcaserin log EC_{50} -5.1, **Fig. 8**). Thus, compound **58** might potentially be used to enhance the therapeutic window by decreasing the chances of 5-HT_{2B}-mediated adverse effect profile.

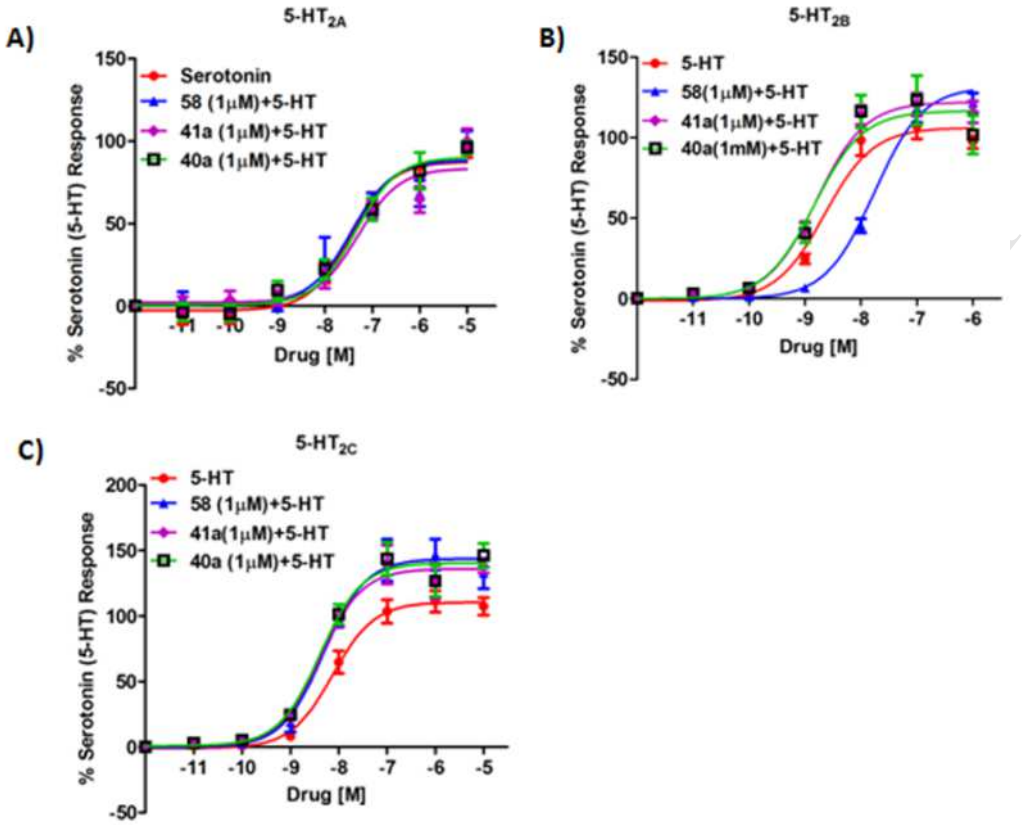


Fig. 7. Selectivity of phenyl cyclopropyl methanones derivates (58, 40a and 41a) on 5-HT receptors for allosteric activity using NFAT- RE luciferase assay. A) Representative dose response curve of 5-HT (E_{max}100% and log EC_{50} -7.5± 0.13) does not show any change in efficacy (E_{max}) or affinity (EC_{50}) of 5-HT upon prior addition of 1μM of compound **58**, **40a** and **41a** in 5-HT_{2A} expressing HEK293T cells. Data were plotted as mean ± sem (n=3). E_{max} was normalized in all the experiments by 5-HT alone response. **B)** Representative dose response curve of 5-HT (E_{max}102% and log EC_{50} -8.75± 0.11) shows very little increase in EC_{50} upon prior addition of 1μM of compound **58**, **40a** and **41a**, whereas compound **58** shows a decrease in EC_{50} of 5-HT on 5-HT_{2B} receptor but no effect by compound **40a** and **41a**. Data were plotted as mean ± SEM (n=3). **C)** Representative dose response curve of 5-HT (E_{max}100% and log EC_{50} -8.1± 0.17) shows increased efficacy (E_{max}) and EC_{50} of 5-HT upon prior addition of 1μM of compound **58**, **40a** and **41a** on the 5-HT_{2C} receptor. Data were plotted as mean ± SEM (n=3-4).

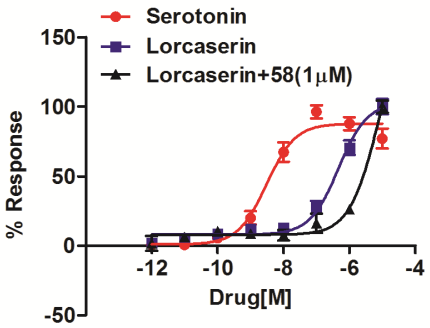
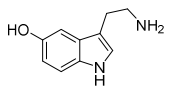
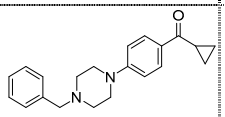
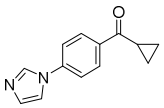
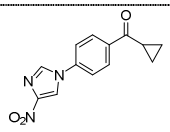


Fig. 8. Compound 58 increases selectivity of lorcaserin compared to 5-HT on 5-HT$_{2B}$ receptor. Representative dose response curve of 5-HT (E_{max}100% and log EC_{50} -8.54 ± 0.11) shows no increase in efficacy upon prior addition of 1μM of compound **58**, whereas compound **58** shows decrease in EC_{50} of lorcaserin from log EC_{50} -6.331 ± 0.08 (100 fold selective compared to 5-HT) to log EC_{50} -5.1 ± 0.22 (> 1000 fold selective compared to 5-HT) on 5-HT$_{2B}$ receptor. Data were plotted as mean ± SEM (n=4).

Table 1. Mean E_{max}(%) and log EC_{50} values obtained after normalizing response with 5-HT on different 5-HT receptors. E_{max} was normalized by the 5-HT individual response.

Compound	Structure	5-HT$_{2C}$		5-HT$_{2B}$		5-HT$_{2A}$	
		E_{max}	Log EC_{50}	E_{max}	Log EC_{50}	E_{max}	Log EC_{50}
5-HT		100	-8.1 ± 0.09	102	-8.75± 0.11	100	7.45± 0.13
5-HT + 58		146*	-8.30± 0.11^{ns}	118*	-7.93± 0.1*	99^{ns}	7.42± 0.16^{ns}
5-HT + 40a		143*	-8.37± 0.09^{ns}	119*	-8.9± 0.09^{ns}	96^{ns}	7.30± 0.15^{ns}
5-HT + 41a		140*	-8.38± 0.1^{ns}	123*	-8.9±.13^{ns}	100^{ns}	7.34± 0.14^{ns}

*p<0.01 compared with 5-HT in all experiments; ns= non significant. Analysis was done by in built statistical analysis of top and EC_{50} comparison using GraphPad Prism 5 software.

Molecular Docking studies at 5-HT_{2C} allosteric site.

To further support our claim regarding allosteric activity of the active compounds, we performed molecular docking studies on predicted allosteric site of 5-HT_{2C} as reported recently by Christopher et.al, [33]. For docking experiments, crystal structure of human serotonin receptor protein 5-HT_{2C} was retrieved from protein data bank (PDB) in its active form co-crystallized with agonist ligand ergotamine (PDB ID: 6BQG, 3A^{o} resolution)[34]. Schrodinger suite was used for all the protein-ligand preparation and docking experiments. Binding site and receptor grid information for the docking of PAMs and serotonin were taken from Christopher et al., [33] as described in the experimental section. Molecular docking studies were carried out on all the three active compounds (**40a**, **41a** and **58**) to identify possible binding to allosteric site for each identified PAM compounds in the extracellular region of the receptor (PDB ID: 6BQG). **Fig. 9** depicted the binding mode of compound **40a** (**A**), **41a** (**B**) and **58** (**C**) in the proposed allosteric site of the 5-HT_{2C} protein. Top scoring poses measured by binding energy (as shown in table 2) were selected for the interaction analysis of PAM compounds and 5-HT_{2C} protein.

Table 2: Binding energies of identified PAM compounds of the 5-HT_{2C} protein

Compound ID	Binding energy (kcal/mol)
40a	-6.091
41a	-6.276
58	-6.182

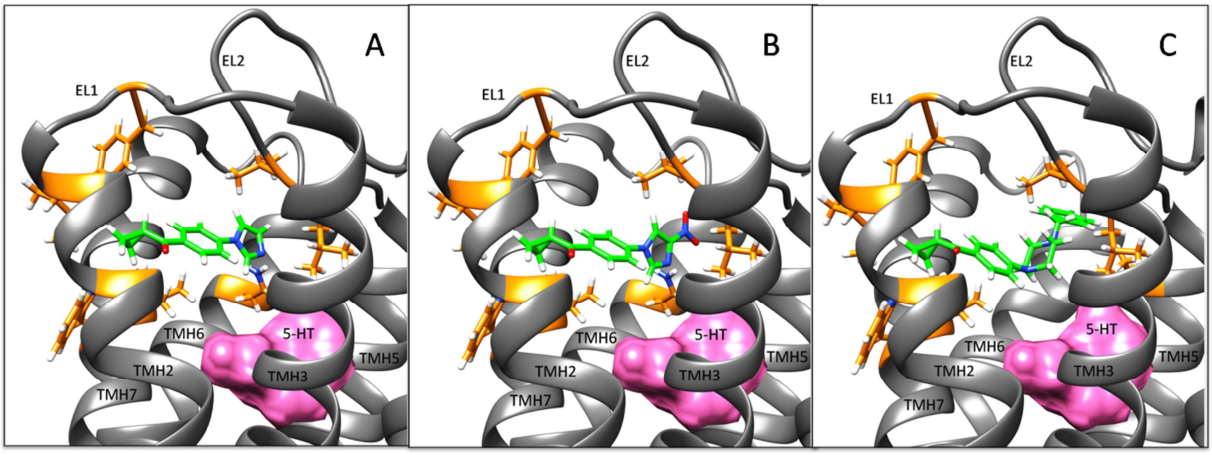


Fig. 9. Binding mode of PAM compounds (green). Binding mode of compound **40a** (**A**), compound **41a** (**B**), and compound **58** (**C**) in the allosteric site with respect to the position of 5-HT (pink) in the orthosteric site of the 5-HT_{2C} protein.

In compound **40a** (**Fig. 10A**, **B**), the N-3 atom of the imidazole ring bonded to the side chain amide group of ASN331 (TMH6) through conventional hydrogen bond while imidazole core was involved in the π-alkyl interactions with VAL208 and LEU209 in the extracellular loop (EL2). VAL354 (TMH7) hold aromatic ring through π-sigma interaction. Bridging carbonyl oxygen atom bonded to SER110 (TMH2) with conventional hydrogen bond. Terminal cyclopropane formed alkyl bonds with ILE114, TYR118, TRP355 and VAL354. These bonding and non-bonding interactions are crucial for the higher affinity of compound **40a** in the allosteric site of the 5-HT_{2C} protein.

Compound **41a** (**Fig. 10C**, **D**) contain 4-nitroimidazole instead of imidazole forming an additional hydrogen bond with the ASN331. Moreover, compound 41a formed same type of interactions as exhibited by compound **40a**, with an additional hydrogen bond between 4-nitroimidazole and ASN331 as depicted in **Fig. 10C** & **10D** directly contributing to binding energy (**Table 2**).

Compound **58** (**Fig. 10E**, **F**) is relatively more complex than compound **40a** and **41a**. It has piperazine ring in place of imidazole which form alkyl-alkyl hydrophobic interactions with VAL208 and LEU209. LEU209 involved in the Carbon-Hydrogen Bond with the methylene bridging piperazine and benzene ring. An extra aromatic ring in the terminal involved in π-alkyl hydrophobic interactions with VAL215. Both the interactions were directly involved in increasing the binding energy of compound **58**. Although crystal structures of 5-HT_{2B} and 5-HT_{1B} are available, nothing is known about allosteric sites in these receptors, and therefore we could not perform docking studies with our active molecules at these receptors. Understandably, this is one of the limitations of this study.

