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# Synthesis of 2-[{4-(t-amino-1-yl) but-2-yn-1-yl }oxy]-1,3-benzothiazole derivatives as $H_3$-antagonists

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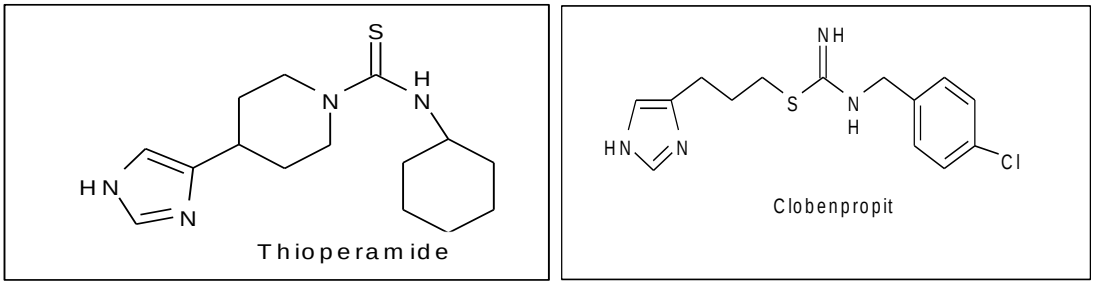
***ABSTRACT :*** *Aminoacetylenicoxybenzothiazole derivatives were synthesized from the reaction of 2-hydroxybenzothiazole with 3-bromoprop-1-yne to generate 2-(prop-2-ynl-1-yloxy)-1,3-benzothiazole* ***(RM-1)****. A mixture of 2-(prop-2-yn-1-yloxy)-1,3-benzothiazole, paraformaldehyde, cyclic amine and cuprous chloride catalytic amount, in peroxide-free dioxane through Mannich reaction yielded the desired aminoacetylenicoxybenzothiazoles* ***(RM- 2-7)****. The mp, IR, 1H-NMR, $^{13}$C-NMR and elemental analysis were consistent with the assigned structures. The design of these compounds as $H_3$ antagonists was based on the rationalization for the important criteria needed to overlap effectively with $H_3$ receptor to induce antagonistic activity. These criteria are: 1) The basic amino group for ionic binding. 2) The acetylenic group for electrostatic interaction. 3) The 2-butyne provide the appropriate distance between the basic nitrogen and benzthiazole. 4) Oxy ether to provide hydrogen bonding with $H_3$ receptor and 5) benzothiazole group found in $H_3$ antagonists and many other biologically active compounds. The docking results showed that all the designed compounds have a good $H_3$ receptor antagonism especially* ***RM-7*** *which have -6 (kcal/mol). These results provide a good lead to design more effective $H_3$ antagonists in managing Alzheimer's and other diseases like depression, epilepsy, schizophrenia and many other CNS disorders.*

