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DESIGN, SYNTHESIS AND STRUCTURAL ELUCIDATION OF ARYLOXYAMINOACETYLENIC DERIVATIVES AS ANTIDEPRESSANT ACTIVITY

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ABSTRACT

Depression is the most common illness that affects a large number of individuals in all countries. It is believed that decreased levels of neurotransmitters such as serotonin, norepinephrine and dopamine are the main cause of depression. Selective serotonin reuptake inhibitors (SSRIs) and norepinephrine reuptake inhibitors (SNRIs), their mechanism is to increase the amount of neurotransmitters in the CNS. Design, synthesis and molecular docking of novel compounds namely amino acetylenic derivatives of aryloxy as isostere for aryloxypropylamine. The reaction of 7-methoxy-2-naphthol with propargylbromide generated 7-methoxy-2-(prop-2-yn-1-yloxy) naphthalene (ZR-1). ZR-1 was subjected to Mannich reaction yielded the derivatives of aryloxybutynylamines (ZR-2 to ZR-7). The Mp, FTIR, ^{1}H-NMR, C^{13}-NMR, DSC, elemental analysis and HPLC were consistent with the assigned structures. The molecular docking results obtained for aminoacetylenic compounds showed that the new novel 7-methoxy-2- {[4-(piperidine) but-2-yn-1-yl]oxy}-naphthalene (ZR-4) provide effective π overlap with binding sites of SERT protein by ionic, hydrogen bonding and overlap of aryl and cyclic amine moieties with the amino acids of transporter protein, which produce the binding energy (-109,69 kcal/mol) for ZR-4 relative to paroxetine (-114.18 kcal/mol), that may lead to promising drug in the treatment of depression.

KEYWORDS: ***Aminoacetylenic, Mannich reaction, Antidepressant, Molecular docking, Isoster, Nucleophilic displacement.***

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INTRODUCTION

Depression is currently conceptualized as a single chronic disease of heterogeneous etiology, which runs from milder forms such as subsyndromal symptomatic depression (SSD), to sever forms of depression including major depression (MD) with melancholic or psychotic features.[1-3] It is believed that the main biochemical theory of depression is the monoamine hypothesis, first proposed by Schildkraut in 1965,[4] which states that depression is caused by functional deficit of monoamine transmitter's serotonin, norepinephrine, and dopamine in the central nervous system.[5-7] In addition, changes in glutamatergic neurotransmission may be involved in depression. The human biogenic amine transporters (BATs) represent important drug targets for the medicinal chemist in drug design for treatment diseases such as depression, anxiety, obesity, drug abuse, obsessive compulsive disorder, attention deficit hyperactivity disorder, and schizophrenia.[8, 9] The BATs includes the serotonin (SERT), norepinephrine (NET) transporters, and dopamine (DAT), responsible for re-uptake the neurotransmitters SERT, NET, and DAT respectively and their function by terminating synaptic signaling.[10-15] Serotonin transporter (SERT) found in the plasma membrane of serotonergic neurons which is responsible for re-uptake of the transmitter. The transporter protein acts as carrier of serotonin molecules across the membrane.[16] Serotonin transporter (SERT) transmembrane ion gradients of Na^+, Cl^-, K^+ and an internal negative membrane potential for transport serotonin.[17] This leads to control extracellular levels of serotonin (5-hydroxytryptamine, 5HT) in the brain by transporting %5HT into neurons and glial cells fall into two gene families. The main target for drugs used for treatment of depressive disorders is the human SERT (hSERT) [18], competitive with a variety of naturally occurring amines and drugs. Drugs which are used as antidepressants block the transport of NE and thereby cause an elevation in the synaptic concentrations of NE and potentiation of the activation of postsynaptic receptors.[19-21] Although details of its mechanism of action remains unknown, NE plays an important role in the CNS. In classifications of antidepressants imipramine, desipramine, amitriptyline, nortriptyline, clomipramine (Figure 1) are widely used, others with different mechanism are used (Figure 2), in spite of the need of other drugs that act more rapidly, produce fewer side effects and are hazardless in overdose. MAOI like phenelzine, tranylcypromine and isocarboxazid are the last new compounds (Figure 3), these drugs cause irreversible inhibition of one or both forms of brain MAOI which lead to increase the cytosolic stores of norepinephrine and 5HT in nerve terminals.[2, 22] Investigation the various drugs structures that are selective, non-selective and miscellaneous antidepressant activity. We envision the design and synthesis of aryloxyaminoacetylenic derivatives as isosteres to aryloxypropylamines. as blocking SSRT or SNRT in the brain, through changing the electronic binding side chain, the basic amino acid group is required for ionic or hydrogen bonding to the corresponding amino acids of the SSRI or SNRI protein, the aromatic ring is to provide lipophilic interaction and π-overlap with aromatic amino acids of SERT or SSRT or both. The newly synthesized compounds may exert drug-drug interaction due to inhibition of cytochrome P450. The docking results verified a possible potent activity of these new novel compounds.

