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SYNTHESIS AND BIOLOGICAL ACTIVITY OF NOVEL ISO-QUINOLINE BASED 1, 2, 4-TRIAZOLE DERIVATIVES

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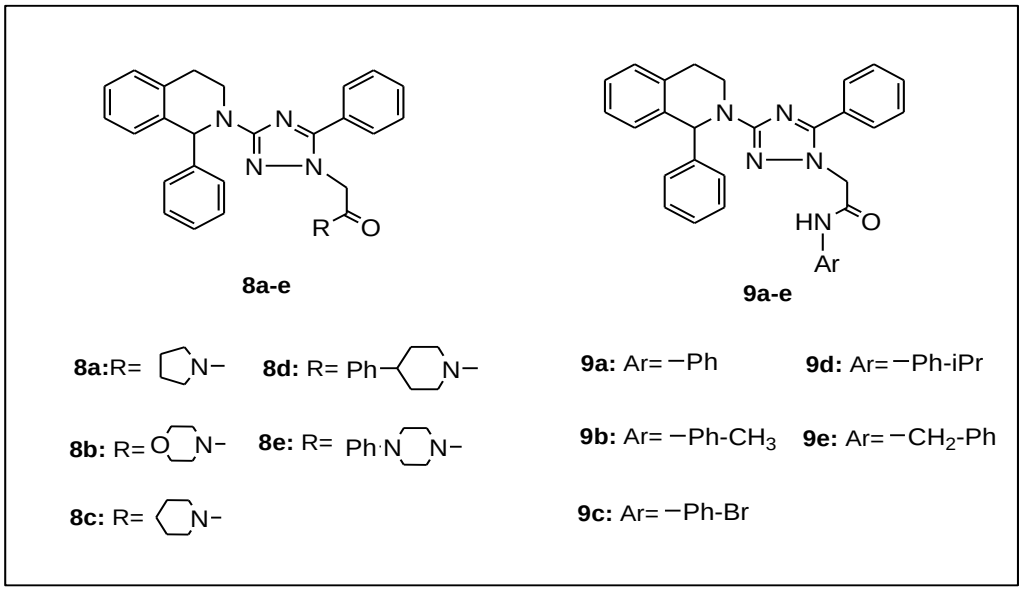


ABSTRACT

Triazole frame is ever-present in pharmaceutically important Compounds. A novel series of quinoline containing triazole with different amides are described, which exhibit antibacterial and antifungal activities. The chemical synthesis strategies employed, complete characterization of the compounds, there in vitro screening and the promising activity as reflected in the MIC values are reported.

INTRODUCTION

The heterocyclic are enjoying their importance as being the center of activity. The nitrogen containing heterocyclic compounds are found in abundance in most of the medicinal compounds. The synthesis of compounds containing 1, 2, 4-triazole rings in their structure have attracted wide spread attention, mainly in connection with their wide range of pharmacological properties. Triazole and its derivatives have distinct status as pharmaceutical agents. A variety of biological activities, such as anti-inflammatory [1], analgesic [2], antibacterial,[3] antifungal [4-6] antitubercular [7], antiviral [8], antimalarial [9], antihypertensive [10], antihyperuricemic [11] antitumor [12]anticonvulsant [13] and antidepressant [14]anticancer agents [15,16]. The new synthesized compounds were characterized by IR, ^{1}H NMR, mass spectrometry, and elemental analysis. Results of biological activities indicate some of compounds possess potential antimicrobial activity.