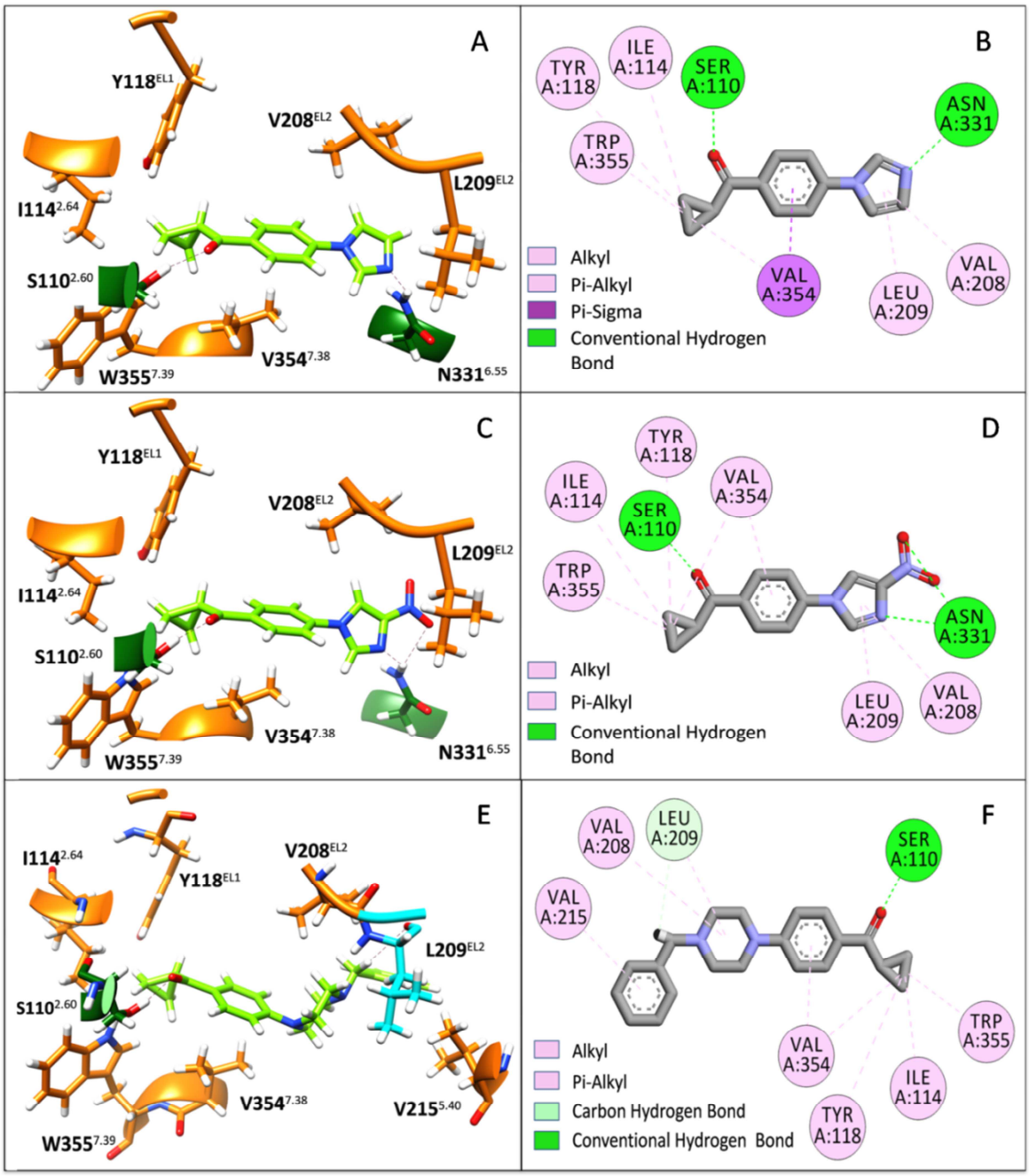


Figure 10: Interaction of PAM compounds (light green/gray) with the 5-HT$_{2C}$ protein. Amino acid residues mediating interaction between 5-HT$_{2C}$ protein and compound **40a** (**A**, **B**), compound **41a** (**C**, **D**), and compound **58** (**E**, **F**). Hydrogen bonds represented in green and cyan. Alkyl/ π-alkyl and π-sigma interactions were represented in pink and purple respectively. Superscripts showed GPCR db labeling [35] of amino acid residues.

Effect of compound 58 on food intake in Sprague Dawley (SD) rats

Since 5-HT_{2C} activation in brain induces anorexia [36-38], we evaluated the effect of compound **58** *in vivo* to determine if this class of molecules can exhibit drug like properties in comparison to full agonist lorcaserin and ultimately induce anorexia. We administered compound **58** (2 pmols/rat/2 µL) via intracerebroventricular (i.c.v.) route and measured suppression of food intake (anorexia) in SD rats. As expected, compound **58** suppressed food intake after 3 and 6 hours of administration and is comparable to reference anti-obesity drug lorcaserin administered at same dose. Since the effect of compound **58** as well as reference drug did not exhibit any effect on cumulative food intake after 24 hrs, most likely both compounds are getting metabolized after 6 hrs (**Fig. 11**). These results suggest that both allosteric modulator (compound **58**) and full agonist (lorcaserin) had similar *in vivo* effect at least in terms of suppression of food intake.

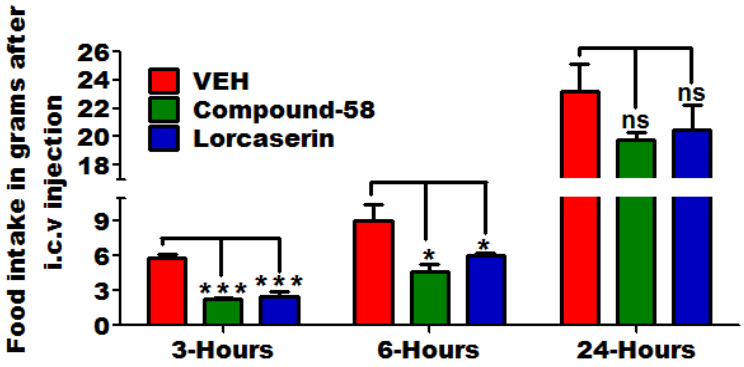


Fig. 11. Acute food intake in SD rats after central administration (*i.c.v.)* of compound **58.** Each histogram represents mean ± SEM (n=4). ***p<0.001 and *p<0.05, one way ANOVA Newman Keuls multiple comparisons *posthoc* analysis**,** ns (non significant).

Conclusions

In this study we evaluated allosteric activity of phenyl-cyclopropyl-linked N-heterocycles at 5-HT_{2C} receptor. Our result suggests that imidazole-linked phenyl cyclopropyl methanones (**40a** and **41a**) and benzylpiperazine linked phenyl cyclopropyl methanones (**58**) acts as 5-HT_{2C} PAM activity. Notably, compound **58** showed unique dual characteristics by exhibiting PAM response at 5-HT_{2C} and NAM at 5-HT_{2B} receptors, which is a unique property that is rarely reported for allosteric modulators. Such molecules could be further developed as adjuvant therapy to enhance selectivity over receptor subtype. Molecular docking studies of compound **58**, **40a** and **41a** further supports our observation of allosteric binding on 5-HT_{2C}. Furthermore, compound **58** exhibited in vivo efficacy and the effect was found to be comparable to FDA approved drug lorcaserin, suggesting the strong potential of compound **58** for further development as therapeutics for obesity. However, further molecular docking studies on allosteric site of serotonin receptor subtype family and experimental pharmaco-kinetic studies are needed to completely understand the dual mechanism exhibited by compound **58**.

ACCEPTED MANUSCRIPT

Experimental Section

General methods

Commercially available reagent grade chemicals were used as received. All reactions were monitored by TLC on E. Merck Kieselgel 60 F254, with detection by UV light, spraying 20% aq. $KMnO^4$ solution or spraying 4% ethanolic H_2SO_4. Column chromatography was performed on Silica Gel (60–120 mesh, E. Merck). IR spectra were recorded as thin films or in KBr pellet with a Perkin-Elmer Spectrum RX-1 (4000–450 cm^{-1}) spectrophotometer. ^1H NMR spectra were recorded on 500, 400 and 300 MHz Bruker NMR spectrometers in $CDCl_3$ or DMSO-d_6. Chemical shift values are reported in δ ppm relative to the residual signals of TMS in $CDCl_3$ or deuterated solvent DMSO-d_6. ^{13}C NMR spectra were recorded on 100 and 75 MHz Bruker NMR spectrometers. Unless otherwise stated; *J* in Hertz. ESI mass spectra were recorded using a Quattro II (Micromass) instrument. HRMS spectra were recorded using a mass spectrometer Q-TOF. The purity of all tested compounds was characterized by HPLC analysis (Discovery HS C-18 HPLC) system. The HPLC system consisted of a pump (LC-10AT VP with FCV-10AL VP), degasser (DGU-14A) and auto-injector (SIL-HTc, fixed with a 100 µl loop) (Shimadzu, Japan). Eluents were monitored at 260 nm with a UV-Vis multiple wavelength detector and chromatograms were integrated using Class-VP (version 6.12 SP5) software (Shimadzu, Japan). Individual compounds with a purity of >95% were used for subsequent experiments.

1-{Azido(cyclopropyl)methyl}-4-(benzyloxy)benzene **(10).** The reaction of **9** (0.5 g, 1.96 mmol) in an ice cold solution (34 ml) of 56% H_2SO_4 and chloroform (1:1) in which NaN_3 (0.38 g, 5.90 mmol) was added slowly in portion at 0 °C and the reaction was stirred at r.t. for about 5 h. After the completion of reaction, the workup was done with ethylacetate and water, then the organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure passed through column to obtain the compound **10** as white solid in 65% yield (0.36 g); mp 62-64 °C; IR (ν_{max}, cm^{-1}): 3010 (C-H), 2095 (N_3 asymmetric), 1610 (C=C), 1510 (C=C), 1457 (C=C), 1240 (N_3 symmetric), 824 (C-H bend); ^1H NMR (400 MHz, $CDCl_3$) 7.40 (m, 4H, Ar-H), 7.34 (m, 1H, Ar-H), 7.28 (d, *J* =

8.66 Hz, 2H, Ar-H), 6.97 (d, *J* = 8.66 Hz, 2H, Ar-H), 5.06 (s, 2H, CH_2), 3.81 (d, *J* = 8.60 Hz, 1H, CH), 1.28 (m, 1H, CH), 0.73 (m, 1H, CH), 0.56 (m, 2H, CH), 0.30 (m, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6 (Ar-C), 136.8 (Ar-C), 132.1 (Ar-C), 128.6 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 127.4 (Ar-C), 114.8 (Ar-C), 70.0 (CH_2), 69.4 (CH), 16.3 (CH), 4.3 (CH_2).

General procedure for the synthesis of compounds 19-26

Substituted propargyl alcohol and selected alkynes **11-18** (1 mmol) and synthesized azide **10** (1 mmol) were suspended in a mixture of 1:1 *t*-butanol-water (20 mL) and kept for stirring at room temperature. To this stirring reaction mixture freshly prepared 0.5 mL solution of sodium ascorbate (20 mol %) and 0.2 mL solution of $CuSO_4.5H_2O$ (10 mol %) in were sequentially added. The reaction mixture was stirred at ambient temperature for 12-16h. After completion of reaction (TLC), the workup was done with EtOAc and water. The organic layer was dried (anhd. Na_2SO_4) and evaporated under reduced pressure to give a crude mass. The latter was purified by silica gel (60-120 mesh) column chromatography using ethylacetate: hexane (1:1) as eluent to give the cycloaddition products **19-26** in excellent yields.

1-{(4-Benzyloxyphenyl)(cyclopropyl)methyl}-1H-1,2,3-triazol-4-yl-methanol **(19).** The reaction of *1-(azido(cyclopropyl)methyl)-4-(benzyloxy)benzene* **10** (0.1 g, 0.367 mmol) and propargyl alcohol **11** (0.02 ml, 0.40 mmol), $CuSO_4{\cdot}5H_2O$ (0.01 g, 0.04 mmol) and sodium ascorbate (0.02 g, 0.08 mmol) in 1:1 *t*-butanol-water (20 ml) in 88 % yield (0.1 g) as white solid; mp 112-114 °C; IR (ν_{max}, cm^{-1}): 3367 (O-H), 1610 (C=C), 1512 (C=C triazole), 1455 (N=N), 1241 (C-O), 755 (C-H bend); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H, triazole-H), 7.44-7.38 (m, 4H, Ar-H), 7.34 (m, 1H, Ar-H), 7.26 (d, *J*= 8.64 Hz ,2H, Ar-H), 6.97 (d, *J* = 8.64 Hz, 2H, Ar-H), 5.075 (s, 2H, CH_2), 4.93 (d, *J* = 9.64 Hz, 1H, CH), 4.81 (s, 2H, CH_2), 2.38 (s, 1H, OH), 1.65 (m, 1H, CH), 0.90-0.72 (m, 2H, CH), 0.53 (m, 2H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8 (Ar-C), 136.7 (Ar-C), 130.9 (Ar-C), 128.6 (Ar-C), 128.2 (Ar-C), 128.0 (Ar-C), 127.4 (Ar-C), 115.0 (Ar-C), 70.0 (CH_2), 69.0 (CH), 56.64 (CH_2), 15.9 (CH), 5.3 (CH_2); Anal. Found: C, 71.61; H, 6.29; N, 12.51. Calcd: C, 71.62; H, 6.31; N, 12.53; HRMS: Calcd. Accurate mass for ($C_{20}H_{22}N_3O_2$): 336.1707. Found 336.1700 $[M+H]^+$, ($C_{17}H_{17}O$):

Calcd. 237.1274. Found 237.1273 [M-98], (C_7H_7): Calcd. 91.0542. Found 91.0545 [M-244].