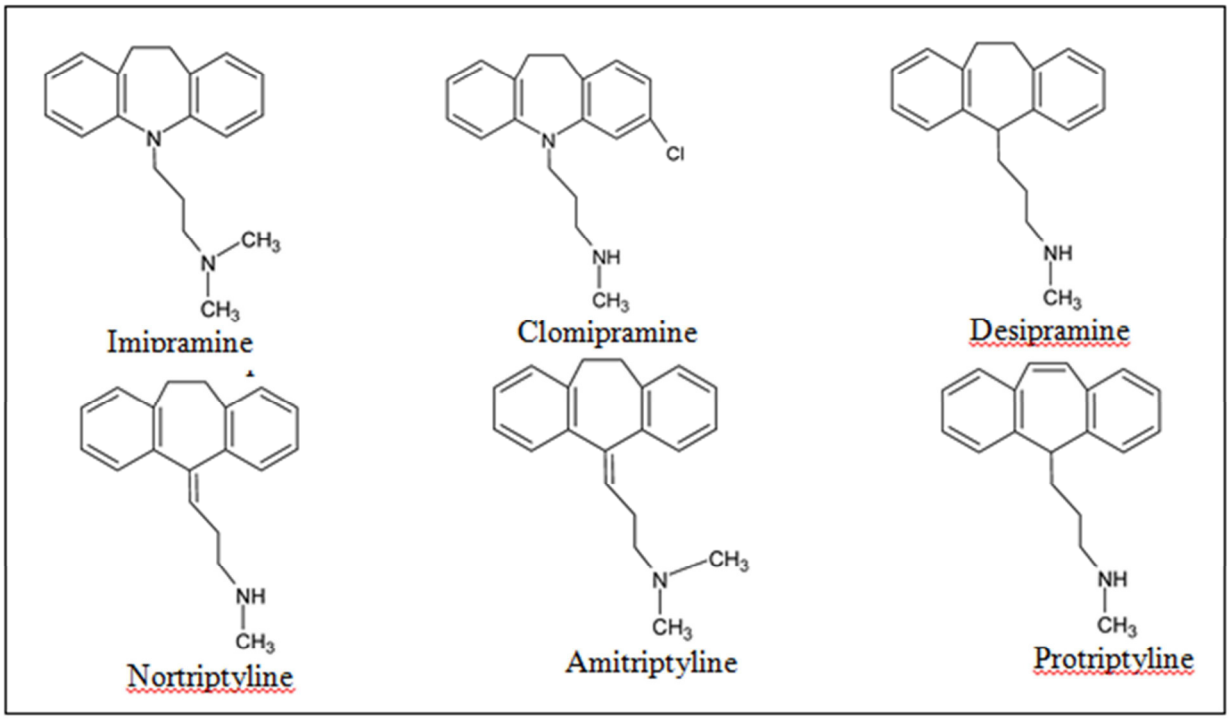


Figure 1
Nonselective antidepressant structures

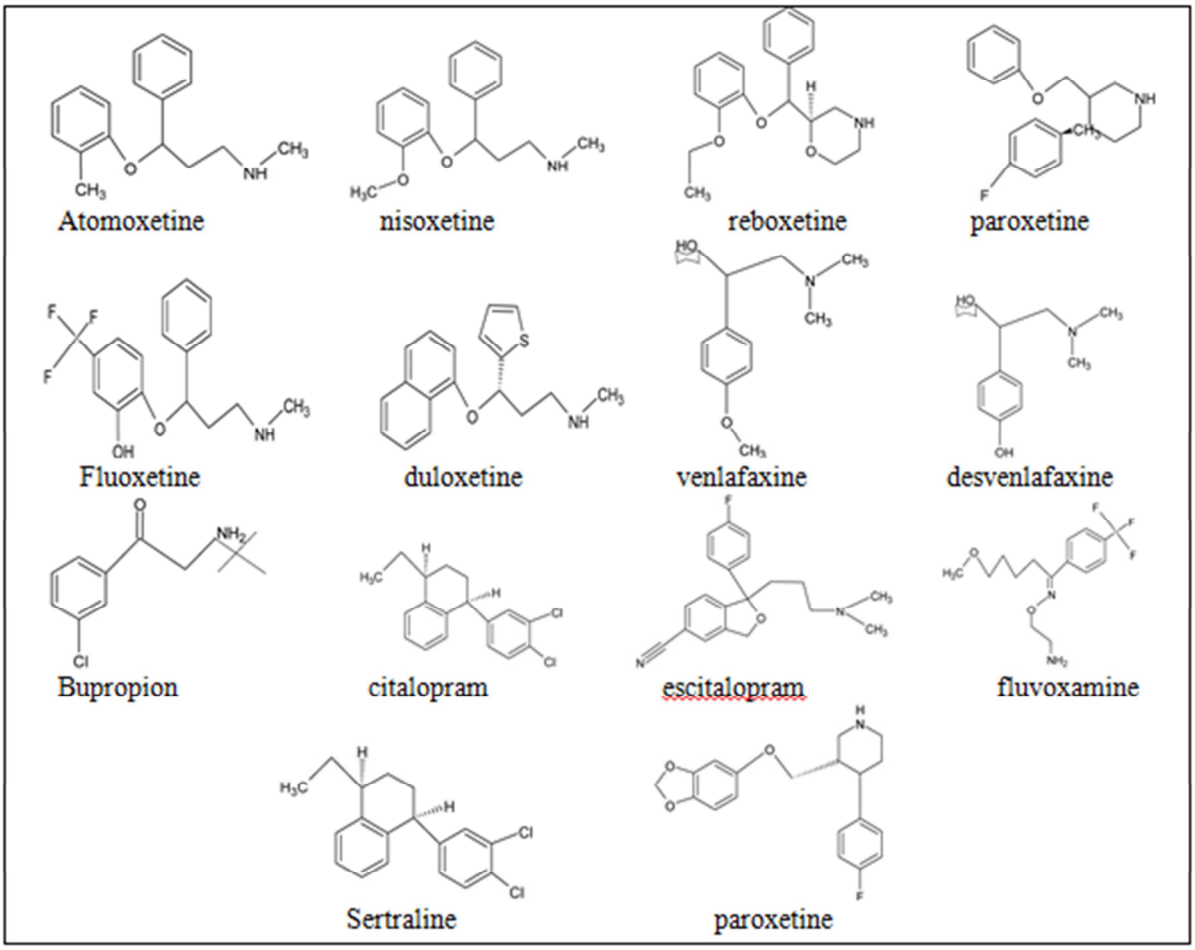


Figure 2
Selective antidepressants

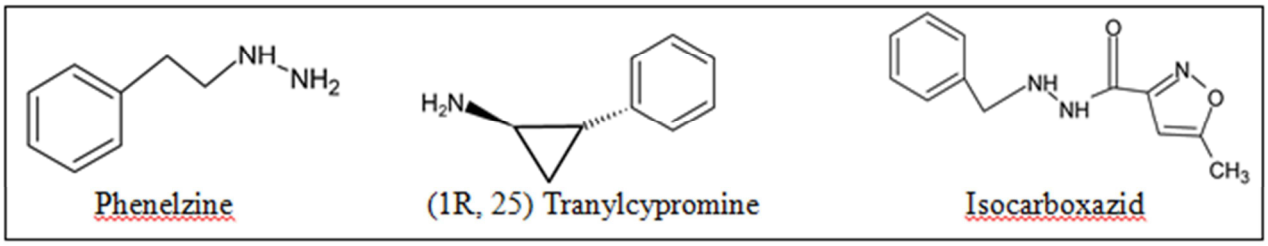


Figure 3
Nonselective antidepressant structures (MAOIs like)

MATERIALS AND METHODS

Chemicals

7-methoxy-2-naphtol, propargyl bromide, cyclic amine, 1-methylpiperazine 99%, 2-methylpiperidine 98%, Cis-2,6-Dimethylpiperidine 98%, hexamethyleneimine (Azepane) 99%, pyrrolidine 99%, piperidine 99% (Sigma Aldrich, USA), potassium carbonate anhydrous (Gainland Chemical Company, UK), potassium hydroxide (Lonover, UK), para formaldehyde polymer (BDH chemicals Ltd Poole, England), potassium bromide (Scharlau, Spain), cuprous chloride LRG (East Anglia Chemicals, Hadleighlpswich), acetonitrile 99.7% (PanReAcQuimca SA, EU), 1,4-dioxane (FULL Time, China), chloroform (TEDIA, USA), dimethyl sulfoxide (DMSO) (BBC Chemicals for lab, EU).

Instrumental

Melting points were determined by using a Gallenkamp Melting Point Apparatus and Differential scanning calorimetry (DSC) thermogram measurement was carried out by using the DSC 1 STARE system v.110x (METTLER TOLEDO). Infrared Spectra (IR) were recorded using WQF-A 520 FT-IR Spectrophotometer, H^1 and C^{13} NMR was acquired with the aid of BRUKER 500 MHZ-AvanceIII Spectrophotometer and DMSO-d_6 as solvent, and TMS as standard (University of Jordan). HPLC (FINNIGAN SURVEYOR) was used, the detector (UV-VIS plus Detector), the pump (LC Pump Plus) and the autosampler (Autosampler Plus). Elemental analysis was indicated by EuroEA 3000 Elemental Analyzer (Euro Vector, University of Hashemite). ChemSKetch was used in the drawing of our schemes.