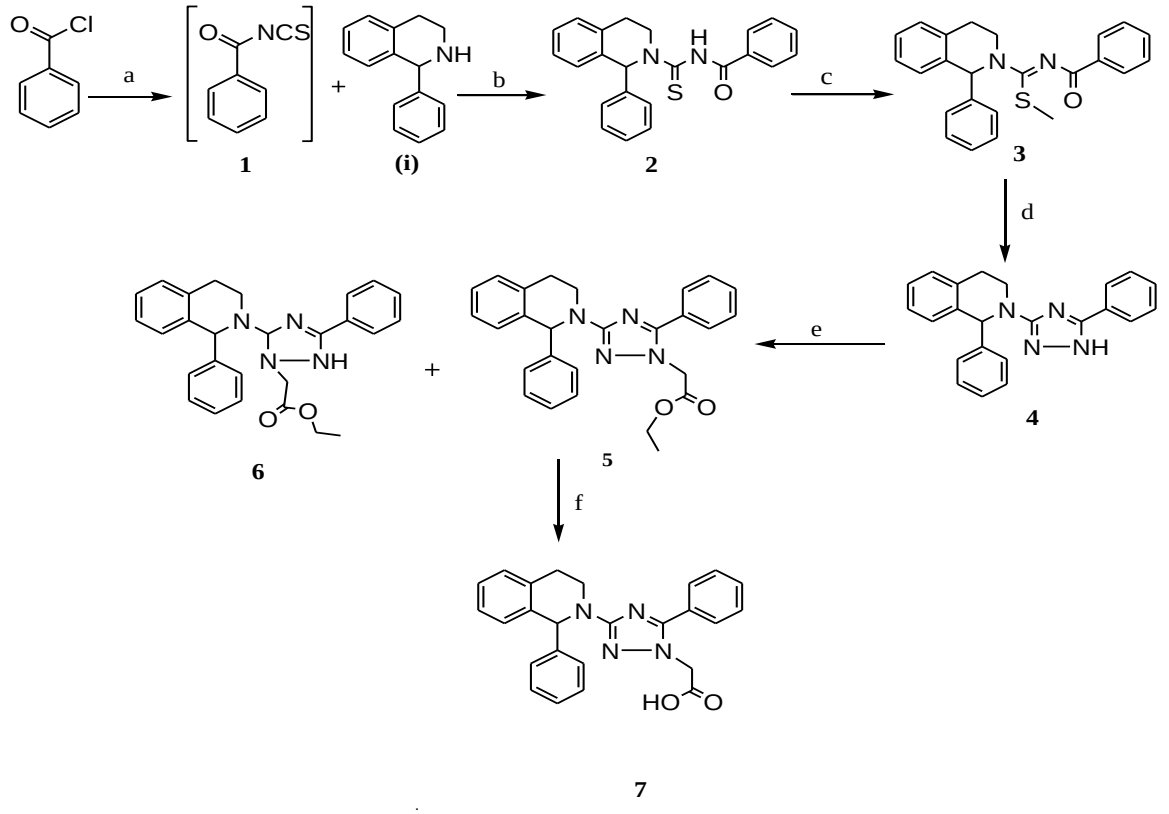
Developing new antimicrobial agents (antibacterial and antifungal) continues to attract attention and is an area of scrupulous research. In spite of a large number of antibiotics and chemotherapeutics presented for medical use, the antimicrobial resistance created a ample need of new class of antimicrobial agents in the last decades [17-19].

During the latest few decades, much attention has been paid to the synthesis of 1*H*-1, 2, 4-triazole derivatives. 1, 2, 4-Triazole scaffold is the structural element of many drugs that have different pharmacological activity. The following 1, 2, 4-triazole derivatives are applicable in medicine: alprazolam (tranquilizer), trazodone (antidepressant, anxiolytic), nefazodone (antidepressant, 5-HT2 A-antagonist), anastazole (antineoplastic, non-steroidal aromatase inhibitor), ribavirin (antiviral), fluconazole, itraconazole and terconazole (antifungal). 1,2,4-Triazoles and their heterocyclic derivatives represent an interesting class of compounds which possess a wide range of biological activities .The 1,2,4-triazole nucleus is associated with diverse pharmacological activities such as antibacterial, Antifungal, antihypertensive and analgesic properties.

RESULTS AND DISCUSSION

Chemistry

The synthetic approach involved synthesis of intermediate and target compounds is outline in **Schemes 1, 2**. The key intermediate [5-Phenyl-3-(1-phenyl-3,4-dihydro-1H-isoquinolin-2-yl)-[1,2,4]triazol-1-yl]-acetic acid **7** was prepared as outline in **Scheme 1** [20-21]. Benzoyl chloride reacted with ammonium thiocyanate to obtained benzoyl thiocyanate **1**, which was treated in-situ with iso-quinoline to provide the addition product N-benzoyl thiourea **2** [22]. The addition product 2 was methylated by methyl iodide to produced N-benzoyl-S-methylisothiurea **3**, which was further cyclized with hydrazine hydrated in refluxing ethanol to give the triazole **4**. The triazole 4 was alkylated by ethyl bromoacetate in the presence of sodium hydride in dry THF to afford two regioisomers **5** and **6**. The isomer **5** was hydrolyzed in presence of aqueous LiOH to give the corresponding acid derivative **7**, which was employed as a key intermediate for synthesis of target compounds.



Scheme-1

Scheme 1. Reagent and condition; **(a)** ammonium thiocynate,acetone,56^{o}C, 30 min; **(b),** acetone 56^{o}C, 60 min; (i) 1-Phenyl-1,2,3,4-tetrahydro-isoquinoline **(c)** methyl iodide, anhydrous K_2CO_3,DMF, room temperature,60 min**;(d)**

Hydrazine hydrate, ethanol, reflux, 5h **(e)** ethyl bromoacetate , NaH, THF, room temperature, 4h; **(f)** Aq,LiOH.H_2O,THF-methanol, room temperature 5h.