***KEYWORDS:*** *Alzheimer, aminoacetylenic derivatives, 2-hydroxythiadiazole derivatives, $H_3$ antagonists.*

## I. INTRODUCTION

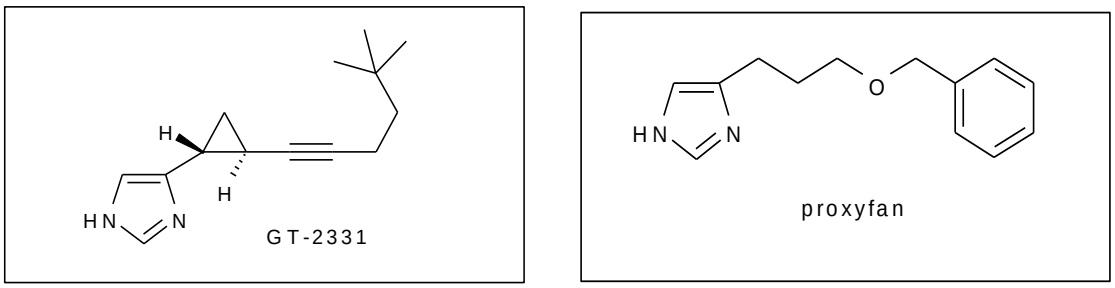
Alzheimer`s disease (AD) is the most common form of dementia, accounting for about 50-60% of all overall cases of dementia among persons over 65 years of age. It is a progressive, degenerative disorder of the brain characterized by loss of memory and cognition. The brain regions that are associated with higher mental functions, particularly the neocortex and hippocampus are the most affected parts. Alzheimer is a multifactorial disease associated with extracellular deposits of amyloid-β (derived from amyloid precursor protein APP) in senile plaques and intracellular formation of neurofibrillary tangles containing an abnormally phosphorylated form of microtubular associated protein tau [1, 2, 3, 4, 5, 6]. Other factors such as cholinergic dysfunctions, oxidative stress, and increase iron and aluminum levels in the brain are involved in AD [3, 7]. Histamine is a biogenic amine that influences a wide range of pathophysiological processes through the activation of different G-protein-coupled receptors (GPCRs). Four subtypes of histamine GPCRs are known [8, 9, 10, 11, 12, 13]. Histamine $H_3$ receptor is a G protein-coupled receptor whose activation inhibits the synthesis and release of histamine; in addition to other neurotransmitters from nerve endings and is involved in the modulation of different central nervous system functions. $H_3$ antagonists have been proposed for their potential usefulness in diseases characterized by impaired neurotransmission and they have demonstrated beneficial effects on learning and food intake in animal models [14, 15]. These observations encouraged medicinal chemists to design new $H_3$ antagonists for treatment of various CNS diseases [8, 16, 17, 18, 19, 20, 6]. Thioperamide, clopenpropit, pyroxifan and perception (GT-2331) are selective $H_3$ antagonists with imidazole ring in their structures (Fig. 1). It is well established that the presence of the imidazole ring may lead to low CNS penetration and interaction with cytochrome P450; such liabilities seem to be avoided by the new classes of non-imidazole antagonists (Fig. 2). These afford some interesting compounds proved to block the $H_3$-receptor at nanomolar concentrations and to posses promising efficacy in several experimental models of central disorders. This approach led to the selection of some imidazole-free compounds for clinical studies [8].

**Figure 1: Imidazole-derived histamine $H_3$ ligands.**



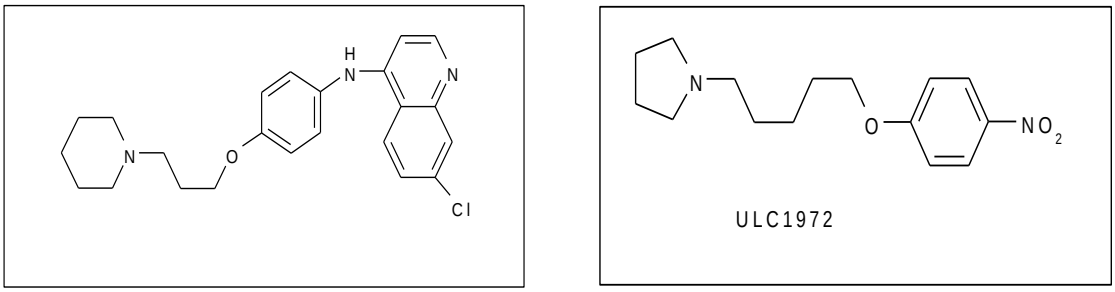

N-cyclohexyl-4-(1H-imidazol-4-yl)piperidin- N-[(4-chlorophenyl)methyl]{[3-(1H- imidazol