Molecular docking

A validated homology model of SERT protein by Wang's group[23] was used in our docking study. Chargers were assigned to all proteins atoms using Kollman united atom model in the Autodock Tool program [24-25] then the active sites of SERT was defined by a known inhibitor. Agrid box of a 50 x 42 x 60 size was created, with a grid spacing of 0.375 Å using autogrid modules. Ligand 3D structures were built using the maestro program[26], and were then minimized using the OPLS force field[27]. Gasteiger-Marsili model[28] was used to give atomic charges for all ligands whose tertiary amine groups were assigned as protonated. Subsequently, ligands were docked into previously identified active site using the Autodock software (version 4.2)[29-30], where Lamarckian Genetic Algorithm[29] was employed for the conformational sampling process. Poses generated by docking were then rated by the Autodock scoring function with estimates binding free energy via calculated van der Waals, hydrogen bond, electrostatic interactions, and the ligand internal energy for each ligand-protein complex.

Synthesis

7-methoxy-2-(prop-2-yn-1-yloxy)-naphthalene (ZR-1)

7-methoxy 2-naphthol (3.485 g, 0.020 mol), potassium carbonate anhydrous (2.75 g, 0.020 mol) and 30-40 ml acetonitrile were heated and stirred under reflux until temperature becomes 75 C, then the propargyl bromide (4.76 g, 0.040 mol) was added dropwise. The mixture was stirred under reflux for hour, filtered and reduced under reduced pressure. The product was extracted with 1:1 chloroform and distilled water. The chloroform layers were collected and concentrated by reduced pressure. The brown powder $C_{12}H_{12}O_2$, 2.64g, 61.8% yield, m.p (47° C-51° C), retention time UV HPLC (3.348 min), IR spectra (KBr cm^{-1}): 3274 (acetylenic C-H stretching), 2129 (acetylenic C≡C stretching), 1500,1600 (Ar C=C stretching),, 1031 (ethers C-O stretching), 2954 (CH_3C-H stretching); H^1 NMR (DMSO-d_6): δ(ppm) 3.6 (1H, ≡CH, singlet), 3.8 (3H, of O-CH_3), 4.9 (2H, of O-CH_2, singlet), 7.0-7.8 (6H, Ar H, multiplet). Elemental analysis: for $C_{14}H_{12}O_2$: Calcd: C, 79.22%; H, 5.70%. Found: C, 79.54%; H, 6.02%.

7-methoxy-2-{[4-(t-amino-1-yl) but-2-yn-1-yl] oxy}-naphthalene by Mannich reaction (ZR-2 to ZR-7)

7-methoxy-2-(prop-2-yn-1-yloxy) naphthalene (ZR-1) (2.12 g, 0.01 mole), Paraformaldehyde (0.5 g, 0.015 mole), 0.01 mole cyclic amine and a catalytic amount of cuprous chloride (0.03g) in 30 ml dioxane was added, stirred for three hours under reflux at 70-75 ^{o}C. The mixture concentrated under reduced pressure, filtered and evaporated. The final products were ZR-2 to ZR-7 (Figure 3).

7-methoxy-2-{[4-(2-methylPiperidine) but-2-yn-1-yl] oxy}-naphthalene (ZR-2)

ZR-2 was prepared according to the same procedure described for the synthesis of ZR-2 to ZR-7. Yield 31.00%, m.p (78 ^{o}C-80 ^{o}C), retention time (UV-HPLC (2.247 min)); FT-IR spectrum (KBr cm^{-1}): δ2921, 2835, 2788 (Alkanes C-H stretching), 1604, 1500 (Ar C=C stretching), 821(Ar C-H bending), 1200 (N-C stretching), 1004 (Ar ether C-O stretching). ^{1}H-NMR (DMSO-d_6) δ (ppm): 0.85 (3H, CH_3, doublet), 0.96-2.56 (9H, protons of cyclic amines, multiplet), 3.51-3.54 (2H, ≡C-CH_2-N, singlet), 4.89 (2H, O-CH_2, singlet), 3.81-3.87 (3H, O-CH_3, singlet), 6.95-7.76 (6H, Ar H, multiplet).^{13}C-NMR (DMSO-d_6) δ (ppm): 20.06 (CH_3 of cyclic amine), 43.26, 34.59, 26.17 24.44 (cyclic amine carbons), 52.93 (CH_2N carbon), 54.35 (OCH_3 carbon in benzene ring), 56.17 (OCH_2 carbon), 82.41, 80.53 (C≡C carbons), 158.23, 156.04, 135.91, 129.50, 124.52, 116.53, 106.93 (naphthalene ring carbons). Elemental analysis: for $C_{21}H_{25}NO_2$: Calcd: C, 77.98%; H, 7.79; N, 4.33%. Found: C, 77.83%; H, 7.99%; N, 4.73%.