***N-1-{(4-benzyloxyphenyl)(cyclopropyl)methyl}-1H-1,2,3-triazol-4-yl-methyl 4-fluorobenzenesulfonamide* (20).** The reaction of 1-(azido(cyclopropyl)methyl)-4-(benzyloxy)benzene **10** (0.1 g, 0.367 mmol) and N-propargyl-4-fluoro-benzenesulfonamide **12** (0.076 g, 0.40 mmol), $CuSO_4{\cdot}5H_2O$ (0.01 g, 0.04 mmol) and sodium ascorbate (0.02 g, 0.08 mmol) in 1:1 *t*-butanol-water (20 ml) in 92% yield (0.16 g) as white solid; mp 170-172 °C; IR (ν_{max}, cm^{-1}): 3583 (N-H), 1612 (C=C), 1531 (C=C triazole), 1216 (C-O), 1148 (S=O), 756 (C-H bend); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 2H, Ar-H), 7.43 (s, 1H, triazole-H), 7.41-7.35 (m, 4H, Ar-H), 7.33 (m, 1H, Ar-H), 7.18 (d, *J* = 8.64 Hz, 2H, Ar-H), 7.09 (m, 2H, Ar-H), 6.94 (d, *J* = 8.64 Hz, 2H, Ar-H), 5.37 (t, *J* = 5.88 Hz, 1H, NH), 5.06 (s, 2H, CH_2), 4.82 (d, *J* = 9.68 Hz, 1H, CH), 4.27 (d, *J* = 6.08 Hz, 2H, CH_2), 1.58 (m, 1H, CH), 0.86-0.68 (m, 2H, CH), 0.46 (m, 2H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.04 (d, $^1J_{CF}$ = 253.1 Hz), 158.93 (Ar-C), 143.06 (Ar-C), 136.66 (Ar-C), 135.92 (Ar-C), 130.65 (Ar-C), 129.85 (d, $^3J_{CF}$ = 9.1 Hz), 128.65 (Ar-C), 128.21(Ar-C), 128.10 (Ar-C), 127.45 (Ar-C), 120.60 (Ar-C), 116.28 (d, $^2J_{CF}$ = 22.43 Hz), 115.15 (Ar-C), 77.22 (CH), 70.10 (CH_2), 69.20 (CH), 38.74 (CH_2), 15.85 (CH), 5.29 (CH_2); Anal. Found: C, 63.17; H, 5.12; N, 11.35. Calcd: C, 63.40; H, 5.12; N, 11.37; HRMS: Calcd. Accurate mass for ($C_{26}H_{26}FN_4O_3S$): 493.1704. Found 493.1694 $[M+H]^+$, ($C_{17}H_{17}O$): Calcd. 237.1274. Found 237.1280 [M-255], (C_7H_7): Calcd. 91.0542. Found 91.0542 [M-401].

***N-1-{(4-benzyloxyphenyl)(cyclopropyl)methyl}-1H-1,2,3-triazol-4-yl-methyl 4-methylbenzenesulfonamide* (21).** The reaction of 1-(azido(cyclopropyl)methyl)-4-(benzyloxy)*benzene* **10** (0.1 g, 0.367 mmol) and N-propargyl-4-methyl-benzenesulfonamide **13** (0.074 g, 0.40 mmol), $CuSO_4{\cdot}5H_2O$ (0.01 g, 0.04 mmol) and sodium ascorbate (0.02 g, 0.08 mmol) in 1:1 *t*-butanol-water (20 ml) in 90% yield (0.16 g) as a white solid; mp 156-158 °C; IR (ν_{max}, cm^{-1}): 3583 (N-H), 1610 (C=C), 1454 (N=N), 1324 (C-N), 1243 (C-O), 1158 (S=O), 753 (C-H bend); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.20 Hz, 2H, Ar-H), 7.44 (s, 1H, triazole-H), 7.42-7.36 (m, 4H, Ar-H), 7.32 (m, 1H, Ar-H), 7.26 (d, *J* = 7.76 Hz, 2H, Ar-H), 7.18 (d, *J* = 8.64 Hz, 2H, Ar-H), 6.94 (d, *J* = 8.64 Hz, 2H, Ar-

H), 5.07 (s, 1H, NH), 5.05 (s, 2H, CH_2), 4.83 (d, *J* = 9.60 Hz, 1H, CH), 4.24 (d, *J* = 6.08, 2H, CH_2), 2.40 (s, 3H, CH_3), 1.57 (m, 1H, CH), 0.88-0.66 (m, 2H, CH), 0.46 (m, 2H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8 (Ar-C), 143.6 (Ar-C), 136.6 (Ar-C), 130.7 (Ar-C), 129.7 (Ar-C), 128.6 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 127.4 (Ar-C), 127.1 (Ar-C), 120.7 (Ar-C), 115.1 (Ar-C), 70.1 (CH_2), 69.1 (CH), 38.9 (CH_2), 21.5 (CH_3), 15.8 (CH), 5.3 (CH_2); Anal. Found: C, 66.36; H, 5.77; N, 11.45. Calcd: C, 66.37; H, 5.78; N, 11.47; HRMS: Calcd. Accurate mass for ($C_{27}H_{29}N_4O_3S$): 489.1955. Found 489.1945 $[M+H]^+$, ($C_{17}H_{17}O$): Calcd. 237.1274. Found 237.1274 [M-251], (C_7H_7): Calcd. 91.0542. Found 91.0541 [M-397].

1-{(4-Benzyloxyphenyl)(cyclopropyl)methyl}-1H-1,2,3-triazol-4-yl-methyl 3,4,5-trimethoxybenzoate **(22).** The reaction of 1-(azido(cyclopropyl)methyl)-4-(benzyloxy)*benzene* **10** (0.1 g, 0.36 mmol) and propargyl-3,4,5-trimethoxybenzoate **14** (0.09 g, 0.36 mmol), $CuSO_4{\cdot}5H_2O$ (0.01 g, 0.04 mmol) and sodium ascorbate (0.02 g, 0.08 mmol) in 1:1 *t*-butanol-water (20 ml) in 85 % yield (165 mg) as white solid; mp 100-102 °C; IR (ν_{max}, cm^{-1}): 2938 (C-H), 1713 (C=O), 1589 (C=C), 1416 (N=N), 1345 (C-N), 1224 (C-O), 1178 (C-O), 863 (C-H bend); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s,1 H, triazole-H), 7.44-7.38 (m, 4H, Ar-H), 7.35 (m, 1H, Ar-H), 7.31 (s, 2H, Ar-H), 7.25 (s, 1H, Ar-H), 6.96 (d, *J* = 8.60 Hz, 2H, Ar-H), 5.40 (s, 2H, CH_2), 5.07 (s, 2H, CH_2), 4.92 (d, *J* = 9.68 Hz, 1H, CH), 3.91 (s, 3H, CH_3), 3.90 (s, 6H, CH_3), 1.69 (m, 1H, CH), 0.88-0.70 (m, 2H, CH), 0.52 (m, 2H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1 (C=O), 158.8 (Ar-C), 152.9 (Ar-C), 142.7 (Ar-C), 136.6 (Ar-C), 130.8 (Ar-C), 128.6 (Ar-C), 128.2 (Ar-C), 128.0 (Ar-C), 127.4 (Ar-C), 124.7 (Ar-C), 115.1 (Ar-C), 107.0 (Ar-C), 70.1 (CH_2), 69.2 (CH), 60.9 (CH_3), 58.1 (CH_3), 56.2 (CH_2), 15.9 (CH), 5.3 (CH_2); Anal. Found: C, 68.02; H, 5.89; N, 7.89. Calcd: C, 68.04; H, 5.90; N, 7.93; HRMS: Calcd. Accurate mass for ($C_{30}H_{32}N_3O_6$): 530.2286. Found 530.2272 $[M+H]^+$, ($C_{17}H_{17}O$): Calcd. 237.1274. Found 237.1270 [M-292], (C_7H_7): Calcd. 91.0542. Found 91.0535 [M-438].

4-{1-((4-Benzyloxyphenyl)(cyclopropyl)methyl)-1H-1,2,3-triazol-4-yl}butan-1-ol **(23).** The reaction of 1-(azido(cyclopropyl)methyl)-4-(benzyloxy)benzene **10** (0.1 g, 0.367 mmol), 5-hexyne-1-ol **15** (0.04 ml 0.367 mmol), $CuSO_4{\cdot}5H_2O$ (0.01 g, 0.04 mmol) and sodium ascorbate (0.02 g, 0.08 mmol) in 1:1 *t*-butanol-water (20 ml) in 85% yield (0.12 g)

as white solid; mp 112-114 °C; IR (ν_{max}, cm^{-1}): 3367 (O-H), 2936 (C-H), 1610 (C=C), 1511 (C=C triazole), 1455 (N=N), 1381 (C-N), 1242 (C-O), 1110 (C-O), 799 (C-H bend); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H, triazole-H), 7.40-7.31 (m, 4H, Ar-H), 7.30 (m, 1H, Ar-H), 7.23 (d, *J*= 8.66 Hz ,2H, Ar-H), 6.94 (d, *J* = 8.66 Hz, 2H, Ar-H), 5.05 (s, 2H, CH_2), 4.88 (d, *J* = 9.64 Hz, 1H, CH), 3.66 (t, *J*= 6.32 Hz, 2H, CH_2), 2.73 (t, *J*= 7.40 Hz, 2H, CH_2), 1.76 (m, 2H, CH_2), 1.65 (m, 2H, CH_2), 1.61 (m, 1H, CH), 0.88-0.68 (m, 2H, CH), 0.49 (m, 2H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7 (Ar-C), 147.9 (Ar-C), 136.7 (Ar-C), 131.3 (Ar-C), 128.6 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 127.4 (Ar-C), 119.2(Ar-C), 115.0(Ar-C), 70.0 (CH_2), 68.7 (CH), 62.44 (CH_2), 32.24 (CH_2), 25.52 (CH_2), 25.41 (CH_2), 15.9 (CH), 5.3 (CH_2); Anal. Found: C, 73.17; H, 7.20; N, 11.13. Calcd: C, 73.18; H, 7.21; N, 11.13; HRMS: Calcd. Accurate mass for ($C_{23}H_{28}N_3O_2$): 378.2171. Found 378.2167 $[M+H]^+$, ($C_{17}H_{17}O$): Calcd. 237.1274. Found 237.1258 [M-100], (C_7H_7): Calcd. 91.0542. Found 91.0538 [M-246].

1-{(4-Benzyloxyphenyl)(cyclopropyl)methyl}-4-phenyl-1H-1,2,3-triazole **(24).** The reaction of 1-(azido(cyclopropyl)methyl)-4-(benzyloxy)benzene **10** (0.1 g, 0.36 mmol), phenylacetylene **16** (0.04 ml 0.36 mmol), $CuSO_4{\cdot}5H_2O$ (0.01 g, 0.04 mmol) and sodium ascorbate (0.02 g, 0.08 mmol) in 1:1 *t*-butanol-water (20 ml) in 90% (0.13 g) as white solid; mp 158-160 °C; IR (ν_{max}, cm^{-1}): 2926 (C-H), 1610 (C=C), 1511 (C=C, triazole), 1455 (N=N), 1244 (C-O), 764 (C-H bend); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (m, 2H, Ar-H), 7.75 (s, 1H, triazole-H), 7.45-7.34 (m, 6H, Ar-H), 7.33-7.26 (m, 4H, Ar-H), 6.96 (d, *J* = 8.72 Hz, 2H, Ar-H), 5.05 (s, 2H, CH_2), 4.97 (d, *J* = 9.64 Hz, 1H, CH), 1.70 (m, 1H, CH), 0.81 (m, 2H, CH), 0.55 (m, 2H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8 (Ar-C), 147.7 (Ar-C), 136.7 (Ar-C), 131.1 (Ar-C), 130.8 (Ar-C), 128.7 (Ar-C), 128.6 (Ar-C), 128.2 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 127.4 (Ar-C), 125.6 (Ar-C), 118.1(Ar-C), 115.1(Ar-C), 70.1 (CH_2), 68.9 (CH), 16.0 (CH), 5.4 (CH_2); Anal. Found: C, 78.68; H, 6.07; N, 11.02. Calcd: C, 78.71; H, 6.08; N, 11.02; HRMS: Calcd. Accurate mass for ($C_{25}H_{24}N_3O$): 382.1914. Found 382.1908 $[M+H]^+$, ($C_{17}H_{17}O$): Calcd. 237.1274. Found 237.1270 [M-144], (C_7H_7): Calcd. 91.0542. Found 91.0548 [M-290].