1-carbothioamide. -4-yl)propyl]sulfanyl}methanimidamide




4-[3-(benzyloxy)propyl]-1H-imidazole. Structural formula of perception

**Figure 2: Non-imidazole-derived histamine $H_3$-receptors**

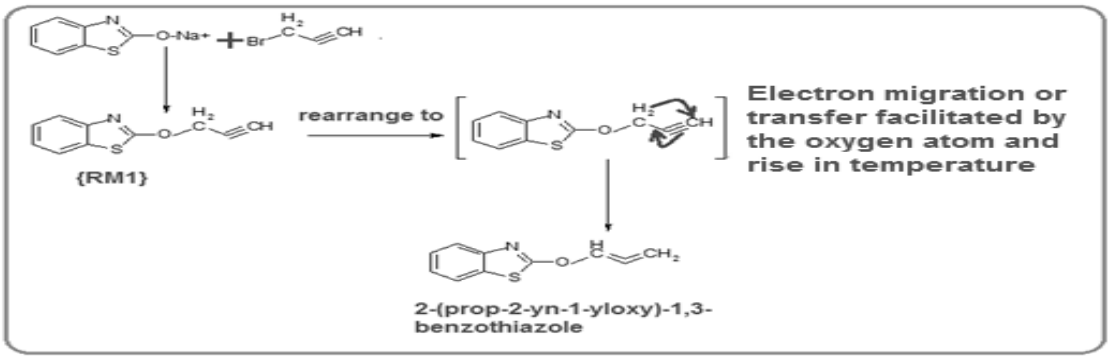



Reviewing various structural features in $H_3$ antagonists and their impressive results in treatment of various CNS diseases promoted our interest to design and synthesize a new series of aminoacetylenicoxybenzothiazole (Fig. 3), for the following criteria: Benzothiazole as a replacement for imidazole ring to overcome limitation of the imidazole ring, the basic cyclic amine to provide hydrogen bonding or ionic interaction with $H_3$ receptor, the unique acetylenic moiety to accommodate for electronic interaction and the appropriate distant between the cyclic amine and benzthiazole moiety, the oxy group for effective hydrogen bonding. This unique approach to design $H_3$ antagonists and the results of their molecular docking may provide a lead compounds in treatment of Alzheimer, depression disorder, Parkinson's, epilepsy and other CNS diseases.

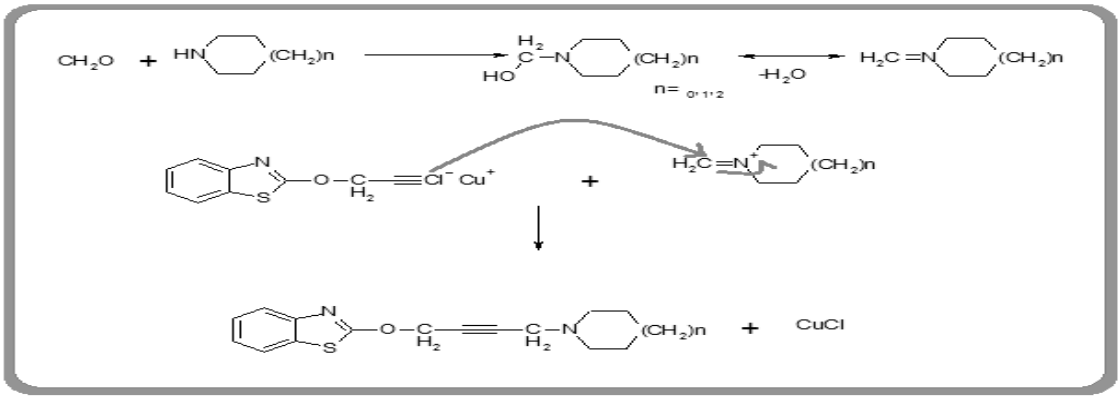
## II. CHEMISTRY

The designed compounds were prepared according to **scheme 1**. To the ethanolic sodium, 3-bromoprop-1-yne was added drop wise. The mixture was heated up to 40-45 $^{o}$C and continued for I hour yielding the desired 2-(prop-2-yn-1-yloxy)-1,3-benzothiazole, (**RM-1**). At higher temperature (65-75$^{o}$C) a side product was obtained namely 2-(propa-1,2-dien-1-yloxy)-1,3-benzothiazole, as shown in **scheme 1**. The mannich reaction of 2-(prop-2-yn-1-yloxy)1,3-benzothiazole with paraformaldehyde, appropriate cyclic amine and catalytic amount of cuprous chloride yielded the desired products (**RM-2 -7**). The IR, $^{1}$H NMR, $^{13}$C NMR

and elemental analysis were consistent with the assigned structures. The proposed mechanism for mannich reaction is outlined in **scheme 2**. In order for mannich reaction to precede a reactive immonium cations intermediates, should be formed from the condensation of the formaldehyde and the appropriate amines (Schiff base formation). The attack of the carbanion in 2-(prop-2-yn-1-yloxy)-1,3-benzothiazole cuprous salt on the Schiff base, generate the desired mannich products (**RM-2 -7**).