7-methoxy-2-{[4-(2, 6-dimethyl Piperidine) but-2-yn-1-yl] oxy}-naphthalene (ZR-3)

ZR-3 was synthesized using the same procedure described for the synthesis of ZR-2 to ZR-7. Yield 50.45%, m.p was (97C-102C), retention time using UV-HPLC (2.335 min). FT-IR spectra (KBr cm^{-1}) δ: 3064 (Ar C-H stretching), 2912, 2822 (alkanes C-H stretching), 1621, 1511, 1442 (Ar C=C stretching), 839, 790 (Ar C-H bending), 1022 (aryl, alkyl C-O stretching), 1201, 1115 (3^{o} amines N-C stretching). ^{1}H-NMR (DMSO-d_6) δ (ppm) was: 0.84 (6H, 3H of each branched methyl group on cyclic amine, singlet), 1.02- 2.20 (8H, cyclic amine, multiplet), 3.49 (2H, ≡V-CH_2N, singlet), 3.84-3.91(3H, OCH_3, and singlet), 4.89-4.94 (2H, O-CH_2, singlet), 6.95-7.75 (6H, Ar H, multiplet). ^{13}C-NMR (DMSO-d_6) δ (ppm): 21.19 (CH_3 carbons on cyclic amine), 37.41, 35.19, 24.48 (cyclic amine carbons), 54.92 (CH_2N carbon), 55.53 (OCH_3 carbon on naphthalene ring), 56.23(O-CH_2 carbon), 82.41, 80.53 (C≡C carbons), 158.20, 155.99, 135.89, 129.47, 124.55, 116.58, 107.04 (naphthalene carbons). Elemental analyses for C22H27NO2 were: Calcd: C, 78.03%; H, 8.06; N, 4.15%. Found: C, 78.41%; H, 8.02%; N, 4.34%.

7-methoxy-2-{[4-(Piperidine) but-2-yn-1-yl] oxy}-naphthalene (ZR-4)

ZR-4 was synthesized using the same procedure described for the synthesis of ZR-2 to ZR-7. Yield 38.83%, m.p was (38C-44C), retention time using UV-HPLC was (2.235 min). FT-IR (KBr cm^{-1}) δ: 3056 (Ar C-H stretching), 2927, 2852 (alkanes C-H stretching), 1625, 1521, 1461 (Ar C=C stretching), 1216, 1125 (3^{o} amines N-C stretching), 1022 (aryl, alkyl C-O stretching), 829 (Ar C-H bending). ^{1}H-NMR (DMSO-d_6): δ (ppm) 1.37-3.20 (10H, cyclic amine, multiplet), 3.53 (2H, ≡C-CH_2-N, singlet), 3.86 (3H, O-CH_3, singlet), 4.91 (2H, O-CH_2, singlet), 6.95-7.75 (6H, Ar H, multiplet). Elemental analysis for $C_{20}H_{23}NO_2$ was: Calcd: C, 77.64%; H, 7.49%; N, 453%. Found: C, 77.94%; H, 7.83%; N, 4.88%.

7-methoxy-2-{[4-(Pyrimidine) but-2-yn-1-yl] oxy}-naphthalene (ZR-5)

ZR-5 was synthesized using the same procedure described for the synthesis ZR-2 to ZR-7. Yield 57.63%, retention time using UV-HPLC was (2.16 min), FT-IR (KBr cm^{-1}): 3045 (Ar C-H stretching), 2948 (alkanes C-H stretching), 1621, 1521, 1465 (Ar C=C stretching), 1224, 1137 (3^{o} amines N-C stretching), 1027 (aryl, alkyl C-O stretching), 833 (Ar C-H bending), ,.^{1}H-NMR (DMSO-d_6) δ(ppm) were 1.55-2.40 (8H, cyclic amine, multiplet), 3.53 (2H, ≡C-CH_2-N, singlet), 3.87-3.96 (3H, O-CH_3, singlet), 4.93, 4.88 (2H, O-CH_2, singlet), 6.95-7.75 (6H, Ar H, multiplet). C^{13}-NMR (DMSO-d_6) δ (ppm): 42.89, 23.72 (cyclic amine carbons), 52.13 (CH_2N carbon), 55.47 (OCH_3 on naphthalene), 56.14 (OCH_2 carbon), 82.79, 80.17 (C≡C carbons), 158.21, 156.05, 135.97, 129.60, 124.59, 116.30, 106.74 (naphthalene carbons). Elemental analysis: ($C_{19}H_{21}NO_2$) were**,** Calcd: C, 77.26%; H, 7.17%; N 4.74%. Found: C, 77.67%; H, 7.34%; N, 5.03%.