1-{(4-Benzyloxyphenyl)(cyclopropyl)methyl}-4-pentyl-1H-1,2,3-triazole **(25).** The reaction of 1-(azido(cyclopropyl)methyl)-4-(benzyloxy)benzene **10** (0.1 g, 0.36 mmol),

heptyne-1 **17** (0.048 ml, 0.36 mmol), $CuSO_4{\cdot}5H_2O$ (0.01 g, 0.04 mmol) and sodium ascorbate (0.02 g, 0.08 mmol) in 1:1 *t*-butanol-water (20 ml) in 85% (0.12 g) as a white solid; mp 86-88 °C; IR (ν_{max}, cm^{-1}): 2927 (C-H), 1610 (C=C), 1531 (C=C, triazole), 1454 (N=N), 1243 (C-O), 665 (C-H bend); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H, triazole-H), 7.40-7.31 (m, 4H, Ar-H), 7.28 (m, 1H, Ar-H), 7.23 (d, *J*= 8.60 Hz ,2H, Ar-H), 6.94 (d, *J* = 8.60 Hz, 2H, Ar-H), 5.05 (s, 2H, CH_2), 4.89 (d, *J* = 9.56 Hz, 1H, CH), 2.69 (t, *J*= 7.72 Hz, 2H, CH_2), 1.64 (m, 2H, CH_2), 1.63 (m, 1H, CH), 1.32 (m, 4H, CH_2), 0.88 (t, *J*= 6.68 Hz, 3H, CH_3), 0.84-0.68 (m, 2H, CH), 0.50 (m, 2H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7 (Ar-C), 136.7 (Ar-C), 131.4 (Ar-C), 128.6 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 127.4 (Ar-C), 119.1(Ar-C), 114.9(Ar-C), 70.0 (CH_2), 68.6 (CH), 31.5 (CH_2), 29.0 (CH_2), 25.8 (CH_2), 22.3 (CH_2), 15.9 (CH), 14.0 (CH_3), 5.3 (CH_2); Anal. Found: C, 76.75; H, 7.77; N, 11.19. Calcd: C, 76.76; H, 7.78; N, 11.19; HRMS: Calcd. Accurate mass for ($C_{24}H_{30}N_3O$): 376.2383 Found 376.2381 $[M+H]^+$, ($C_{17}H_{17}O$): Calcd. 237.1274. Found 237.1253 [M-138], (C_7H_7): Calcd. 91.0542. Found 91.0539 [M-284].

1-{(4-Benzyloxyphenyl)(cyclopropyl)methyl-4-(1',2':5',6'-di-O-isopropylidene-α-D-glucofuranos-3'-yloxy)methyl}-1H-1,2,3-triazole **(26).** The reaction of 1-(azido(cyclopropyl)methyl)-4-(benzyloxy)benzene (0.1 g, 0.36 mmol), propargylated diacetonide protected glucose **18** (0.11 g, 0.40 mmol), $CuSO_4{\cdot}5H_2O$ (0.01 g, 0.04 mmol) and sodium ascorbate (0.02 g, 0.08 mmol) in 1:1 *t*-butanol-water (5 ml), purification by column chromatography using 60-120 mesh silica gel (50% EtOAc/Hexane), gave the titled compound **26** (0.18 g, 86%) as a sticky glassy solid; IR (ν_{max}, cm^{-1}): 2988 (C-H), 2929 (C-H), 1611 (C=C), 1512 (C=C, triazole), 1456 (N=N), 1377 (C-N), 1220 (C-O), 848 (C-H bend); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H, triazole-H), 7.46-7.35 (m, 4H, Ar-H), 7.32 (m, 1H, Ar-H), 7.23 (d, *J*= 8.60 Hz ,2H, Ar-H), 6.95 (d, *J* = 8.60 Hz, 2H, Ar-H), 5.85 (d, *J* = 3.4 Hz, 1H, CH), 5.05 (s, 2H, CH_2), 4.91 (d, *J* = 9.52 Hz, 1H, CH), 4.81 (m, 2H, CH_2), 4.58 (d, *J* = 4.08 Hz, 1H, CH), 4.29 (m, 1H, CH), 4.10 (m, 1H, CH), 4.04 (m, 2H, CH), 3.99 (d, *J* = 5.46 Hz, 1H, CH), 1.66 (m, 1H, CH), 1.48 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 0.86-0.70 (m, 2H, CH), 0.52 (m, 2H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8 (Ar-C), 136.6 (Ar-C), 131.0 (Ar-C), 128.6 (Ar-C), 128.2 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C),

127.4 (Ar-C), 121.0 (Ar-C), 115.1 (C-O), 111.8 (Ar-C), 109.0 (C-O), 105.2 (C-O), 82.6 (C-O), 81.8 (C-O), 81.1 (C-O), 72.4 (C-O), 70.9 (CH_2), 68.9 (CH), 67.4 (C-O), 64.3 (CH_2), 29.7 (CH_3), 26.8 (CH_3), 26.2 (CH_3), 25.4 (CH_3), 15.9 (CH), 5.3 (CH_2); HRMS: Calcd. Accurate mass for ($C_{32}H_{40}N_3O_7$): 578.2861. Found 578.2849 $[M+H]^+$, ($C_{17}H_{17}O$): Calcd. 237.1274. Found 237.1255 [M-340], (C_7H_7): Calcd. 91.0542. Found 91.0540 [M-485].

Cyclopropyl-{4-(1H-benzo[d]imidazol-1-yl)-phenyl}methanone **(39a).** Following the same procedure and the workup used for the synthesis of (40a), the reaction of 4-chloro-4-fluorobutyrophenone **7** (0.5 mL, 3.04 mmol), benzimidazole **27** (0.36g, 3.04 mmol) and K_2CO_3 (1 g, 7.23 mmol) in DMSO gave the title compound as white solid in 78% yield (0.62 g); mp 138-140 °C; IR (ν_{max}, cm^{-1}): 3016 (C-H), 1667 (C=O), 1531 (C=C), 1514 (C=N), 1419 (C-N), 1385 (C-C), 843 (C-H bend); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J*= 8.52 Hz ,2H, Ar-H), 8.10 (s, 1H, Ar-H), 7.82 (m, 1H, Ar-H), 7.58 (d, *J* = 8.52 Hz, 2H, Ar-H), 7.52 (m, 1H, Ar-H), 7.29 (m, 2H, Ar-H), 2.63 (m, 1H, CH), 1.24 (m, 2H, CH), 1.04 (m, 2H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2 (C=O),144.2 (Ar-C), 141.8 (Ar-C), 139.9 (Ar-C), 137.1 (Ar-C), 133.2 (Ar-C), 130.0 (Ar-C), 124.1 (Ar-C), 123.4 (Ar-C), 123.2 (Ar-C), 120.9 (Ar-C), 110.4 (Ar-C), 17.3 (CH), 12.0 (CH_2); Anal. Found: C, 77.81; H, 5.37; N, 10.64. Calcd: C, 77.84; H, 5.38; N, 10.68; HRMS: Calcd. Accurate mass for ($C_{17}H_{15}N_2O$): 263.1179. Found 263.1168 $[M+H]^+$, ($C_{13}H_{10}N_2$): Calcd. 194.0838. Found 194.0840 [M-68], ($C_{10}H_9O$): Calcd. 145.0648. Found 145.0623 [M-117].

Cyclopropyl-{4-(1H-imidazol-1-yl)phenyl}methanone **(40a)**[39]. The reaction carried out with 4-chloro-4-fluorobutyrophenone **7** (0.5 ml, 3.04 mmol) with imidazole **28** (0.21 g, 3.04 mmol) and K_2CO_3 (1 g, 7.23 mmol) in DMSO at 140 °C till the completion of reaction (TLC). After the completion of reaction, the workup was done with ethylacetate and water and then the organic layer was separated, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The latter was purified by silica gel (60-120 mesh) column chromatography using ethylacetate: hexane (1:1) as eluent to give the title compound in 80% yield (0.51 g); mp 108-110 °C; IR (ν_{max}, cm^{-1}): 3392 (C-H), 1663 (C=O), 1604 (C=C), 1520 (C=N), 1485 (C-N), 1305 (C-N), 840 (C-H bend); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.70 Hz, 2H, Ar-H), 8.01 (s, 1H, Ar-H), 7.53 (d, *J* = 8.70 Hz, 2H, Ar-H),

7.38 (s, 1H, Ar-H), 7.27 (s, 1H, Ar-H), 2.69 (m, 1H, CH), 1.30 (m, 2H, CH), 1.10 (m, 2H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0 (C=O),140.5 (Ar-C), 136.6 (Ar-C), 135.4 (Ar-C), 131.1 (Ar-C), 130.0 (Ar-C), 120.7 (Ar-C), 117.7 (Ar-C), 17.2 (CH), 11.9 (CH_2); Anal. Found: C, 73.55; H, 5.67; N, 13.19. Calcd: C, 73.56; H, 5.70; N, 13.20; HRMS: Calcd. Accurate mass for ($C_{13}H_{13}N_2O$): 213.1022. Found 213.1013 $[M+H]^+$, ($C_9H_7N_2$): Calcd. 143.0604. Found 143.0600 [M-69], ($C_{10}H_9O$): Calcd. 145.0648. Found 145.0756 [M-67].

Cyclopropyl-{4-(4-nitro-1H-imidazol-1-yl)-phenyl}methanone **(41a).** Following the same procedure and the workup used for the synthesis of (**40a**), the reaction of 4-chloro-4-fluorobutyrophenone **7** (0.5 mL, 3.04 mmol), 4-nitro imidazole **29** (0.34 g, 3.04 mmol) and K_2CO_3 (1 g, 7.23 mmol) in DMSO gave the title compound as creamy solid in 76% yield (0.60 g); mp 210-212 °C; IR (ν_{max}, cm^{-1}): 2923 (C-H), 1659 (C=O), 1544 (N-O), 1514(C=N), 1348 (N-O), 1315 (C-N), 755 (C-H bend); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, *J*= 1.60 Hz ,1H, Ar-H), 8.43 (d, *J* = 1.60 Hz, 1H, Ar-H), 8.19 (d, *J* = 8.80 Hz, 2H, Ar-H), 7.92 (d, *J* = 8.80 Hz, 1H, C-H), 2.81 (m, 1H, CH), 1.15 (m, 2H, C-H), 1.10 (m, 2H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1 (C=O), 148.3 (Ar-C), 138.3 (Ar-C), 136.8 (Ar-C), 134.8 (Ar-C), 129.3 (Ar-C), 120.6 (Ar-C), 118.6 (Ar-C), 16.5 (CH), 11.3 (CH_2); Anal. Found: C, 60.68; H, 4.32; N, 16.31. Calcd: C, 60.70; H, 4.31; N, 16.33; HRMS: Calcd. Accurate mass for ($C_{13}H_{12}N_3O_3$): 258.0873. Found 258.0868 $[M+H]^+$, ($C_{13}H_{11}N_3O_2$): Calcd. 241.0846. Found 241.0844 [M-16], ($C_{13}H_{11}N_2O$): Calcd. 211.0866. Found 211.0864 [M-46], ($C_{10}H_9O$): Calcd. 145.0648. Found 145.0646 [M-112].