**Scheme 1**: Alkylation reaction of benzothiazole moiety.



**RM-(2-7)**

Scheme 2**: Proposed Mannich reaction**

## III. RESULTS AND DISCUSSION

The design of these compounds as $H_3$ antagonists was based on our rationalization for the important criteria needed to overlap effectively with $H_3$ receptor to induce antagonistic activity. These criteria are, the basic amino group for ionic binding, the acetylenic group for electrostatic interaction, the oxy-2-butyne to provide hydrogen bonding and the appropriate distant between the basic nitrogen and benzthiazole group; furthermore, benzothiazole group is found in $H_3$ antagonist and in many other biologically active compounds [21]. Validated homology models of $H_3$ receptor was prepared and compounds **RM-(2-7)** were docked into. Asp114 or Glu206 are considered to be crucial for binding of $H_3$ receptor natural messengers (i.e. histamine), and this was illustrated by site-directed mutagenesis studies [14]. Classical $H_3$ receptor antagonists seem always to have an ionic interaction with one of these residues in the receptor binding site. In fact, some docking studies showed that both key aminoacids could be involved in binding of some known $H_3$ receptor antagonist [14]. This was confirmed by our current study where thioperamide had two Hydrogen bonding with both Asp114 and Glu206 Consistent with the above data, similar results were obtained by our docking studies of benzothiazole derivatives into $H_3$ receptor. The ionic interaction was always made by the cyclic amino group with one of the key aminoacids; the highest scoring poses had it mainly with the glutamate side chain. Additionally, all docked ligands seem to have a favorable binding mode with the $H_3$ receptor binding site (energies < 0,

Table **1**) which indicates having the important $H_3$ antagonist pharmacophoric features in their structures.

Compound RM-7 had the best score among the benzothiazole compounds (-6.0 kcal/mol). RM-7 also had an ionic interaction with the same key residue (Glu206) and a good fit inside the $H_3$ receptor pocket represented by multiple van der Waals interactions with the surrounding aminoacids. An additional electrostatic interaction was detected between the RM-7 ether and the side chain of Tyr115. On the other hand, no specific role was found for the benzothiazol heteroatoms in binding with the $H_3$ receptor binding site.

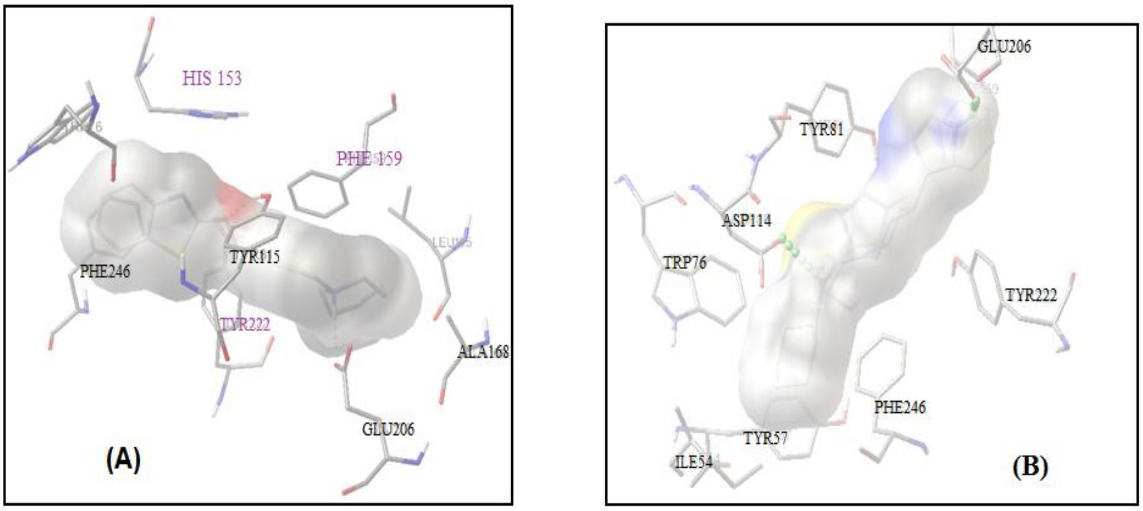
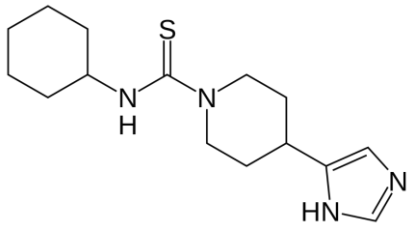



**Figure 6:** (A) and (B) shows the multiple binding modes demonstrated by **RM-7** and thioperamide in the $H_3$ receptor active site (sticks), respectively. Some protein chains are not shown for clarity.