The two regioisomers 5 and 6 were separated by chromatography on silica gel, and the regioisomer [5-Phenyl-3-(1-phenyl-3, 4-dihydro-1H-isoquinolin-2-yl)-[1, 2, 4] triazol-1-yl]-acetic acid ethyl ester 5 was the major product. The structures of these two regioisomers 5 and 6 were assigned based on NMR analysis and confirmed by NOE NMR experiments [23] **(Figure 1).**

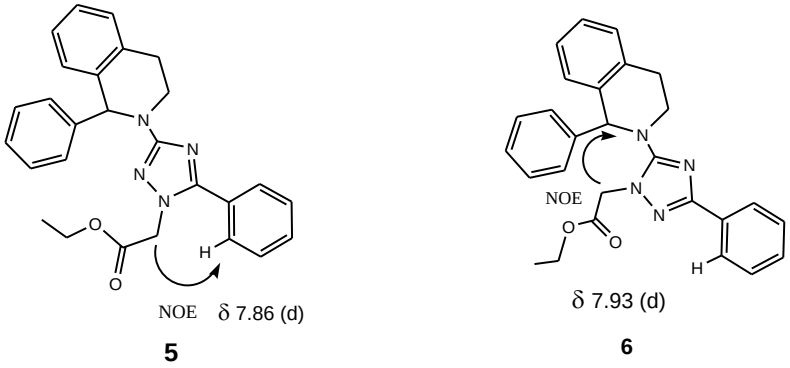
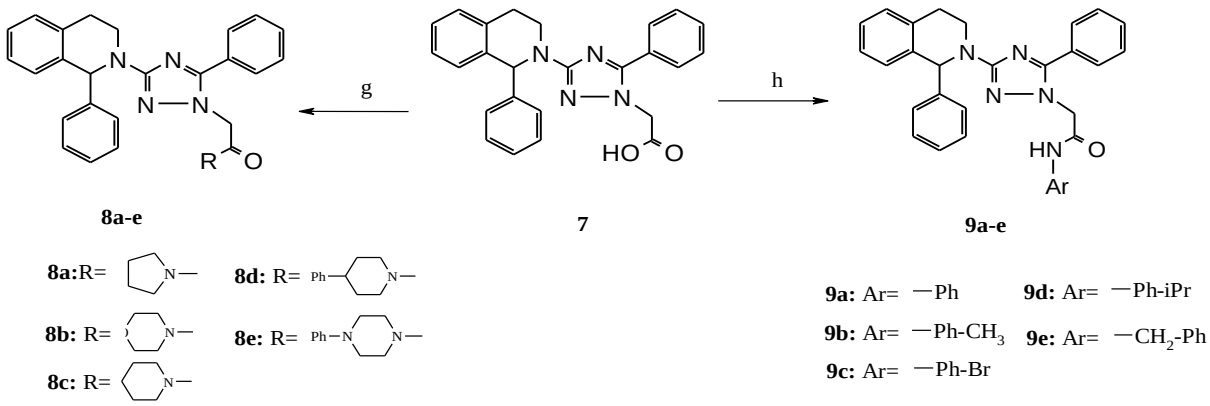


Figure 1

Figure 1.NOE was observed between I-methyl and ortho-proton of compound **5** and between I-methelene and N-methelene group of compound **6**. Chemical shift of ortho-hydrogen of phenyl in compound **6** was more downfield because of extra from the triazole ring.

The synthesis of target compounds **8a-e** and **9a-e** is outline in **Scheme 2**. The amide coupling of [5-Phenyl-3-(1-phenyl-3,4-dihydro-1H-isoquinolin-2-yl)-1,2,4]triazol-1-yl]-acetic acid **7** was carried out with different amines in presence of EDCI in THF at room temperature with excellent yield.



Scheme-2

Scheme 2: Reagents and conditions. **(g)** Corresponding secondary cyclic amine, EDCI, DIPEA, THF, rt, 5-10 h. **(h)** corresponding aromatic amine, EDCI, DIPEA, THF, rt, 5-8 h.

The structures of all the intermediates and final compounds **8a-e** and **9a-e** were established on basis of elemental analysis and spectrographic (IR, ^{1}H NMR, and Mass) data. The physical characterization data are listed in **Table 1.**

Table 1

Physical characterization data of compounds **8a-e** and **9a-e**

Compound	Physical state	Time hours	Mp ^{0}C	Yield %	Molecular Formula/M.W
8a	Off-white crystal	5	185-189	77	$C_{29}H_{29}N_5O$ 463
8b	Off-white crystal	5	183-186	73	$C_{29}H_{29}N_5O_2$ 479
8c	Off-White crystal	4	136-141	69	$C_{30}H_{31}N_5O$ 477
8d	White crystal	5	188-191	78	$C_{36}H_{35}N_5O$ 553
8e	White crystal	4	175-179	75	$C_{35}H_{34}N_6O$ 554
9a	White crystal	4	187-192	70	$C_{31}H_{27}N_5O$ 485
9b	Off-White crystal	5	177-181	75	$C_{32}H_{29}N_5O$ 499

9c	Off-White crystal	6	198-202	79	$C_{31}H_{26}BrN_5O$ 564
9d	Off-white crystal	5	186-188	69	$C_{35}H_{35}N_5O$ 541
9e	White crystal	4	202-207	78	$C_{32}H_{29}N_5O$ 499

Biological Activities

The newly synthesized derivatives were evaluated for their in-vitro antibacterial activity against Gram-negative *E. coli, P. aeruginosa,* Gram-positive *S. aureus, S. pyogenes*, and antifungal activity against C. *albicans and A. niger* by micro broth dilution methods [24-26]. The standard strains used for screening of antibacterial and antifungal activities were procured from Institute of Microbial Technology (IMTECH), Chandigarh, India. The MIC values are given in **Table 2**. The standard drug used for antibacterial activity was ciprofloxacin, and nystatin for antifungal activity.