Cyclopropyl-{4-(2-methyl-1H-benzo[d]imidazol-1-yl)phenyl}methanone **(42a).** Following the same procedure and the workup used for the synthesis of (**40a**), the reaction of 4-chloro-4-fluorobutyrophenone **7** (0.5 mL, 3.04 mmol), 2-methylbenzimidazole **30** (0.40 g, 3.04 mmol) and K_2CO_3 (1 g, 7.23 mmol) in DMSO gave the title compound as white solid in 80% yield (0.67 g); mp 164-166 °C; IR (ν_{max}, cm^{-1}): 3017 (C-H), 1667 (C=O), 1602 (C=C), 1515 (C=C), 1457 (C=N), 1390 (C-N), 743 (C-H bend); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.52 Hz ,2H, Ar-H), 7.79 (d, *J* = 7.92 Hz, 1H, Ar-H), 7.44 (d, *J* = 8.52 Hz, 2H, Ar-H), 7.22 (m, 1H, Ar-H), 7.15 (m, 1H, Ar-H), 7.09 (m, 1H, Ar-H), 2.65 (m, 1H, C-H), 2.48 (s, 3H, CH_3), 1.28 (m, 2H, CH), 1.06 (m, 2H, CH); ^{13}C NMR (100

MHz, $CDCl_3$) δ 199.4 (C=O), 151.0 (Ar-C), 142.8 (Ar-C), 139.8 (Ar-C), 137.9 (Ar-C), 136.0 (Ar-C), 129.7 (Ar-C), 126.9 (Ar-C), 122.9 (Ar-C), 122.7 (Ar-C), 119.2 (Ar-C), 109.7 (Ar-C), 17.4 (CH), 14.6 (CH_3), 12.1 (CH_2); Anal. Found: C, 78.22; H, 5.83; N, 10.13. Calcd: C, 78.24; H, 5.84; N, 10.14; HRMS: Calcd. Accurate mass for ($C_{18}H_{17}N_2O$): 277.1335. Found 277.1327 $[M+H]^+$, ($C_{14}H_{12}N_2$): Calcd. 208.0995. Found 208.1009 [M-68], (C_4H_5O): Calcd. 69.0335. Found 69.0347 [M-207].

Cyclopropyl-{4-(1H-benzo[d][1,2,3]triazol-1-yl)phenyl}methanone **(43a).** Following the same procedure and the workup used for the synthesis of (**40a**), the reaction of 4-chloro-4-fluorobutyrophenone **7** (0.5 mL, 3.04 mmol), benzotriazole **31** (0.36 g, 3.04 mmol) and K_2CO_3 (1 g, 7.23 mmol) in DMSO gave the title compound as white solid in 70% yield (0.56 g); mp 134-136 °C; IR (ν_{max}, cm^{-1}): 3019 (C-H), 1661 (C=O), 1600 (C=C), 1285 (C-N), 748 (C-H bend); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.76 Hz, 2H, Ar-H), 8.19 (m, 1H, Ar-H), 7.99 (d, *J* = 8.76 Hz, 2H, Ar-H), 7.83 (m, 1H, Ar-H), 7.62 (m, 1H, Ar-H), 7.49 (m, 1H, Ar-H), 2.74 (m, 1H, CH), 1.34 (m, 2H, CH), 1.14 (m, 2H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3 (C=O),146.8 (Ar-C), 140.3 (Ar-C), 137.5 (Ar-C), 129.8 (Ar-C), 128.7 (Ar-C), 124.7 (Ar-C), 122.1 (Ar-C), 120.6 (Ar-C), 118.0 (Ar-C), 110.3 (Ar-C), 17.4 (CH), 12.0 (CH_2); Anal. Found: C, 73.02; H, 5.00; N, 15.96. Calcd: C, 72.99; H, 4.98; N, 15.96; HRMS: Calcd. Accurate mass for ($C_{16}H_{14}N_3O$): 264.1131. Found 264.1125 $[M+H]^+$, ($C_{12}H_{19}N_3$): Calcd. 195.0791. Found 195.0780 [M-68], ($C_{10}H_9O$): Calcd. 145.0648. Found 145.0629 [M-118], (C_4H_5O): Calcd. 69.0335. Found 69.0336 [M-194].

Cyclopropyl-{4-(6-Amino-9H-purin-9-yl/-7yl)phenyl}methanone **(44a & 44a').** Following the same procedure and the workup used for the synthesis of (**40a**), the reaction of 4-chloro-4-fluorobutyrophenone **7** (0.5 mL, 3.04 mmol), adenine **32** (0.41 g, 3.04 mmol) and K_2CO_3 (1 g, 7.23 mmol) in DMSO gave the two regeoisomers in 70% (0.60 g) of overall yield.

Major Isomer (44a): White solid, 38 % (0.32 g) of yield; mp 206-208 °C; IR (ν_{max}, cm^{-1}): 3321 (N-H), 1663 (C=O), 1601 (C=C), 1531 (C=N), 1324 (C-N), 758 (C-H bend); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H, Ar-H), 8.25(s, 1H, Ar-H), 8.18 (d, *J* = 8.60 Hz Ar-H), 8.24 (d, *J* = 8.60 Hz Ar-H), 7.44 (s, 2H, NH_2), 2.96 (m, 2H), 1.08 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 198.7 (C=O), 156.3 (Ar-C), 153.3 (Ar-C), 149.1 (Ar-C), 139.3 (Ar-C), 138.9 (Ar-C), 135.4 (Ar-C), 129.3 (Ar-C), 122.0 (Ar-C), 119.4 (Ar-C), 16.6 (CH), 11.4 (CH_2); Anal. Found: C, 64.26; H, 5.01; N, 24.96. Calcd: C, 64.27; H, 5.03; N, 24.98; HRMS: Calcd. Accurate mass for ($C_{15}H_{14}N_5O$): 280.1193 Found 280.1190 $[M+H]^+$, ($C_{11}H_9N_5$): Calcd. 211.0852. Found 211.0848 [M-68], (C_4H_5O): Calcd. 69.0335. Found 69.0336 [M-210].

Minor Isomer: (44a'). White solid, 18 % (0.15 g) of yield; mp 224-226 °C; IR (ν_{max}, cm^{-1}): 3583 (N-H), 1648 (C=O), 1603 (C=C), 756 (C-H bend); ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H, Ar-H), 8.33 (s, 1H, Ar-H), 8.26 (d, *J* = 8.55 Hz Ar-H), 7.70 (d, *J* = 8.55 Hz Ar-H), 6.38 (s, 2H, NH_2), 2.99 (m, 2H), 1.09 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9 (C=O), 160.4 (Ar-C), 152.9 (Ar-C), 151.2 (Ar-C), 145.9 (Ar-C), 138.8 (Ar-C), 136.7 (Ar-C), 129.5 (Ar-C), 125.2 (Ar-C), 110.0 (Ar-C), 16.8 (CH), 11.4 (CH_2); Anal. Found: C, 64.25; H, 5.04; N, 24.94. Calcd: C, 64.27; H, 5.03; N, 24.98; HRMS: Calcd. Accurate mass for ($C_{15}H_{14}N_5O$): 280.1193 Found 280.1188 $[M+H]^+$, ($C_{15}H_{11}N_4O$): Calcd. 263.0927. Found 263.0922 [M-16], ($C_{10}H_9O$): Calcd. 145.0648. Found 145.0646 [M-134].

Cyclopropyl-{4-(6-(benzylamino)-9H-purin-9-yl)phenyl}methanone **(45a).** Following the same procedure and the workup used for the synthesis of (**40a**), the reaction of 4-chloro-4-fluorobutyrophenone **7** (0.5 mL, 3.04 mmol), 6-benzylaminopurine **33** (0.68 g, 3.04 mmol) and K_2CO_3 (1 g, 7.23 mmol) in DMSO gave the title compound as creamy solid in 76% yield (0.85 g); mp 192-194 °C;IR (ν_{max}, cm^{-1}): 3283 (N-H), 1652 (C=O), 1603 (C=C), 1475 (C-N), 755 (C-H bend); ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H, Ar-H), 8.21 (d, *J* = 8.64 Hz, 2H, Ar-H), 8.043 (s, 1H, Ar-H), 7.99 (d, *J* = 8.64, 2H, Ar-H), 7.41 (m, 2H, Ar-H), 7.35 (m, 2H, Ar-H), 7.29 (m, 1H, Ar-H), 6.38 (s, 1H, NH), 4.92 (s, 2H, CH_2), 2.69 (m, 1H, CH), 1.29 (m, 2H, CH), 1.10 (m, 2H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3 (C=O), 155.0 (Ar-C), 154.1 (Ar-C), 138.5 (Ar-C), 138.3 (Ar-C), 138.2 (Ar-C), 137.0 (Ar-C), 129.7 (Ar-C), 128.7 (Ar-C), 127.8 (Ar-C), 127.6 (Ar-C),122.7 (Ar-C), 17.3 (CH), 11.9 (CH_2); Anal. Found: C, 71.52; H, 5.18; N, 18.95. Calcd: C, 71.53; H, 5.18; N, 18.96; HRMS: Calcd. Accurate mass for ($C_{22}H_{20}N_5O$): 370.1662. Found 370.1653 $[M+H]^+$, ($C_{16}H_{14}N_5O$): Calcd. 292.1193. Found 292.1270 [M-77], (C_7H_7): Calcd. 91.0542. Found 91.0542 [M-278].

Cyclopropyl-{4-(Benzo[d]thiazol-2-ylamino)phenyl}methanone **(46a).** Following the same procedure and the workup used for the synthesis of (**40a**), the reaction of 4-chloro-4-fluorobutyrophenone **7** (0.5 mL, 3.04 mmol), 2-aminobenzothiazole **34** (0.45 g, 3.04 mmol) and K_2CO_3 (1g, 7.23 mmol) in DMSO gave the title compound as creamy solid in 70% yield (0.62 g); mp 128-132 °C; IR (ν_{max}, cm^{-1}): 3400 (N-H), 3019 (C-H), 1654 (C=O), 1538 (C=N), 1385 (C-N), 1067 (C-S), 770 (C-H bend); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 10.91 (s, 1H, NH), 8.10 (d, *J*=8.60, 2H, Ar-H), 7.94 (d, *J*=8.60, 2H, Ar-H), 7.87 (d, *J*=7.90, 1H, Ar-H), 7.69 (d, *J*=7.90, 1H, Ar-H), 7.38 (t, *J*=7.44, 1H, Ar-H), 7.22 (t, *J*=7.54, 1H, Ar-H), 2.87 (m, 1H), 1.01 (d, *J=5.56*, 4H); ^{13}C NMR (100 MHz , DMSO-d_6): 198.3, 161.4, 152.2, 145.1, 131.3, 130.6, 130.0, 126.5, 123.3, 121.7, 120.2, 117.3, 16.5, 11.3; ESMS: Calcd. Accurate mass for ($C_{17}H_{15}N_2OS$): 295.09 Found 295.19 $[M+H]^+$.

Cyclopropyl-{4-((1H-benzo[d]imidazol-2-yl)amino)phenyl}methanone **(47a).** Following the same procedure and the workup used for the synthesis of (**40a**), the reaction of 4-chloro-4-fluorobutyrophenone (0.5 mL, 3.04 mmol), 2-aminobenzimidazole **35** (0.40 g, 3.04 mmol) and K_2CO_3 (1g, 7.23 mmol) in DMSO gave the title compound as white solid in 72% yield (0.60 g); mp 118-123 °C; IR (ν_{max}, cm^{-1}): 3398 (N-H), 3019 (C-H), 1653 (C=O), 1542 (C=N), 1405 (C-N), 771 (C-H bend); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 8.26 (d, *J=8.55*, 2H, Ar-H), 7.25 (d, *J*=8.57, 2H, Ar-H), 7.04 (m, 1H, Ar-H), 6.93 (m, 2H, Ar-H), 6.36 (s, 2H, Ar-H), 2.96 (m, 1H), 1.09 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6): 199.5, 154.4, 143.5, 139.5, 136.7, 134.7, 130.2, 126.9, 122.1, 119.4, 115.7, 108.2, 17.3, 11.9; HRMS: Calcd. Accurate mass for ($C_{17}H_{16}N_3O$): 278.1288 Found 278.1285 $[M+H]^+$.