**Table 1.** Docking scores of different benzothiazole derivatives in the $H_3$ receptor active site.

| **Molecule** | **Autodock Score (kcal/mol)** |
|---|---|
|  | -6.8 |
| RM-4 | -5.4 |
| RM-2 | -5.9 |
| RM-3 | -5.8 |
| RM-5 | -4.5 |
| RM-6 | -5.0 |
| RM-7 | -6.0 |

## IV. EXPERIMENTAL PROTOCOLS

**General methods :** All melting points (mp) were measured in open capillaries on an electrothermal apparatus and are uncorrected. For all compounds Infrared spectra (IR) were recorded using a Nicolet Impact 410 FT-IR spectrophotometer. The absorption band expressed in ($Cm^{-1}$). [1] HNMR spectra were recorded on a Varian mercury 300 MHz spectrometer. Chemical shifts are expressed in ppm down field from internal TMS as reference. $^{1}H$ data are reported in order: multiplicity (br, broad; s, singlet; d, doublet; t, triplet, m, multiplet). $^{13}CNMR$ spectra were recorded on varian Mercury 300 MHZ spectrometer, DMSO-$d_6$ as solvent and TMS as reference. Elemental analysis (C,H,N) for all compounds were carried out in the laboratories of Oil Exploration Company, Iraq and were within ± 0.4% of the theoretical values.

**Docking Methods :** Validated homology models of $H_3$ receptor were kindly provided by Mor's group [14] from Italy and Sippl group [22] from Germany. Next, ligand and water molecules were removed and partial charges were assigned to all atoms using Kollman united atom model in the Autodock Tool program [23, 24] Subsequently, the $H_3$ receptor active site was identified by the already bound ligand then a grid box of a 50 x 42 x 60 Å size was created with a grid spacing of 0.375 Å using Autogrid (part of the Autodock software package) [25, 26]. On the other hand, ligand 3D structures were built using the MOE software package (Molecular Operating Environment (MOE), 2009) [27] and were then minimized using MMFF94 force field [28, 29, 30, 31]. Gasteiger-Marsili partial charges [32] were assigned for all prepared ligand in the Autodock program. Tertiary amines in all compounds were assigned as protonated (ligands with two tertiary amines with only one positive charge). Following the preparation of the protein and ligands structures, the ligands were docked into the previously identified active site using Autodock [25, 26] (version 4.2). Lamarckian Genetic Algorithm [25] was employed for the conformational sampling of the ligand structures while the protein was treated as rigid (default settings used). Docked conformations were rated by the Autodock scoring function that includes terms for van der Waals, hydrogen bond, electrostatic interactions, and the ligand internal energy.

**General synthetic procedure:**

Synthesis of 2-(prop-2-yn-1-yloxy)-1,3-benzothiazole **(RM-1)**

2-(prop-2-yn-1-yloxy)-1,3-benzothiazole (RM-1). This compound prepared by a solution of 2-Hydroxybenzothiazole sodium (1.51gm 0.01 mole) in 30 ml ethanol was refluxed up to 40-45C°. 3-bromoprop-1-yne (2.4 gm 0.02mole) was added drop wise to the solution for 15 minutes. The mixture was stirred for 1 hour and filtered to give light yellowish orange solution. The solvent was removed under reduced pressure to afford the desired powder, recrystallization from ethanol ether to afforded compound RM-1 ($C_{10}H_{17}NOS$); yield 1.5g 52% as yellow solid. 1H-NMR (DMSO- d6 300 MHz): δ 2.49 (s, 1H, C≡ CH), 3.38 (s, 2H, $CH_2$-C≡), 6.85-7.17 (m, 4H, ArH).13C NMR (DMSO-d6 100 MHz): 62(CH2), 74(CH), 81(C≡CH), 114, 116, 122, 124, 132, 151(Ar C), 174 (N=C-S). mp 120-121°C. IR (KBr $cm^{-1}$): 3075, 2913, (ArH, stretch), 2294 (C≡CH, stretch), 1611, 1423(Ar, C=C, stretch), 1252, 1109, 1019 (Ar, C=C bending), 893, 750 (ArH, bending).

Elemental analysis for $C_{10}H_7NOS$ (189):

| | C | H | N |
|---|---|---|---|
| calculated | 63.47% | 3.73% | 7.40% |
| found | 63.24% | 3.51% | 7.31% |

Synthesis of 2-{[4-(amino-1-yl)but-2-yn-1- yl]oxy}-1,3-benzothiazole (RM2-RM7)

A mixture of 2-(prop-2-yn-1-yloxy)-1,3-benzothiazole (1.5 gm 0.01 mole), paraformaldehyde ( 0.5 0.015 mole) and the cyclic amine around (0.01 mole ), and cuprous chloride catalytic amount (0.03 gm), in peroxide-free dioxane 20 ml was refluxed for 1 hour. Filtered and evaporated under reduced pressure. Diethyl ether was added to the residue resulting in the desired products. Recrystallization from ethanol-ether afforded the crystalline compounds, **RM-2, RM-3, RM-4, RM-5, RM-6, RM-7**. The mp, IR, 1H-NMR, 13C-NMR and elemental analysis are shown for each compound.