Mueller Hinton Broth was used as nutrient medium for bacteria and sabouraud dextrose broth for fungal to grow. Inoculum size for test strain was adjusted to 108 CFU/ml by comparing the turbidity.

The serial dilutions were prepared in primary and secondary screening. The target compounds and standard drugs were dissolved in DMSO water at a concentration of 2.0 mg/ml. In primary screening, 500 µg/ml, 250 µg/ml and 125 µg/ml concentrations of the synthesized drugs were taken. Data were not taken for the initial solution because of the high DMSO concentration (10 %). The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. In secondary screening, the drugs found active in primary screening were similarly diluted to obtain 100 µg/ml, 50 µg/ml, 25 µg/ml, 12.5 µg/ml and 6.250 µg/ml concentrations. The inoculated wells were incubated overnight at 37 °C in a humid atmosphere overnight. The highest dilution showing at least 99 % inhibition zone is taken as MIC.

Table 2

Antimicrobial activity data of newly synthesized compounds **8a-e** and **9a-e**

Compounds	Antibacterial MIC in µg/ml				Antifungal MIC in µg/ml	
	E.coli MTCC 443	*P. aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442	*C. albicans* MTCC 227	*A. niger* MTCC 82
9a	100	100	100	500	1000	500

9b	200	62.5	125	250	1000	1000
9c	62.5	125	62.5	250	500	1000
9d	100	100	250	500	500	500
9e	100	100	100	125	1000	1000
10a	200	500	200	250	500	1000
10b	250	500	500	500	1000	1000
10c	200	200	250	200	1000	1000
10d	500	500	500	125	200	200
10e	500	250	500	500	500	500
Ciprofloxacin	25	25	50	50	-	-
Nystatin	-	-	-	-	100	100

Results of antibacterial and antifungal activities of screened compounds indicate that some compounds possess comparable antibacterial activity with respect to reference drug ciprofloxacin. Compounds **8a-e** with secondary amide functionality exhibited moderate to excellent activity against all the tested bacteria strains, but not showed satisfactory activity against fungal strains. Compound **8a** exhibited excellent activity against *E. coli*, while moderate activity against *P. aeruginosa* and *S. aureus*. Compound **8b** showed very good active against *P. aeruginosa* only, while compound **8c** exhibited moderate activity against all the tested bacteria except *S. pyogenes*. Compound **8e** showed excellent activity against *S. aureus* and moderate activity against all other tested bacteria. While the other series with aromatic amide functionality, compounds **9a-e** did not show comparable inhibition with any tested bacterial and fungal organisms.

EXPERIMENTAL

Melting points were determined with a Buchi B-545 melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer PE-1600 FTIR spectrometer in KBr disc. ^{1}H NMR spectra were recorded on a Varian 400 spectrometer in DMSO-d_6 as a solvent and TMS as an internal standard. Peak values are shown in δ ppm. EI-MS spectra were measured on a Waters mass spectrometer. Progress of the reaction was checked by thin layer chromatography (TLC) on silica gel coated aluminum sheets (silica gel 60 F254) using a mixture of ethyl acetate

and hexane (5:5 v/v). All of the solvents and materials were reagent grade and purified as required.

N-(1-Phenyl-3,4-dihydro-1H-isoquinoline-2-carbothioyl)-benzamide (2). To a solution of Ammonium thiocynate NH_4SCN (2.00 g, 0.026 mole) in acetone (25 mL) was added slowly benzoyl chloride 3.37 g (0.024 mole) under dry condition within 10 min. After completion of addition reaction mixture was refluxed for 15 min. A solution of 1-Phenyl-1, 2, 3, 4-tetrahydro-isoquinoline (5.0 g, 0.024 mole) in acetone (30 mL) was added to above stirred suspension at such a rate that reflux gently. Reaction mixture was cooled to room temperature and poured in to water; resulting white solid was filtered and washed with water. Solid was recrystallized in ethanol giving pure compound **2** as off-white solid. 7.65 g (86.0 %), mp 152-155 °C; ^{1}H-NMR (DMSO-d_6) : δ 3.14-3.22 (t, 2H, CH_2, J=8.5 Hz), 2.38-2.93 (t, 2H, CH_2, J=8.6 Hz), 4.88-4.96 (s, 1H, CH), 6.99-7.23 (m, 2H, ArH), 6.86-7.24 (d, 1H, ArH), 7.44-7.59 (m, 3H, ArH), 7.86-7.78 (m, 3H, ArH), 7.15-7.28 (m, 3H, ArH), 6.92-7.05 (d, 2H, ArH),12.3 (br.s, 1H, NH, deuterium oxide exchangeable); ms: *m/z* 374 (M+1). *Anal*. Calc. for $C_{23}H_{20}N_2OS$: C, 74.16; H, 5.41; N, 7.52 Found: C, 74.18; H, 5.39; N, 7.54.