Cyclopropyl-{4-((4-methylbenzo[d]thiazol-2-yl)amino)phenyl}methanone **(48a).** Following the same procedure and the workup used for the synthesis of (**40a**), the reaction of 4-chloro-4-fluorobutyrophenone (0.5 mL, 3.04 mmol), 2-amino-4-methyl-benzothiazole **36** (0.50 g, 3.04 mmol), and K_2CO_3 (1g, 7.23 mmol) in DMSO gave the title compound as white solid in 75% yield (0.70 g); mp 135-138 °C; IR (ν_{max}, cm^{-1}): 3399 (N-H), 3019 (C-H), 1644 (C=O), 1523 (C=C), 1404 (C-N), 771 (C-H bend); ^{1}H NMR (400 MHz , DMSO-d_6): δ_H 10.89 (s, 1H, NH), 8.10 (d, *J* = 8.75, 2H, Ar-H), 7.97 (d, *J* = 8.75, 2H, Ar-H), 7.68 (d, *J* = 7.72, 1H, Ar-H), 7.21 (d, *J* = 7.29, 1H, Ar-H), 7.12 (t, *J* = 7.63, 1H, Ar-H), 2.88

(m, 1H), 2.60 (s, 3H), 1.01 (m, 4H); ^{13}C NMR (100 MHz , DMSO-d_6): 198.3, 160.4, 151.1, 145.2, 131.2, 130.2, 130.0, 129.4, 127.0, 123.2, 119.0, 117.2, 18.5, 16.5, 11.2; Anal. Found: C, 70.07; H, 5.21; N, 9.05. Calcd: C, 70.10; H, 5.23; N, 9.08; HRMS: Calcd. Accurate mass for ($C_{18}H_{17}N_2OS$): 309.1056 Found 309.1059 $[M+H]^+$.

Cyclopropyl-{4-((6-ethoxybenzo[d]thiazol-2-yl)amino)phenyl}methanone **(49a).** Following the same procedure and the workup used for the synthesis of (**40a**), the reaction of 4-chloro-4-fluorobutyrophenone (0.5 mL, 3.04 mmol), 2-amino-6-ethoxy-benzothiazole **37** (0.59 g, 3.04 mmol), and K_2CO_3 (1g, 7.23 mmol) in DMSO gave the title compound as white solid in 65% yield (0.67 g); mp 142-145 °C; IR (ν_{max}, cm^{-1}): 3401 (N-H), 3019 (C-H), 1644 (C=O), 1599 (C=C), 1541 (C=N), 1385 (C-N), 1062 (C-S), 771 (C-H bend); ^{1}H NMR (400 MHz , DMSO-d_6): δ_H 10.74 (s, 1H, NH), 8.08 (m, 2H, Ar-H), 7.90 (m, 2H, Ar-H), 7.58 (m, 1H, Ar-H), 7.47 (s, 1H, Ar-H), 6.95 (m, 1H, Ar-H), 4.05 (m, 2H), 2.87 (m, 1H), 1.35 (m, 3H), 1.01 (m, 4H); ^{13}C NMR (100 MHz , DMSO-d_6): 198.6, 159.5, 155.3, 146.1, 145.2, 131.7, 131.0, 130.0, 120.7, 117.2, 114.8, 106.3, 64.1, 16.5, 15.1, 11.3; HRMS: Calcd. Accurate mass for ($C_{19}H_{19}N_2O_2S$): 339.1162 Found 339.1162 $[M+H]^+$.

Cyclopropyl-{4-((6-fluorobenzo[d]thiazol-2-yl)amino)phenyl}methanone **(50a).** Following the same procedure and the workup used for the synthesis of (**40a**), the reaction of 4-chloro-4-fluorobutyrophenone (0.5 mL, 3.04 mmol), 2-amino-6-fluoro-benzothiazole **38** (0.51 g, 3.04 mmol), and K_2CO_3 (1g, 7.23 mmol) in DMSO gave the title compound as light yellow solid in 72% yield (0.68 g); mp 110-112 °C; IR (ν_{max}, cm^{-1}): 3487 (N-H), 3019 (C-H), 1663 (C=O), 1603 (C=C), 1508 (C=N), 1411 (C-N), 1068 (C-S), 845 (C-H bend); ^{1}H NMR (400 MHz , DMSO-d_6): δ_H 10.90 (s, 1H, NH), 8.09 (d, *J* = 8.77, 2H, Ar-H), 7.91 (d, *J* = 8.77, 2H, Ar-H), 7.79 (m, 1H, Ar-H), 7.68 (m, 1H, Ar-H), 7.21 (m, 1H, Ar-H), 2.87 (m, 1H), 1.00 (m, 4H); ^{13}C NMR (100 MHz , DMSO-d_6): 198.3, 161.4, 159.8, 157.4, 148.9, 144.9, 131.8, 131.7 131.3, 130.0, 120.9, 117.3, 114.2, 114.0, 108.6, 108.4, 16.5, 11.3; HRMS: Calcd. Accurate mass for ($C_{17}H_{14}FN_2OS$): 313.0805 Found 313.0805 $[M+H]^+$.

Cyclopropyl-{4-(1H-benzo[d]imidazol-1-yl)phenyl}methanol **(39b).** The reduction of keto product **39a** (0.1 g, 0.038 mmol) by $NaBH_4$ (0.05 g, 0.12 mmol) in methanol at room temperature. The resulted mixture was stirred till the completion of reaction (TLC). After

the completion of reaction, the workup was done with ethylacetate and water then the organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give product as a white solid in 100% yield, mp 120-122 °C; IR (ν_{max}, cm^{-1}): 3273 (O-H), 3005 (C-H), 1608 (C=C), 1490 (C=N), 1231 (C-O), 1142, 949 (C-H bend); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H, Ar-H), 7.86 (m, 1H, Ar-H), 7.66 (d, *J* = 8.34 Hz, 2H, Ar-H), 7.54 (m, 1H, Ar-H), 7.49 (d, *J* = 8.34 Hz, 2H, Ar-H), 7.34 (m, 2H, Ar-H), 4.16 (d, *J* = 8.32 Hz, 1H, CH), 3.14 (s, 1H, OH), 1.27 (m, 1H, CH), 0.68 (m, 2H, CH), 0.53 (m, 2H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1 (Ar-C), 143.9 (Ar-C), 142.3 (Ar-C), 135.4 (Ar-C), 133.7 (Ar-C), 127.7 (Ar-C), 123.9 (Ar-C), 123.7 (Ar-C), 122.8 (Ar-C), 120.5 (Ar-C), 110.5 (Ar-C), 77.8 (CH), 19.5 (CH), 3.7 (CH_2); Anal. Found: C, 77.24; H, 6.08; N, 10.54. Calcd: C, 77.25; H, 6.10; N, 10.60; HRMS: Calcd. Accurate mass for ($C_{17}H_{17}N_2O$): 265.1335. Found 265.1323 $[M+H]^+$, ($C_{17}H_{15}N_2$): Calcd. 247.1230. Found 247.1232 [M-17], ($C_{14}H_{11}N_2O$): Calcd. 223.0866. Found 223.0869 [M-41], (C_4H_7O): Calcd. 71.0491. Found 71.0491 [M-193].

Cyclopropyl-{4-(1H-imidazol-1-yl)phenyl}methanol **(40b).** The reduction of keto product **40a** (0.1 g, 0.047 mmol) by $NaBH_4$ (0.06g, 0.15 mmol) in methanol at room temperature. The resulted mixture was stirred till the completion of reaction (TLC). After the completion of reaction, the workup was done with ethylacetate and water then the organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give product as a white solid in 100% yield, mp 106-108 °C; IR (ν_{max}, cm^{-1}): 3368 (O-H), 3004 (C-H), 1611 (C=C), 1522 (C=N), 1304 (C-N), 1247 (C-O), 824 (C-H bend); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H, Ar-H), 7.57 (d, *J* = 8.52 Hz, 2H, Ar-H), 7.38 (d, *J* = 8.52 Hz, 2H, Ar-H), 7.29 (s, 1H, Ar-H), 7.20 (s, 1H, Ar-H), 4.10 (d, *J* = 8.28 Hz, 1H, CH), 2.63 (s, 1H, OH), 1.24 (m, 1H, CH), 0.66 (m, 2H, CH), 0.49 (m, 2H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8 (Ar-C), 136.4 (Ar-C), 135.5 (Ar-C), 130.0 (Ar-C), 127.5 (Ar-C), 121.4 (Ar-C), 118.3 (Ar-C), 77.5 (CH), 19.4 (CH), 3.6 (CH_2); Anal. Found: C, 72.86; H, 6.58; N, 13.07. Calcd: C, 72.87; H, 6.59; N, 13.07; HRMS: Calcd. Accurate mass for ($C_{13}H_{15}N_2O$): 215.1179. Found 215.1169 $[M+H]^+$, ($C_{13}H_{13}N_2$): Calcd. 197.1073. Found 197.1059 [M-17],

($C_{10}H_9N_2O$): Calcd. 173.0709. Found 173.0709 [M-41], (C_4H_7O): Calcd. 71.0491. Found 71.0497 [M-143].

Cyclopropyl-{4-(4-nitro-1H-imidazol-1-yl)-phenyl}methanol **(41b).** The reduction of keto product **41a** (0.1 g, 0.038 mmol) by $NaBH_4$ (0.05 g, 0.12 mmol) in methanol at room temperature. The resulted mixture was stirred till the completion of reaction (TLC). After the completion of reaction, the workup was done with ethylacetate and water then the organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give product as a creamy solid in 100% yield, mp 136-138 °C; IR (ν_{max}, cm^{-1}): 3583 (O-H), 3019 (C-H), 1543 (N-O), 1518 (C=N), 1407 (C-N), 1353 (N-O), 1215 (C-O), 823 (C-H bend); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J*= 1.60 Hz ,1H, Ar-H), 7.77 (d, *J* = 1.60 Hz, 1H, Ar-H), 7.64 (d, *J* = 8.42 Hz, 2H, Ar-H), 7.43 (d, *J* = 8.42 Hz, 2H, Ar-H), 4.10 (d, *J* = 8.44 Hz, 1H, CH), 2.14 (s, 1H, OH), 1.21 (m, 1H, CH), 0.67 (m, 2H, C-H), 0.51 (m, 2H, C-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5 (Ar-C), 134.7 (Ar-C), 134.5 (Ar-C), 127.9 (Ar-C), 121.9 (Ar-C), 118.2 (Ar-C), 77.6 (C-O), 19.6 (CH), 3.6 (CH_2); Anal. Found: C, 60.22; H, 5.04; N, 16.21. Calcd: C, 60.23; H, 5.05; N, 16.21; HRMS: Calcd. Accurate mass for ($C_{13}H_{14}N_3O_3$): 260.1024. Found 260.1026 $[M+H]^+$, ($C_{13}H_{13}N_2O$): Calcd. 243.1002. Found 243.0998 [M-16], ($C_{10}H_{10}O$): Calcd. 146.0726. Found 146.0606 [M-113].

Cyclopropyl-{4-(2-methyl-1H-benzo[d]imidazol-1-yl)phenyl}methanol **(42b).** The reduction of keto product **42a** (0.1 g, 0.036 mmol) by $NaBH_4$ (0.045 g, 0.11 mmol) in methanol at room temperature. The resulted mixture was stirred till the completion of reaction (TLC). After the completion of reaction, the workup was done with ethylacetate and water then the organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give product as a white solid in 100% yield; mp 142-144 °C; IR (ν_{max}, cm^{-1}): 3224 (O-H), 3004 (C-H), 1609 (C=C), 1515 (C=N), 1324 (C-N), 1248 (C-O), 831 (C-H bend); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.92 Hz, 1H, Ar-H), 7.66 (d, *J* = 8.12 Hz, 1H, Ar-H), 7.35 (d, *J* = 8.24 Hz, 2H, Ar-H), 7.26 (m, 1H, Ar-H), 7.21-7.12 (m, 2H, Ar-H), 4.13 (d, *J* = 8.40 Hz, 1H, CH), 2.51 (s, 3H, CH_3), 1.28 (m, 1H, CH), 0.67 (m, 2H, CH), 0.51 (m, 2H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6 (Ar-C), 144.7 (Ar-C), 142.5 (Ar-C), 136.5 (Ar-C), 135.1 (Ar-C), 127.5 (Ar-C), 126.9 (Ar-C), 122.5 (Ar-C), 122.4

(Ar-C), 118.9 (Ar-C), 109.9 (Ar-C), 77.9 (CH), 19.5 (CH), 3.6 (CH_2); Anal. Found: C, 77.67; H, 6.51; N, 10.05. Calcd: C, 77.64; H, 6.52; N, 10.06; HRMS: Calcd. Accurate mass for ($C_{18}H_{19}N_2O$): 289.1492 Found 289.1478 $[M+H]^+$.