7-methoxy-2-{[4-(N-methylpiperazine) but-2-yn-1-yl] oxy}-naphthalene (ZR-6)

ZR-6 was synthesized using the same procedure described for the synthesis of ZR-2 to ZR-7. Yield (58.82%) and UV-HPLC retention time: (2.205 min). FT-IR (KBr cm^{-1}): δ 3064 (Ar C-H stretching), 2929 (alkanes C-H stretching), 1506, 1440 (Ar C=C stretching), 829 (Ar C-H bending),

1272 (aryl, alkyl C-O stretching), 1220 (3º amines N-C stretching). ^{1}H-NMR: δ (ppm) 2.09 (3H, of N-CH3, singlet), 2.39-3.255 (8H of cyclic amine, multiplet), 3.53 (2H, ≡C-CH_2-N, singlet), 3.88-3.98 (3H, O-CH3, singlet), 4.94, 4.88, (2H, O-CH_2, singlet), 6.95-7.76 (6H, Ar H). C^{13}-NMR (DMSO-d_6) δ (ppm): 40.3 (N-CH3), 34, 23, 7 (cyclic amine carbons), 52.6 (CH_2), 56.01 (O-CH_2) 81.8, 80.9 (C≡C, carbons), 158.40, 155.11, 136, 21, 124.9, 106.64 (naphthalene carbons). Elemental analysis: $C_{20}H_{24}N_2O_2$ were, Calcd: C, 74.04%; H, 7.46%; N, 8.64%. Found: C, 47.42%; H, 7.85%; N, 8.97%.

7-methoxy-2-{[4-(hexamethyleneimine) but-2-yn-1-yl] oxy}-naphthalene (ZR-7)

ZR-7 was synthesized using the same procedure described for the synthesis ZR-2 to ZR-7. Yield (49.38%) and retention time (UV-HPLC (2.205 min)). FTIR (KBr cm^{-1}): δ 3066 (Ar C-H stretching), 2931,2854 (alkanes C-H stretching), 1517, 1457 (Ar C=C stretching), 856, 839 (Ar C-H bending), 1224 (aryl, alkyl C-O stretching), 1027 (3º amines N-C stretching).^{1}H-NMR: δ (ppm) 1.40-3.31 (12H of cyclic amine, multiplet), 3.53 (2H, ≡C-CH2-N, singlet), 3.82 (3H, O-CH3, singlet), 4.88 (2H, O-CH2, singlet), 6.95-7.76 (6H, Ar H). C^{13}-NMR (DMSO-d_6) δ (ppm): 36.1 (N-$(CH_2)_2$ of the imine), 34.8 (CH_2-cyclic imine), 52.42 (CH_2N), 56.7 (O-CH_2), 82.0, 81.1 (C≡C), 157.2, 136.11, 124.6, 106.44 (naphthalene cabons). Elemental analysis: **$C_{21}H_{25}NO_2$** were, Calcd: C, 77.98; H, 7.79%; N, 4.33%. Found: C, 78.29%; H, 7.63%; N, 4.63%.

RESULTS AND DISCUSSION

Chemistry

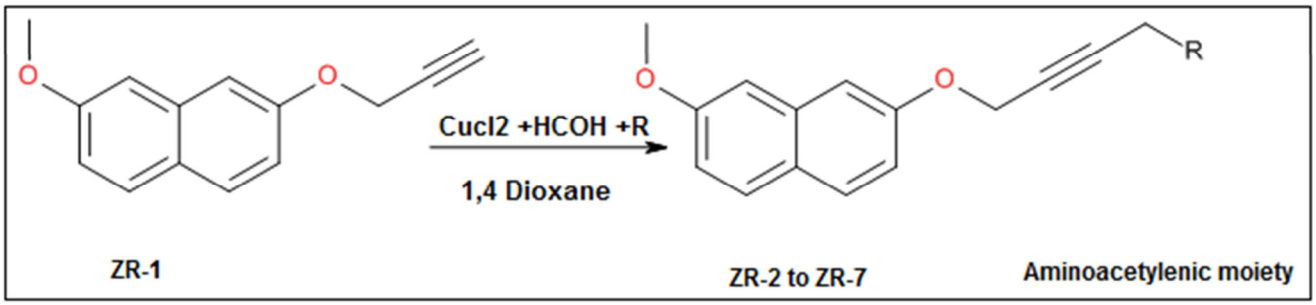
Compounds (ZR-2 to ZR-7) were prepared from ZR-1 as illustrated in figure 3. ZR-1 was synthesized through the formation of phenolate anion that displaces the bromine on β-carbon of propargyl bromide to afforded 7-methoxy-2-(prop-2-oxy)-naphthalene (ZR-1). ZR-1 was subjected to Mannich reaction that involves first condensation of formaldehyde with the cyclic amine, followed by loss of water and the formation of Schiff base. The attack of the acetylenic anion of the methoxy-2-(prop-2-yn-1-yloxy) on the carbon double bond of the imine (Schiff base) to generate the desired compounds (ZR-2 to ZR-7).