N-[Methylsulfanyl-(1-phenyl-3, 4-dihydro-1H-isoquinolin-2-yl)-methylene]-benzamide (3). Methyl iodide (2.93 g, 0.020 mole) was added to a stirred suspension of compound **2** (7.0 g, 0.018 mole) and anhydrous K_2CO_3 (3.68 g, 0.026 mole) in DMF (50 mL) and stirred for 1 h at room temperature. Reaction mixture was poured in water (200 mL) and stirred for 15 min. The resulting off-white solid was filtered, washed with water and dried under vacuum. Solid was crystallized from rectified spirit gave compound **3** as off-white solid. 6.17 g (85.0 %), mp 114-116 ºC; ^{1}H NMR (DMSO-d_6): δ 2.234 (s, 3H, CH_3); 3.17-3.25 (t, 2H, CH_2, J=8.5 Hz), 4.17-4.25 (t, 2H, CH_2, J=8.5 Hz), 4.95-5.03 (S, 1H, CH), 7.02-7.20 (m, 2H, ArH), 7.28-7.32 (d, 1H, ArH), 7.41-7.56 (m, 3H, ArH), 8.02-8.09 (m, 3H, ArH); 7.15-7.28 (m, 3H, ArH), 6.92-7.05 (d, 2H, ArH) ; ms: m/z 387.81 (M+1). *Anal*. Calcd. For $C_{24}H_{22}N_2OS$: C, 74.58; H, 5.74; N, 7.25 Found: C, 74.56; H, 5.76; N, 7.23.

1-Phenyl-2-(5-phenyl-1H-[1, 2, 4] triazol-3-yl)-1, 2, 3, 4-tetrahydro-isoquinoline (4). A solution of compound **3** (6.0 g,0.017 mole) and hydrazine hydrate (1.35gm ,0.05 mole) in

ethanol (50 mL) was at reflux for 5h, cooled, and poured into water (100 mL), and the mixture was stirred at room temperature. The resulting white solid was collected by filtration and washed with water gave crude compound **4**. The solid was recrystallized in ethanol gave pure compound **4** as white solid. 4.37 g (80 %), mp 148-151 ºC; ^{1}H NMR (DMSO-d_6): δ 3.16-3.25 (t, 2H, CH_2, J=8.2 Hz), 3.92-4.01 (t, 2H, CH_2, J=8.2 Hz), 4.95-5.03 (S, 1H, CH), 6.72-6.81 (t, 1H, ArH), 6.92-7.05 (d, 2H, ArH) 7.13-7.21 (m, 2H, ArH), 7.49-7.53 (m, 3H, ArH), 7.15-7.28 (m, 3H, ArH), 7.69-7.73 (m, 2H,ArH), 7.81-7.86 (m, 1H, ArH), 12.9 (s, 1H, NH); ms: m/z 353.05 (M+1). *Anal*. Calcd. For $C_{23}H_{20}N_4$: C, 78.38; H, 5.72; N, 15.90 Found: C, 78.39; H, 5.74; N, 15.88.

[5-Phenyl-3-(1-phenyl-3, 4-dihydro-1H-isoquinolin-2-yl)-[1, 2,4]triazol-1-yl]-acetic acid ethyl ester (5) and [3-Phenyl-5-(1-phenyl-3, 4-dihydro-1H-isoquinolin-2-yl)-[1, 2, 4] triazol-1-yl]-acetic acid ethyl ester (6). A solution of compound **4** (4.3g, 0.012 mole) in dry THF was treated with NaH 0.732 g at room temperature for 20 min, followed by ethyl bromoacetate (2.28 g, 0.011 mole). The reaction mixture was stirred for 4 h at room temperature, and TLC indicated two products. The mixture was evaporated and the product was separated by chromatography on silica gel (20 % Ethyl Acetate/hexane) to afford **5** and **6.**

5: The major product, white solid, 3.37 g (63 %), mp 172-175 ºC; ^{1}H-NMR (DMSO-d_6): δ 1.28-1.30 (t, 3H, CH_3, J=7.10 Hz), 3.17-3.20 (t, 2H, CH_2, J=8.30 Hz), 4.02-4.06 (t, 2H, CH_2, J=8.30 Hz), 4.11-4.13 (q, 2H, CH_2, J=7.11 Hz), 4.99 (s, 2H, CH_2), 4.95-5.03 (S, 1H, CH), 6.77-6.81 (t, 1H, ArH), 6.92-7.05 (d, 2H, ArH) 7.11-7.15 (t, 1H, ArH), 7.17-7.19 (d, 1H, ArH), 7.55-7.57 (m, 3H, ArH), 7.15-7.28 (m, 3H, ArH), 7.70-7.73 (m, 2H, ArH), 7.84-7.86 (d, 1H, ArH); ms: m/z 439.2 (M+1). *Anal*. Calcd. For $C_{27}H_{26}N_4O_2$: C, 73.95; H, 5.98; N, 12.78 Found: C, 73.93; H, 5.96; N, 12.76.