Cyclopropyl-{4-(6-amino-9H-purin-9-yl)phenyl}methanol **(44b).** The reduction of keto product **44a** (0.1 g, 0.038 mmol) by $NaBH_4$ (0.05 g, 0.12 mmol) in methanol at room temperature. The resulted mixture was stirred till the completion of reaction (TLC). After the completion of reaction, the workup was done with ethylacetate and water then the organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give product as a white solid in 100% yield, mp 246-248 °C; IR (ν_{max}, cm^{-1}): 3583 (N-H), 1587 (C=C), 1531 (C=N), 1403 (C-N), 1345 (C-N), 1215 (C-O), 758 (C-H bend); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H, Ar-H), 8.20 (s, 1H, Ar-H), 7.78 (d, *J* = 8.40 Hz, 2H, Ar-H), 7.57 (d, *J* = 8.40 Hz, 2H, Ar-H), 7.33 (s, 2H, NH_2), 5.38 (d, *J* = 4.44 Hz, 1H, CH), 1.07 (m, 1H, CH), 0.52-0.35 (m, 4H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7 (Ar-C), 153.6 (Ar-C), 149.6(Ar-C), 145.8 (Ar-C), 140.2 (Ar-C), 133.9 (Ar-C), 127.4 (Ar-C), 123.2 (Ar-C), 119.6 (Ar-C), 75.4 (CH), 19.8 (CH), 3.8 (CH_2); Anal. Found: C, 64.04; H, 5.36; N, 24.89. Calcd: C, 64.04; H, 5.37; N, 24.90; HRMS: Calcd. Accurate mass for ($C_{15}H_{16}N_5O$): 282.1349 Found 282.1339 $[M+H]^+$, ($C_{15}H_{14}N_5$): Calcd. 264.1244. Found 264.1237 [M-17], ($C_{12}H_{10}N_5O$): Calcd. 240.0880. Found 240.0872 [M-41].

Cyclopropyl-{4-(6-(benzylamino)-9H-purin-9-yl)phenyl}methanol **(45b).** The reduction of keto product **45a** (0.1 g, 0.038 mmol) by $NaBH_4$ (0.05 g, 0.12 mmol) in methanol at room temperature. The resulted mixture was stirred till the completion of reaction (TLC). After the completion of reaction, the workup was done with ethylacetate and water then the organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give product as a white solid in 100% yield; mp 190-192 °C;IR (ν_{max}, cm^{-1}): 3583 (N-H), 3019 (C-H), 1620 (C=C), 1328 (C-N), 1215 (C-O), 756 (C-H bend); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H, Ar-H), 7.97 (s, 1H, Ar-H), 7.66 (d, *J* = 6.8 Hz, 2H, Ar-H), 7.62 (d, *J* = 6.8 Hz, 2H, Ar-H), 7.41 (m, 2H, Ar-H), 7.35 (m, 2H, Ar-H), 7.29 (m, 1H, Ar-H), 6.27 (s, 1H, NH), 4.91 (s, 2H, CH_2), 4.09 (d, *J* = 6.68 Hz, 2H, CH), 2.31 (s, 1H, OH), 1.23 (m, 1H, CH), 0.64 (m, 2H, CH), 0.47 (m, 2H, CH); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 155.0 (Ar-C), 153.9 (Ar-C), 144.0 (Ar-C), 138.8 (Ar-C), 133.9 (Ar-C), 128.7 (Ar-C), 127.8 (Ar-C), 127.5 (Ar-C), 127.4 (Ar-C), 123.5 (Ar-C), 120.1 (Ar-C), 77.9 (CH), 19.5 (CH), 3.6 (CH_2); Anal. Found: C, 71.13; H, 5.71; N, 18.85. Calcd: C, 71.14; H, 5.70; N, 18.85; HRMS: Calcd. Accurate mass for ($C_{22}H_{22}N_5O$): 372.1819. Found 372.1814 $[M+H]^+$, ($C_{16}H_{16}N_5O$): Calcd. 294.1349. Found 294.1359 [M-77], (C_7H_7): Calcd. 91.0542. Found 91.0538 [M-280].

Cyclopropyl-{4-(Benzo[d]thiazol-2-ylamino)phenyl}methanol **(46b).** The reduction of keto product **46a** (0.1 g, 0.034 mmol) by $NaBH_4$ (0.04 g, 0.11 mmol) in methanol at room temperature. The resulted mixture was stirred till the completion of reaction (TLC). After the completion of reaction, the workup was done with ethylacetate and water then the organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give product as a white solid in 100% yield, mp 140-145 °C; IR (ν_{max}, cm^{-1}): 3390 (O-H), 1604 (C=C), 1402 (C-N), 1217 (C-O), 1068 (C-S), 771 (C-H bend); ^1H NMR (400 MHz , DMSO-d_6): δ_H 10.40 (s, 1H, NH), 7.79 (d, *J*=7.91, 1H, Ar-H), 7.71 (d, *J*=8.50, 2H, Ar-H), 7.58 (d, *J*=7.68, 1H, Ar-H), 7.36 (d, *J*=8.50, 2H, Ar-H), 7.32 (t, *J*=7.63, 1H, Ar-H), 7.14 (t, *J*=7.63, 1H, Ar-H), 5.10 (d, *J*=4.32, 1H), 3.95 (m, 1H), 1.04 (m, 1H), 0.39 (m, 4H); ^{13}C NMR (400 MHz , DMSO-d_6): 198.3, 161.4, 152.2, 145.1, 131.3, 130.6, 130.0, 126.5, 123.3, 121.7, 120.2, 117.3, 16.5, 11.3; HRMS: Calcd. Accurate mass for ($C_{17}H_{17}N_2OS$): 297.1056 Found 297.1133 $[M+H]^+$.

Cyclopropyl-{4-(1H-benzo[d]imidazol-2-yl)amino)phenyl}methanol (**47b**). The reduction of keto product **47a** (0.1 g, 0.036 mmol) by $NaBH_4$ (0.045 g, 0.11 mmol) in methanol at room temperature. The resulted mixture was stirred till the completion of reaction (TLC). After the completion of reaction, the workup was done with ethylacetate and water then the organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give product as a white solid in 100% yield, mp 110-113 °C; IR (ν_{max}, cm^{-1}): 3400 (N-H), 3019 (C-H), 1628 (C=C), 1534 (C=N), 1405 (C-N), 1216 (C-O), 1068 (C-S), 771 (C-H bend); ^1H NMR (400 MHz , DMSO-d_6): δ_H 7.62 (d, *J*=8.34, 2H, Ar-H), 7.43 (d, *J*=8.34, 2H, Ar-H), 7.22 (d, *J*=7.75, 1H, Ar-H), 7.00 (m, 1H, Ar-H), 6.86 (m, 2H, Ar-H), 6.21 (s, 2H, Ar-H), 4.08 (d, *J*=7.44, 1H, Ar-H), 1.11 (m, 1H), 0.47 (m, 4H); ^{13}C

NMR (100 MHz , DMSO-d_6): 154.6, 146.2, 143.1, 135.3, 133.7, 128.0, 126.4, 121.6, 119.3, 115.5, 108.1, 75.5, 19.7, 3.7, 3.0; HRMS: Calcd. Accurate mass for ($C_{17}H_{18}N_3O$): 280.1444 Found 280.1436 $[M+H]^+$, ($C_{17}H_{16}N_3$): Calcd. 262.1339. Found 262.1334 [M-17], ($C_{14}H_{12}N_3O$): Calcd. 238.0975. Found 238.0975 [M-41], ($C_7H_6N_3$): Calcd. 132.0556. Found 132.0547 [M-147].

***Cyclopropyl-{4-((3-(1H-imidazol-1-yl)propyl)amino)phenyl}methanone* (52).** The reaction of 4-chloro-4-fluorobutyrophenone **7** (0.5mL, 3.04 mmol) with 1-(3-aminopropyl)-imidazole **51** (0.38 mL, 3.04 mmol) and Potassium carbonate (1 g, 7.23 mmol) in DMSO at 120 °C temperature. The resulted mixture was stirred with heat till the completion of reaction (TLC). After the completion of reaction, the workup was done with ethylacetate and water and then the organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give product 1 as a creamy solid in 76% yield (0.62 g); mp 128-130 °C; IR (ν_{max}, cm^{-1}): 3407 (N-H), 3019 (C-H), 1648 (C=O), 1599 (C=C), 1385 (C-N), 771 (C-H bend); ^{1}H NMR (400 MHz , $CDCl_3$): δ_H 7.90 (d, *J*=8.80, 2H, Ar-H), 7.48 (s, 1H, Ar-H), 7.09 (s, 1H, Ar-H), 6.93 (s, 1H, Ar-H), 6.55 (d, *J*=8.80, 2H, Ar-H), 4.77 (s, 1H, NH), 4.09 (t, *J=6.79*, 2H), 3.20 (t, *J=6.70*, 2H), 2.59 (m, 1H), 2.12 (m, 2H), 1.16 (m, 2H), 0.952 (m, 2H); ^{13}C NMR (100 MHz , $CDCl_3$): 198.3, 151.5, 137.1, 130.4, 129.8, 127.8, 118.7, 111.5, 44.4, 40.1, 30.5, 16.1, 10.7; Anal. Found: C, 71.32; H, 7.10; N, 15.59. Calcd: C, 71.35; H, 7.11; N, 15.60; HRMS: Calcd. Accurate mass for ($C_{16}H_{20}N_3O$): 270.1601 Found 270.1617 $[M+H]^+$, ($C_{13}H_{16}NO$): Calcd. 202.1226. Found 202.1247 [M-67], ($C_{12}H_{14}NO$): Calcd. 188.1070.. Found 188.1062 [M-81], ($C_{11}H_{12}NO$): Calcd. 174.0913. Found 174.0312 [M-95].

***Cyclopropyl-{4-(4-benzylpiperazin-1-yl)phenyl}methanone* (58)**. Following the same procedure and the workup used for the synthesis of (**40a**), the reaction of 4-chloro-4-fluorobutyrophenone **7** (0.5 ml, 3.04 mmol) and 1-benzylpiperazine **53** (0.54 ml, 3.04 mmol), with K_2CO_3 (1 g, 7.23 mmol) in DMSO gave the title compound as white solid in 90% yield (0.87 g); mp 125-128 °C; IR (ν_{max}, cm^{-1}): 3018 (C-H), 1646 (C=O), 1598 (C=C), 1387 (C-N), 926 (C-H bend); ^{1}H NMR (400 MHz , $CDCl_3$): δ_H 7.94 (d, *J* = 9.04, 2H, Ar-H), 7.36-7.31 (m, 4H, Ar-H), 7.27 (m, 1H, Ar-H), 6.87 (d, *J* = 9.04, 2H, Ar-H), 3.56 (s, 2H), 3.35

(m, 4H), 2.62 (m, 1H), 2.59 (m, 4H), 1.17 (m, 2H), 0.94 (m, 2H); ^{13}C NMR (100 MHz , $CDCl_3$): 198.5, 154.1, 137.8, 130.0, 129.2, 128.3, 128.2, 127.2, 113.4, 63.0, 52.7, 47.4, 16.3, 10.8; Anal. Found: C, 78.70; H, 7.54; N, 8.71. Calcd: C, 78.71; H, 7.55; N, 8.74; HRMS: Calcd. Accurate mass for ($C_{21}H_{25}N_2O$): 321.1961 Found 321.1977 $[M+H]^+$, ($C_{18}H_{18}N_2O$): Calcd. 278.1419. Found 278.1808 [M-42], ($C_{14}H_{17}N_2O$): Calcd. 229.1335. Found 229.2378 [M-91], (C_7H_7): Calcd. 91.0548. Found 91.1013 [M-229].

Cyclopropyl-{4-(4-Allylpiperazin-1-yl)phenyl}methanone **(59).** Following the same procedure and the workup used for the synthesis of (**40a**), the reaction of 4-chloro-4-fluorobutyrophenone **7** (0.5 ml, 3.04 mmol) and 1-allylpiperazine **54** (0.42 ml, 3.04 mmol), with K_2CO_3 (1 g, 7.23 mmol) in DMSO gave the title compound as white solid in 84% yield (0.69 g); mp 110-112 °C; IR (ν_{max}, cm^{-1}): 3018 (C-H), 1653 (C=O), 1598 (C=C), 1386 (C-N), 770 (C-H bend); ^{1}H NMR (400 MHz , $CDCl_3$): δ_H 7.95 (d, *J* = 9.06, 2H, Ar-H), 6.89 (d, *J* = 9.06, 2H, Ar-H), 5.89 (m, 1H), 5.25-5.18 (m, 2H), 3.37 (m, 4H), 3.06 (dt, J_1 = 6.55, J_2 = 1.15, 2H), 2.62 (m, 1H), 2.59 (m, 4H), 1.18 (m, 2H), 0.95 (m, 2H); ^{13}C NMR (100 MHz , $CDCl_3$): 198.5, 154.0, 134.6, 129.9, 128.3, 118.4, 113.5, 61.7, 52.7, 47.4, 16.2, 10.8; Anal. Found: C, 75.49; H, 8.18; N, 10.36. Calcd: C, 75.52; H, 8.20; N, 10.36; HRMS: Calcd. Accurate mass for ($C_{17}H_{23}N_2O$): 271.1805 Found 271.1820 $[M+H]^+$, ($C_{14}H_{18}N_2O$): Calcd. 230.1414. Found 230.1407 [M-40], ($C_{12}H_{14}NO$): Calcd. 188.1070. Found 188.1071 [M-82], ($C_5H_{10}N$): Calcd. 84.0808. Found 84.0805 [M-186].