Preparation of 2-{[4-(2,6-dimethylpiperidin-1-yl)but-2-yn-1- yl]oxy}-1,3-benzothiazole **(RM-2).**

The titled compound was prepared following the general procedure for synthesis of 2-{[4-(amino-1-yl)but-2-yn-1- yl]oxy}-1,3-benzothiazole (**RM2-RM7**), yielded 1.8gm 57.3 as yellow solid. 1H-NMR (DMSO- d6 300 MHz): δ, 1.1-1.12(d, 6H, J= 6.01 Hz, CH- CH3), 1.4, 1.5, 1.7, 1.8, 1.9(m, various proton of cyclicamine), 3.3(s,

2H, C≡C-$CH_2$N), 3.7 (s, 2H, O-CH2-C≡C), 7-7.6 (m, 4H, ArH). 13C (DMSO- d6 100 MHZ): δ, 23,25,35 (various C of cyclic amine), 66(C-N), 78(C≡C), 80(O-C), 114, 117, 120, 123, 132, 153(Ar C), 174(N=C-S). mp 160-163. IR (KBr $cm^{-1}$): 3066, 2960, 2951 (ArH, stretch), 2276 (C≡C, stretch), 1665, 1620, 1594, 1414 (Ar, C=C, stretch), 1297, 1055, 956 (Ar, C=C bending), 780,760 (ArH, bending).

Elemental analysis for $C_{18}H_{22}N_2OS$ (314):

| | C | H | N |
|---|---|---|---|
| calculated | 68.75% | 7.05% | 8.91% |
| found | 68.60% | 7.21% | 8.92% |

Preparation of 2-{[4-(2-methylpiperidin-1-yl)but-2-yn-1-yl]oxy}-1,3-benzothiazole **(RM-3).**

The titled compound was prepared following the general procedure for synthesis of 2-{[4-(amino-1-yl)but-2-yn-1- yl]oxy}-1,3-benzothiazole (**RM2-RM7**), yielded 1.53gm 51.01% as a yellow solid, 1H-NMR (DMSO- d6 300 MHz): δ, 1.1- (d, 3H, J= 5.9 Hz, CH- CH3), 1.34, 1.5, (m, various proton of cyclic amine), 3.4 (s, 2H, CH2-N), 3.7 (s, 2H, O-CH2), 6.6-7.2(m, 4H, ArH). 13C (DMSO- d6 100 MHZ): δ, 23,25,37 (various C of cyclic amine), 69(C-N), 81(C≡C), 82(O-C), 115, 119, 120, 123, 131, 148(Ar C), 176(N=C-S). . mp 130-134. IR (KBr $cm^{-1}$): 3048, 2976, 2951 (ArH, stretch), 3030, 2312 (C≡C, stretch), 1665, 1611, 1486(Ar, C=C, stretch), 1387, 1252, 1072 (Ar, C=C bending), 893,732 (ArH, bending).

Elemental analysis for $C_{17}H_{20}N_2OS$ (300):

| | C | H | N |
|---|---|---|---|
| calculated | 67.97% | 6.71% | 9.32% |
| found | 67.90% | 6.44% | 9.18% |

Preparation of 2-{[4-(piperidin-1-yl)but-2-yn-1- yl]oxy}-1,3-benzothiazole **(RM-4)**

The titled compound was prepared following the general procedure for synthesis of 2-{[4-(amino-1-yl)but-2-yn-1- yl]oxy}-1,3-benzothiazole (**RM2-RM7**), yielded 1.80gm 62,93% as yellow solid. 1H-NMR (DMSO- d6 300 MHz): δ, 1.2-1.6 (m, various proton of cyclic amine), 3.2 (s, 2H, ≡C-CH2-N), 3.7(s, 2H, O-CH2-C≡), 6.6-7.2 (m, 4H, ArH). 13C (DMSO- d6 100 MHZ): δ, 23,25,37 (various C of cyclic amine), 69(C-N), 80(C≡C), 82(O-C), 115, 119, 120, 123, 131, 148(Ar C), 176(N=C-S). mp 148-150. IR (KBr $cm^{-1}$): 3057, 2985, 2913 (ArH, stretch), 3030, 2330 (C≡C, stretch), 1602, 1540, 1504, (Ar, C=C, stretch), 1279, 1216, 1172 ( Ar, C=C bending), 893,759, 705 (ArH, bending.