6: The minor product, white solid, 0.53 g (10 %), mp 182-185 ºC; ^{1}H-NMR (DMSO-d_6): δ 1.27-1.29 (t, 3H, CH_3, J=7.10 Hz), 3.14-3.16 (t, 2H, CH_2, J=8.25 Hz), 3.28-3.34 (m, 2H, CH_2), 4.10-4.12 (q, 2H, CH_2, J=7.10 Hz), 4.99-5.10 (S, 1H, CH), 5.05 (s, 2H, CH_2), 6.85-6.89 (t, 1H, ArH), 6.85-6.96 (d, 2H, ArH) , 7.13-7.52 (m, 3H, ArH), 7.17-7.19 (t, 1H, ArH), 7.22-7.24 (t, 1H, ArH), 7.57-7.60 (m, 3H, ArH), 7.77-7.79 (m, 2H, ArH), 7.91-7.93 (dd, 1H, ArH); ms: m/z 439 (M+1). *Anal*. Calcd. For $C_{27}H_{26}N_4O_2$: C, 73.95; H, 5.98; N, 12.78 Found: C, 73.92; H, 5.97; N, 12.77.

[5-Phenyl-3-(1-phenyl-3, 4-dihydro-1H-isoquinolin-2-yl)-[1, 2, 4] triazol-1-yl]-acetic acid (7). A solution of compound **5** (3.30g, 0.0075 mole) in THF-MeOH (20:20 mL) was treated with LiOH.$H_2$0 (0.63g, 0.015 mol) at room temperature for 5 h and the mixture was evaporated under vacuum. Water (50 mL) was added to residue and washed with ethyl acetate (20 mL). Aqueous layer was acidified to pH-4 by adding dil HCl and resulting precipitate was filtered, washed with water and dried under vacuum gave compound **7** as white solid. 2.50 g (81 %), mp 203-205 ºC; ^{1}H-NMR (DMSO-d_6): δ 3.13-3.21 (t, 2H, CH_2, J=8.31 Hz), 4.00-4.08 (t, 2H, CH_2, J=8.31 Hz), 4.98-5.08 (S, 1H, CH), 4.99 (s, 2H, CH_2), 6.75-6.83 (t, 1H, ArH), 6.95-7.03 (d, 2H, ArH) 7.10-7.20 (m, 2H, ArH), 7.10-7.16 (m, 3H, ArH), 7.54-7.57 (m, 3H, ArH), 7.70-7.74 (m, 2H, ArH), 7.84-7.88 (d, 1H, ArH), 13.51 (s, 1H, COOH); ms: m/z 411 (M+1). *Anal*. Calcd. For $C_{25}H_{22}N_2O_2$: C, 73.15; H, 5.40; N, 13.65 Found: C, 73.18; H, 5.49; N, 13.66.

General procedure for synthesis of compound (8a-e) and (9a-e). A stirred solution of compound **7** (0.487 mmole), corresponding amino derivative (0.535 mmole), and diisopropylethylamine (0.974 mmole) in anhydrous THF (10 mL) was cooled to 0 ºC. EDCI (0.584 mmole) was added to above; the resulting solution was stirred at room temperature 5-7 h. The reaction mixture was evaporated under vacuum, water (50 mL) was added to residue, and acidified to pH-4 by adding dil HCl. The solid separated was collect filtration, washed with water and dried. Compound was re-crystallized from 95 % ethanol gave pure compound **(8a-e), (9a-e)**. The yield, reaction time and physical properties are reported in **Table 1**.

2-[5-Phenyl-3- (1-phenyl-3,4-dihydro-1H-isoquinolin-2-yl)-[1,2,4]triazol-1-yl]-1-pyrrolidin-1-yl-ethanone (8a). IR (KBr) υ (cm^{-1}): 1675 (C=O); ^{1}H NMR (DMSO-d_6): δ 2.12-2.20 (m, 4H, $2CH_2$), 3.12-3.23 (t, 2H, CH_2, J=8.25 Hz), 3.41-3.63 (m, 4H, $2CH_2$), 3.91-4.00 (t, 2H, CH_2, J=8.25 Hz), 4.95-5.00 (S, 1H, CH), 5.21 (s, 2H, CH_2), 6.78-6.80 (t, 1H, ArH), 6.85-6.96 (d, 2H, ArH),7.13-7.52 (m, 3H, ArH),7.13-7.19 (m, 2H, ArH), 7.52-7.55 (t, 3H, ArH), 7.66-7.80 (m, 2H, ArH), 7.85-7.90 (dd, 1H, ArH); ms: m/z 464.3 (M+1). *Anal*. Calcd. For $C_{29}H_{29}N_5O$: C, 75.14; H, 6.31; N, 15.11 Found: C, 75.16; H, 6.30; N, 15.10.