Molecular Docking

The design compounds as SERT blockers are based on isoteric concept of the important criteria needed to overlap effectively with SERT protein to induce reuptake inhibition activity. These criteria are

A- The basic cyclic amine is required for ionic and hydrogen interactions.
B- The unique acetylenic moiety required to accommodate for electronic interaction with amino acid of the protein transporter.
C- The oxy group for hydrogen bonding.
D- 2-butyne to provide the appropriate distance between the basic cyclic amine and the oxy group of naphthol moiety.
E- The naphthol ring generates appropriate π-overlap with SERT to strengthen reuptake inhibitors activity.

Studies of SERT protein binding sites illustrate the importance of hydrogen bonding, electrostatic interaction and hydrophobic interactions, to inhibit the action of SERT. In a comparison between the docking binding modes of paroxetine and ZR-4 compound (figure 4 a, b). It was obvious that the amine group of the SSRI paroxetine form direct hydrogen bonds with main chain carbonyl groups of Tyr21, Ala22 and Ser254. While the benzodioxol group of paroxetine insert in to a groove forming hydrophobic interactions with Val104, Tyr108 and Ser355, and/or van der Waals interactions with the main chain carbonyl groups of Ser354 and Gly359 amino acid. In addition, the fluorophenyl ring of paroxetine forming hydrophobic interactions, van der Waals contacts and hydrogen bonding interactions with Tyr107, Phe253, Asp404 and/or Val104 amino acid. In contrast, the amine group of our compound ZR-4 form direct hydrogen bonds with main chain carbonyl group of Ala22, Ser254, and Phe253. While the naphthalene ring insert into the same groove formic hydrophobic interaction with Val105, Tyr108, and/or van der Waals interaction with main chain carbonyl groups of Ser354 and Gly359 amino acid. The acetylenic 2-butyne seems to act as an appropriate spacer in linking a protonated amino group and naphthalene ring to inhibit reuptake process of SERT as shown in table 4 and figure 4a-b.Therefore, docking of our compounds, which they are belong to aryloxybutynylamine, along with the co-crystal ligand, paroxetine, into the binding sites of SERT protein domain has resulted in energetically favorable binding modes (table 4.1). ZR-4 (binding energy= -109.69 kcal/mol) has the lowest binding energy, although it is higher than the famous SSRI paroxetine (binding energy= -114.18 kcal/mol). These results verify our approach in the design of antidepressant compounds.



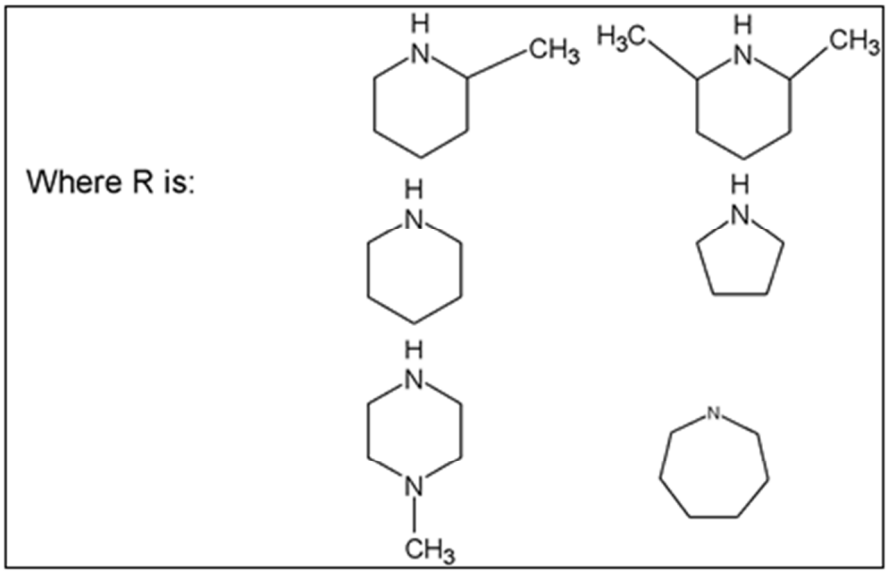


Figure 3

Synthesis of 7-methoxy-2- {[4-(amino-1-yl) but-2-yn-1-yl] oxy}-naphthalene (ZR-2 to ZR-7)