Elemental analysis for $C_{16}H_{18}N_2OS$ (286):

| | C | H | N |
|---|---|---|---|
| calculated | 67.1% | 6.33% | 9.78% |
| found | 67.3% | 6.13% | 9.81% |

Preparation of 2-{[4-(4-methylpiperazin-1-yl)but-2-yn-1-yl]oxy}- 1,3-benzothiazole **(RM-5).**

The titled compound was prepared following the general procedure for synthesis of 2-{[4-(amino-1-yl)but-2-yn-1- yl]oxy}-1,3-benzothiazole (**RM2-RM7**), yielded 1.76 gm 58.47% as yellow solid. 1H-NMR (DMSO- d6 300 MHz)): δ, 1.3-1.7 (m, various proton of cyclic amine), 3.3 (s, 2H, ≡C-CH2-N), 3.7(s, 2H, O-CH2-C≡), 6.6-7.2(m, 4H, ArH). 13C (DMSO- d6 100 MHZ): δ, 39,41,45,50(various C of cyclic amine), 68(C-N), 79(C≡C), 81(O-C), 120, 121, 125, 128, 131, 148(Ar C), 178(N=C-S). mp 166-170. IR (KBr $cm^{-1}$): 3057, 2985, 2922 ( ArH, stretch), 3030, 2321 (C≡C, stretch), 1665, 1540, (Ar, C=C, stretch), 1252, 1118, 1073 ( Ar, C=C bending), 911, 723, (ArH, bending).Anal. Calcd. for C16H19N3OS: C, 63.76; H,6.35; N, 13.94; Found: C, 61,21; H, 5,70; N, 12.39.

Elemental analysis for $C_{16}H_{19}N_3OS$ (301):

| | C | H | N |
|---|---|---|---|
| calculated | 63.76% | 6.35% | 13.94% |
| found | 63.52% | 6.50% | 13.88% |

Preparation of 2-{[4-(pyrrolidin-1-yl)but-2-yn-1-yl]oxy}-1,3- benzothiazole **(RM-6).**

The titled compound was prepared following the general procedure for synthesis of 2-{[4-(amino-1-yl)but-2-yn-1- yl]oxy}-1,3-benzothiazole. RM2-RM7, yielded 1.6gm 58.82% as a yellow solid 1H-NMR (DMSO- d6 300 MHz): δ, 1.4-1.6 (m, various proton of cyclic amine), 3.2 (s, 2H, ≡C-CH2-N), 3.8(s, 2H, O-CH2-C≡), 6.6-7.2( m, 4H, ArH). 13C (DMSO- d6 100 MHZ): δ, 33,42,50(various C of cyclic amine), 66(C-N), 81(C≡C), 82(O-CH2), 120, 123, 124, 125, 131, 148(Ar C), 176(N=C-S). mp 157-159. IR (KBr $cm^{-1}$): 2913 (ArH, stretch), 3030, 2357 (C≡C, stretch), 1602, 1414, (Ar, C=C, stretch), 1252, 1136, (Ar, C=C bending), 866, 759, (ArH, bending).

Elemental analysis for $C_{15}H_{16}N_2OS$:

| | C | H | N |
|---|---|---|---|
| calculated | 66.15% | 5.92% | 10.29% |
| found | 66.30% | 5.91% | 10.30% |

Preparation of 2-{[4-(azepan-1-yl)but-2-yn-1-yl]oxy}-1,3- benzothiazole **(RM-7)**

The titled compound was prepared following the general procedure for synthesis of 2-{[4-(amino-1-yl)but-2-yn-1- yl]oxy}-1,3-benzothiazole (**RM2-RM7**), yielded 1.4gm 56.06% as a yellow solid. 1H-NMR (DMSO- d6 300 MHz): δ, δ 1.7-1.6 (m, various proton of cyclic amine), 3.3 (s,2H, ≡C-CH2-N), 3.8 (s, 2H, O-CH2-C≡), 6.6-7.2( m, 4H, ArH).13C (DMSO- d6 100 MHz): δ, 26 , 28 ,32 (various C of cyclic amine) , 66 (C-N), 83(C≡C), 86(O-C) , 114,117 , 120 ,123 , 132 , 153(Ar C) , 174(N=C-S). mp 122-125. IR (KBr $cm^{-1}$): 3066. 3003, 2976 (ArH, stretch), 3030, 2321 (C≡C, stretch), 1594, 1414, (Ar, C=C, stretch), 1252, 1100, ( Ar, C=C bending), 911, 750, (ArH, bending).