Cyclopropyl-{4-(4-Benzhydrylpiperazin-1-yl)phenyl}methanone **(60).** Following the same procedure and the workup used for the synthesis of (**40a**), the reaction of 4-Chloro-4-Fluoro butyrophenone **7** (0.5 mL, 3.04 mmol), and 1-(diphenyl methyl) piperazine **55** (0.76g, 3.04 mmol), with K_2CO_3 (1 g, 7.23 mmol) in DMSO gave the title compound as white solid in 82% yield (0.98 g); mp 132-135 °C; IR (ν_{max}, cm^{-1}): 3019 (C-H), 1650 (C=O), 1597 (C=C), 1386 (C-N), 771 (C-H bend); ^{1}H NMR (400 MHz , $CDCl_3$): δ_H 7.93 (d, *J* = 8.82, 2H, Ar-H), 7.44 (d, *J* = 7.40, 4H, Ar-H), 7.28 (t, *J* = 7.40, 4H, Ar-H), 7.19 (m, 2H, Ar-H), 6.85 (d, *J* = 8.82, 2H, Ar-H), 4.26 (s, 1H), 3.34 (m, 4H), 2.61 (m, 1H), 2.54 (t, *J* = 4.74, 4H), 1.17 (m, 2H), 0.94 (m, 2H); ^{13}C NMR (100 MHz , $CDCl_3$): 198.5, 154.1, 142.4,

129.9, 128.6, 127.9, 127.1, 113.3, 76.1, 51.6, 47.5, 16.3, 10.8; HRMS: Calcd. Accurate mass for ($C_{27}H_{29}N_2O$): 397.2274 Found 397.2384 $[M+H]^+$.

***Cyclopropyl-{4-(4-(Benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)phenyl}methanone* (61).** Following the same procedure and the workup used for the synthesis of (**40a**), the reaction of 4-chloro-4-fluorobutyrophenone **7** (0.5mL, 3.04 mmol) and 1-piperonyl piperazine **56** (0.66 g, 3.04 mmol), and K_2CO_3 (1 gm, 7.23 mmol) in DMSO gave the title compound as white solid in 84% yield (0.93 g); mp 118-120 °C; IR (ν_{max}, cm^{-1}): 3390 (C-H), 1652 (C=O), 1599 (C=C), 1386 (C-N), 1218 (C-O), 771 (C-H bend); ^{1}H NMR (400 MHz , $CDCl_3$): δ_H 7.94 (d, *J* = 8.96, 2H, Ar-H), 6.88 (m, 2H, Ar-H), 6.86 (m, 1H, Ar-H), 6.76 (s, 2H), 5.95 (s, 2H), 3.46 (s, 2H), 3.34 (m, 4H), 2.62 (m, 1H), 2.57 (m, 4H), 1.17 (m, 2H), 0.95 (m, 2H); ^{13}C NMR (100 MHz , $CDCl_3$): 198.5, 154.1, 147.7, 146.7, 131.7, 130.0, 128.2, 122.2, 113.5, 109.4, 107.9, 100.9, 62.7, 52.6, 47.4, 16.3, 10.8; Anal. Found: C, 72.48; H, 6.63; N, 7.66. Calcd: C, 72.51; H, 6.64; N, 7.69; HRMS: Calcd. Accurate mass for ($C_{22}H_{25}N_2O_3$): 365.1860 Found 365.2002 $[M+H]^+$, ($C_{18}H_{21}N_2O_2$): Calcd. 297.1603. Found 297.1600 [M-67], ($C_8H_7O_2$): Calcd. 135.0441. Found 135.0430[M-229].

***Cyclopropyl-{4-(4-(2-((4-(Cyclopropanecarbonyl)phenyl)amino)ethyl)piperazin-1-yl)phenyl}methanone* (62).** Following the same procedure and the workup used for the synthesis of (**40a**), the reaction of 4-chloro-4-fluorobutyrophenone **7** (0.5mL, 3.04 mmol), 1-(2-aminoethyl) piperazine **57** (0.39mL, 3.04 mmol), and K_2CO_3 (1 gm, 7.23 mmol) in DMSO gave the title compound as white solid in 38% yield (.0.48 g); mp 130-132 °C; IR (ν_{max}, cm^{-1}): 3396 (C-H), 1648 (C=O), 1596 (C=C), 1391 (C-N), 770 (C-H bend); ^{1}H NMR (400 MHz , $CDCl_3$): δ_H 7.97-7.91 (m, 4H, Ar-H), 6.90 (d, *J* = 8.72, 2H, Ar-H), 6.61 (d, *J* = 8.72, 2H, Ar-H), 4.87 (s, 1H, NH), 3.38 (m, 4H), 3.29 (m, 2H), 2.71 (t, *J* = 6.05, 2H), 2.64 (m, 4H), 2.58 (m, 2H), 1.18 (m, 4H), 0.95 (m, 4H); ^{13}C NMR (100 MHz , $CDCl_3$): 198.6, 198.3, 153.9, 152.0, 130.4, 130.0, 128.5, 127.3, 113.6, 111.5, 56.2, 52.5, 47.5, 39.5, 16.3, 16.1, 10.9, 10.7; HRMS: Calcd. Accurate mass for ($C_{26}H_{32}N_3O_2$): 418.2489 Found 418.2471 $[M+H]^+$.

Materials & Methods

Culture and maintenance of HEK293 cells:

HEK293T cells were grown in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% FBS. All cells were supplemented with an antibiotic anti-mycotic solution (100 units penicillin, 0.1 mg mL1 streptomycin, and 0.25 mg mL1 amphotericin B) and grown at 37° C under standard cell culture conditions (5% CO_2, 95% humidity). HEK293T cells were transfected and plated in 96 well assay plate (Corning clear bottom) 24 hrs before treatment.

Reagents and compound preparation:

Serotonin creatinine sulfate was purchased from TCI chemicals. For NFAT-RE luciferase assays all test compounds were dissolved in DMSO (Sigma Aldrich) or drug buffer (Gibco, 1×HBSS with 20 mM HEPES, pH 7.4) at a concentration of 10 mM. To test compounds for agonist activity, compounds were diluted in cell compatible drug buffer from their 10 mM stock (prepared in DMSO or drug buffer) to prepare dose response (serially starting from 10 µM to 0.01 nM) and were added in triplicate on the assay plate followed by 6-8 hrs incubation. To test compounds for PAM activity, compounds were added at a concentration of 10 µM, 1 µM and 100 nM in triplicate followed by addition of orthosteric ligand (5-HT or lorcaserin) concentration response (serially starting from 10 µM to 0.01 nM) was added to the assay plate and incubated for 6-8 hrs.

NFAT-RE Luciferase Assay:

For NFAT-RE assay, HEK 293T cells were transiently transfected by mixxing PEI max (1 µg/µl) transfection reagent with 0.1 µg DNA/well of 5-HT_{2C} or 5-HT_{2B} or $5HT_{2A}$ plasmid (a kind gift from Bryan Roth, University of North Carolina) and 0.1 µg DNA/well of NFAT-RE luciferase (luc2P/NFAT-RE/Hygro, Promega Corp.) plasmid and plating (50,000 cells/well) in white 96 well clear bottom assay plate as described previously [40]. All primary screening of synthetic compounds were performed at final concentration of 10 µM concentration (in triplicate). To measure agonist or PAM activity, compounds were added at desired concentration and incubated for 12 hrs. Post-treatment, luciferase

activity was measured within 5 minutes of addition of Bright-Glo substrate solution (1mg/ml, final concentration) using multi-mode plate reader (BMG, Labtech). The Relative luminescence units (RLU) values obtained were analyzed via non-linear regression using GraphPad Prizm (version V). The E_{max} value of serotonin was set/normalized to 100% for comparisons.

Intracellular calcium flux assay [iCa^{++}] in HEK293T cells:

HEK293T cells were plated (50,000 cells/well) in a black 96-well optical bottom plate (Corning). The [iCa^{++}] assay was performed in 5-HT_{2C} transfected HEK293T cells as described previously [41]. Briefly, Calcium-binding dye Fluo-4NW (Invitrogen, F36206, excitation 494 nm, emission 516 nm) loaded into 5-HT_{2C} expressing cells and measurement of test compound induced [iCa^{++}] for 120s were performed using FlexStation (Molecular devices) as per manufacturer's protocol. Fold change [iCa^{++}] was calculated from baseline fluorescence during the first 5s before the addition of ligands. To determine the PAM activity of **58** (1µM), 5-HT was added 15 min after incubation with compound **58**, at a rate of 35 µl/min.

Evaluation of cumulative food intake in normal SD rats.

All *in vivo* experiments and procedures were performed in accordance with the guidelines established in the guide for the care and use of laboratory animals and were approved by the Institutional Animal Ethics Committee (IAEC) of CSIR-Central Drug Research Institute, Lucknow, India. The IAEC is certified by Animal Welfare Board of India (AWBI) and Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), which are statutory bodies of Government of India. Adult SD rats with 150-200g body weight were housed on a 12 h light/dark cycle (lights on at 8.00 am) at 22 °C. Cannula (28G, plastic one) was implanted on the right ventricle (AP -0.9, ML -1.5, DV -3.5) for i.c.v delivery of VEH (aCSF) or lorcaserin or compound **58**. To evaluate food intake, cannulated SD rats were starved for four hours (from 9 am to 1 pm) with free access to water. After 4 hour of food deprivation, aCSF (VEH), test compound **58** (2pmol) and lorcaserin (2pmol/rat, Selleck Chemicals) as positive control were administrated through i.c.v route. After 10 minutes of drug administration, a weighed

amount of diet pellets were placed in the clean food rack. After three, six and twenty four hours, all food remaining in the cage (including spillage in the cage) was collected and weighed.

Molecular docking on 5-HT_{2C}

In order to determine the possible binding mode and molecular interactions involved in the binding of the identified PAM compounds in the allosteric site of the 5-HT_{2C} protein, molecular docking experiments were performed using Schrodinger suite [42]. The crystal structure of human serotonin receptor protein 5-HT_{2C} for docking experiments was retrieved from PDB (PDB ID: 6BQG), in its active form bound with the agonist ergotamine [34]. Protein and ligands were prepared with Protein preparation wizard and LigPrep modules of the Schrodinger suite respectively. Protein was optimized at physiological pH using PROPKA and minimized using OPLS2005 forcefield. Default settings were used for protein and ligand preparation. Receptor grid was generated as described by Christopher *et al.* [33]. Grid was placed around center of the extracellular loop (EL2) in the space dimensions of (X: 26.98, Y: 35.54, Z: 66.61). Ligand diameter midpoint box was rescaled to 20 A^o. Two excluded volumes were created in the orthosteric site to avoid the entry of any ligand in the defined space. Volume 1 sphere occupied space X: 22.53, Y: 36.04, Z: 51.66 with radius 4.6. Volume 2 sphere occupied X: 16.19, Y: 35.55, Z: 50.64 with radius 3. Receptor grid for serotonin (5-HT) docking was defined by selecting the crystal structure bound ligand ergotamine (ERG) [34] and ligand diameter midpoint box in X, Y, Z direction was set to 12 A^o as described by Christopher *et al.* [33]. Molecular docking was performed using Glide XP module of the Schrodinger suite [43]. Excluded volume penalties were applied for the docking of positive allosteric modulators (PAMs). Molecular graphics and analysis were performed with the Schrodinger suite [42], Discovery studio 2016 [44] and UCSF chimera package [45].

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Author Contributions

[#]Authors contributed equally. This manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Highlights

- A series of *N*-heterocycle linked phenyl cyclopropyl methanones were synthesized.
- Three molecules were found active as allosteric modulators on serotonin receptors.
- Compound **58** at 1μM selectively exhibited PAM on 5-HT_{2C} and NAM on 5-HT_{2B}.
- Compound **58** decreased food intake similar to full agonist lorcaserin in SD rats.

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