1-Morpholin-4-yl-2-[5-phenyl-3-(1-phenyl-3,4-dihydro-1H-isoquinolin-2-yl)-[1,2,4]triazol-1-yl]-ethanone (8b). IR(KBr) υ (cm^{-1}): 1698 (C=O); 3410(-N-H Str. of –CONH) ^{1}H NMR (DMSO-d_6): δ 3.11-3.25 (t, 2H, CH_2, J=8.20 Hz), 3.45-3.68 (m, 8H, $4CH_2$), 3.99-4.05 (t, 2H, CH_2, J=8.20 Hz),), 4.95-4.99 (S, 1H, CH),5.22 (s, 2H, CH_2), 6.77-6.80 (t, 1H, ArH), 6.93-7.01 (d, 2H, ArH), 7.05-7.10 (m, 3H, ArH) 7.11-7.19 (m, 2H, ArH), 7.54-7.57 (t, 3H, ArH), 7.68-7.85 (m, 2H, ArH), 7.87-7.94 (dd, 1H, ArH); ms: m/z 480.03 (M+1). *Anal*. Calcd. For $C_{29}H_{29}N_5O_2$: C, 72.63; H, 6.10; N, 14.60 Found: C, 72.66; H, 6.13; N, 14.58.

2-[5-Phenyl-3-(1-phenyl-3,4-dihydro-1H-isoquinolin-2-yl)-[1,2,4]triazol-1-yl]-1-piperidin-1-yl-ethanone (8c).IR (KBr) υ (cm^{-1}): 1664 (C=O); ^{1}H NMR (DMSO-d_6): δ 1.62-1.71 (m, 6H, $3CH_2$), 3.13-3.24 (t, 2H, CH_2, J=8.20 Hz), 3.38-3.43 (m, 4H, $2CH_2$), 3.91-3.99 (t, 2H, CH_2, J=8.20 Hz), 4.96-5.05 (S, 1H, CH), 5.20 (s, 2H, CH_2),), 6.99-7.08 (d, 2H, ArH), 6.80-7.19 (m, 3H, ArH),), 7.10-7.17 (m, 3H, ArH) 7.54-7.57 (t, 3H, ArH), 7.69-7.81 (m, 2H, ArH), 7.85-7.90 (m, 1H, ArH); ms: m/z 478.4 (M+1). *Anal*. Calcd. For $C_{30}H_{31}N_5O$: C, 75.44; H, 6.54; N, 14.66 Found: C, 75.45; H, 6.56; N, 14.63.

2-[5-Phenyl-3-(1-phenyl-3, 4-dihydro-1H-isoquinolin-2-yl)-[1, 2, 4] triazol-1-yl]-1-(4-phenyl-piperidin-1-yl)-ethanone (8d). IR (KBr) υ (cm^{-1}): 1679 (C=O); ^{1}H NMR (DMSO-d_6): δ 1.80-1.86 (m, 4H, $2CH_2$), 2.78-2.81 (m, 1H, CH), 3.13-3.24 (t, 2H, CH_2, J=8.25 Hz), 3.40-3.44 (m, 4H, $2CH_2$), 3.96-4.07 (t, 2H, CH_2, J=8.25 Hz), 4.95-5.02 (S, 1H, CH), 5.21 (s, 2H, CH_2), 6.80-7.19 (m, 3H, ArH), 7.54-7.57 (t, 8H, ArH), 7.69-7.81 (m, 6H, ArH), 7.85-7.90 (m, 1H, ArH); ms: m/z 534.5 (M+1). *Anal* Calcd. For $C_{36}H_{35}N_5O$: C, 78.09; H, 6.37; N, 12.65 Found: C, 78.06; H, 6.39; N, 12.66.

2-[5-Phenyl-3-(1-phenyl-3, 4-dihydro-1H-isoquinolin-2-yl)-[1, 2, 4] triazol-1-yl]-1-(4-phenyl-piperazin-1-yl)-ethanone (8e). IR υ (cm^{-1}): 1668 (C=O); ^{1}H NMR (DMSO-d_6): δ 3.13-3.24 (t, 2H, CH_2, J=8.22 Hz), 3.40-3.44 (m, 4H, $2CH_2$), 3.61-3.64 (m, 4H, $2CH_2$), 3.96-4.07 (t, 2H, CH_2, J=8.20 Hz), 4.98-5.08 (S, 1H, CH), 5.23 (s, 2H, CH_2), 6.83-7.21 (m, 3H, ArH), 7.58-7.62 (t, 8H, ArH), 7.71-7.83 (m, 6H, ArH), 7.85-7.90 (m, 1H, ArH); ms: m/z 555.4 (M+1). *Anal*. Calcd. For $C_{35}H_{34}N_6O$: C, 75.79; H, 6.18; N, 15.15 Found: C, 75.81; H, 6.21; N, 15.13.

N-Phenyl-2-[5-phenyl-3-(1-phenyl-3, 4-dihydro-1H-isoquinolin-2-yl)-[1, 2, 4] triazol-1-yl]-acetamide (9a). IR (KBr) υ (cm^{-1}): 3420 (N-H), 1678 (C=O); ^{1}H NMR (DMSO-d_6): δ 3.16-3.18

(t, 2H, CH_2, J=8.24 Hz), 3.97-4.12 (t, 2H, CH_2, J=8.22 Hz), 4.93-5.03 (S, 1H, CH),5.13 (s, 2H, CH_2), 6.78-6.86 (t, 1H, ArH), 7.08-7.18 (m, 3H, ArH), 7.32-7.41 (t, 3H, ArH), 7.55-7.60 (m, 6H, ArH), 7.81-7.97 (m, 6H, ArH), 10.56 (bs, 1H, NH); ms: m/z 486 (M+1). *Anal*. Calcd. For $C_{31}H_{27}N_5O$: C, 76.68; H, 5.60; N, 14.42 Found: C, 76.65; H, 5.62; N, 14.39.