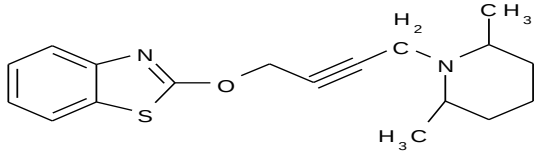
Elemental analysis for $C_{17}H_{20}N_{2O}S$ (300):

| | C | H | N |
|---|---|---|---|
| calculated | 67.97% | 6.71% | 9.32% |
| found | 67.93% | 6.89% | 9.34% |

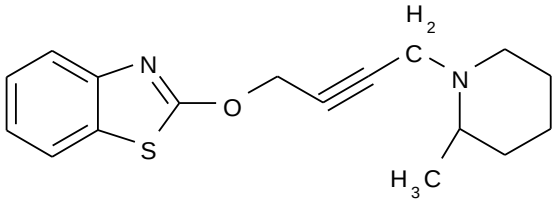
## V. CONCLUSIONS

The synthesis and characterization of a new series of 2-{[4-(amino-1-yl)but-2-yn-1- yl]oxy}-1,3-benzothiazole, (RM2-RM7) were accomplished. Docking of the new aminoacetylenic oxybenzothiazoles showed promising approach in managing Alzheimer`s, depression, epilepsy and other CNS disorders through inhibition of H3 receptor. Further structural modifications are under investigation to find out more potential derivatives.

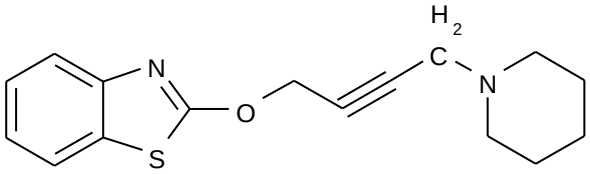
**Figure 3:** The Synthesized $H_3$ antagonists, **RM2-RM7**.



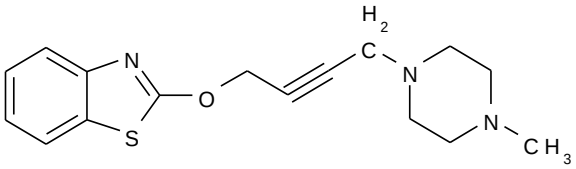
**RM-2:** 2-{[4-(2,6-dimethylpiperidin-1-yl)but-2-yn-1- yl]oxy}-1,3-benzothiazole.



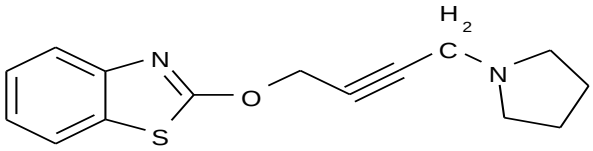
**RM-3:** 2-{[4-(2-methylpiperidin-1-yl)but-2-yn-1- yl]oxy}-1,3-benzothiazole .



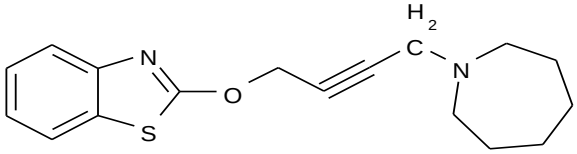
**RM-4:** 2-{[4-(piperidin-1-yl)but-2-yn-1- yl]oxy}-1,3-benzothiazole.



**RM-5:** 2-{[4-(4-methylpiperazin-1-yl)but-2-yn-1-yl]oxy}- 1,3-benzothiazole.



**RM-6:** 2-{[4-(pyrrolidin-1-yl)but-2-yn-1-yl]oxy}-1,3- benzothiazole.



**RM-7:** 2-{[4-(azepan-1-yl)but-2-yn-1-yl]oxy}-1,3- benzothiazole.

## VI. CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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