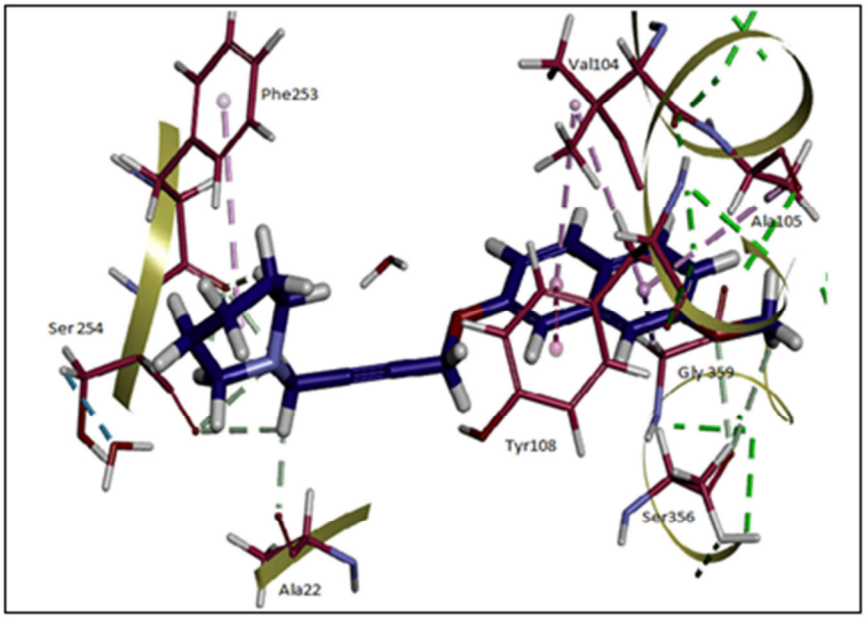


Figure 4a

Shows the binding mode demonstrated by ZR-4 (the blue stick) in the active site of SERT (golden), the interaction ligands were expressed by dashed lines while the hydrogen bindings were in (gray), ionic interactions were (green) and pi –overlaps were (purple).

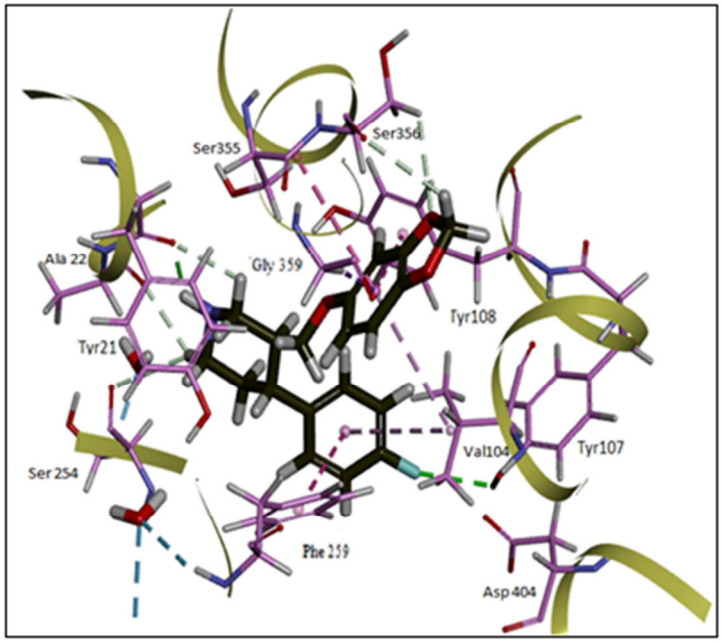
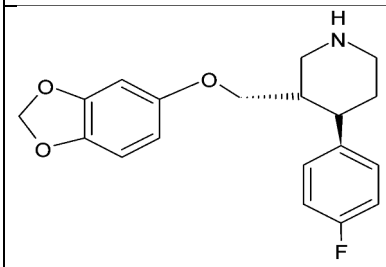


Figure 4b

Shows the binding mode demonstrated by paroxetine (brown) in the active site of SERT (golden), the interaction ligands were expressed by dashed lines while the hydrogen bonding (gray), the ionic bonding (green), and the pi- overlap (purple).

Table 4

Binding energies of our docked compounds into the active binding site of SERT protein.

Molecule	Autodock score (kcal/mol)
 **Paroxetine**	-114.18
ZR-2	-102.76
ZR-3	-103.46
ZR-4	-109.69
ZR-5	-106
ZR-6	-95.83
ZR-7	-106.79

CONCLUSION

The synthesis and characterization of the new series of 7-methoxy-2-{[4-(t, amino-1-yl) but-2-yn-1-yl] oxyl}naphthalene (ZR-2 to ZR-7) were accomplished. Docking of the new amino acetylenic-7-methoxynaphthalene compounds showed promising approach for synthesis of compounds which may be of potential use in treatment of diseases such as depression, ADHD, bipolar depression. Obesity.

AUTHOR CONTRIBUTION STATEMENT

Prof. Zuhair Muhi-eldeen conducted and conceived the design of the compounds and supervised the reaction of synthesis, Prof. Elham Alkaissi, Ibrahim Al-Adham Dr. Najah Al-Muhtaseb wrote and analyzed the data, Dr. Mohammed Ghattas did the molecular docking, Dr. Rana Abu-Safiah carried out the chemical reaction and the draft writing.

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CONFLICT OF INTEREST

Conflict of interest declared none.

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