2-[5-Phenyl-3-(1-phenyl-3,4-dihydro-1H-isoquinolin-2-yl)-[1,2,4]triazol-1-yl]-N-p-tolyl-acetamide (9b). IR(KBr) υ (cm^{-1}): 3450 (N-H), 1679 (C=O); ^{1}H NMR (DMSO-d_6): δ 2.41 (s, 3H, CH_3), 3.20-3.21 (t, 2H, CH_2, J=8.21 Hz), 3.89-3.93 (t, 2H, CH_2, J=8.20 Hz), 4.93-5.03 (S, 1H, CH), 5.10 (s, 2H, CH_2), 6.80-6.82 (m, 1H, ArH), 7.10-7.16 (m, 3H, ArH), 7.30-7.37 (m, 2H, ArH), 7.60-7.65 (m, 6H, ArH), 7.91-7.97 (m, 6H, ArH), 10.66 (bs, 1H, NH); ms: m/z 500 (M+1). *Anal*. Calcd. For $C_{32}H_{29}N_5O$: C, 76.93; H, 5.85; N, 14.02 Found: C, 76.90; H, 5.87; N, 14.03.

N-(4-Bromo-phenyl)-2-[5-phenyl-3-(1-phenyl-3, 4-dihydro-1H-isoquinolin-2-yl)-[1, 2, 4] triazol-1-yl] - acetamide (9c). IR(KBr) υ (cm^{-1}): 3446 (N-H), 1683 (C=O); ^{1}H NMR (DMSO-d_6): δ 3.18-3.21 (t, 2H, CH_2, J=8.22 Hz), 3.96-4.10 (t, 2H, CH_2, J=8.21 Hz), 4.95-5.02 (S, 1H, CH), 5.31 (s, 2H, CH_2), 6.78-6.86 (t, 1H, ArH), 6.95-7.05 (d, 4H, ArH) 7.12-7.16 (m, 3H, ArH), 7.55-7.60 (m, 4H, ArH), 7.81-7.97 (m, 6H, ArH), 10.86 (bs, 1H, NH); ms: m/z 565.45 (M+1). Anal. Calcd. For $C_{31}H_{26}BrN_5O$: C, 65.96; H, 4.64; N, 12.41 Found: C, 65.97; H, 4.66; N, 12.39.

N-(4-Isopropyl-phenyl)-2-[5-phenyl-3-(1-phenyl-3, 4-dihydro-1H-isoquinolin-2-yl)-[1, 2, 4] triazol-1-yl]-acetamide (9d). IR (KBr) υ (cm^{-1}): 3433 (N-H), 1678 (C=O); ^{1}H NMR (DMSO-d_6): δ 1.32-1.41 (d, 6H, $2CH_3$), 3.16-3.23 (m, 3H, CH_2 & CH), 3.93-4.02 (t, 2H, CH_2, J=8.22 Hz), 4.99-5.07 (S, 1H, CH), 5.23 (s, 2H, CH_2), 6.86-7.16 (m, 4H, ArH), 6.92-7.03 (m, 4H, ArH),7.55-7.60 (m, 4H, ArH), 7.81-7.97 (m, 6H, ArH), 10.71 (bs, 1H, NH); ms: m/z 528.60 (M+1). *Anal*. Calcd. For $C_{34}H_{33}N_5O$: C, 77.39; H, 6.30; N, 13.27 Found: C, 77.40; H, 6.31; N, 13.26.

N-Benzyl-2-[5-phenyl-3-(1-phenyl-3, 4-dihydro-1H-isoquinolin-2-yl)-[1, 2, 4] triazol-1-yl]-acetamide (9e). IR (KBr) υ (cm^{-1}): 3411 (N-H), 1683 (C=O); ^{1}H NMR (DMSO-d_6): δ 3.26-3.31 (t, 2H,CH_2, J=8.20 Hz), 3.93-4.17 (t, 2H, CH_2, J=8.20 Hz), 4.56-4.61 (d, 2H, CH_2), 4.92-5.01 (S,

1H, CH), 5.23 (s, 2H, CH_2), 6.89-7.14 (m, 4H, ArH), 7.32-7.41 (m, 3H, ArH), 7.55-7.60 (m, 6H, ArH), 7.73-7.80 (m, 6H, ArH), 9.81 (bs, 1H, NH); ms: m/z 500.05 (M+1). *Anal*. Calcd. For $C_{32}H_{29}N_5O$: C, 76.93; H, 5.85; N, 14.02 Found: C, 76.90; H, 5.87; N, 14.01.

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