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DESIGN, SYNTHESIS AND CHARACTERIZATION OF SOME NOVEL ISOQUINOLINE ASSOCIATED 1,2,3-TRIAZOLES AS MODERN ANTIFUNGAL AGENTS

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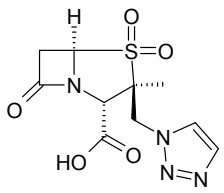
Abstract
A novel series of 5-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline-1-yl)-2-phenyl-2*H*-1,2,3-triazol-4-amines **(IVa-e)** were synthesized in good yields from the raw material, 2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1yl)acetonitrile **(I)** and by involving (*Z*)-2-(2-phenylhydrazono)-2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1yl)-acetonitriles **(IIa-e)** and (1*Z*, 2*Z*)-2-(2-phenylhydrazono)-2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1yl)-*N*′-hydroxy-acetamides **(IIIa-e)** as intermediates. The resulted compounds have been characterized via elemental analysis and different spectroscopic techniques. In addition, an antifungal screening of the title compounds was also done against four representative fungal strains and all tested compounds exhibited moderate to good growth inhibition activity with degree of variation.

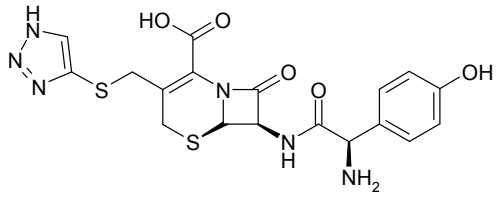
Keywords
2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1yl)acetonitrile,(*Z*)-2-(2-phenylhydrazono)-2-(1,2,3,4-tetrahydro-6,7-di-methoxyisoquinolin-1yl)-acetonitrile,(1*Z*, 2*Z*)-2-(2-phenylhydrazono)-2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1yl)-*N*′-hydroxy-acetamide, 5-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline-1-yl)-2-phenyl-2*H*-1,2,3-triazol-4-amine.

Introduction
1,2,3-Triazoles are an important class of heterocycles due to their wide range of applications as synthetic intermediates and pharmaceuticals[i]. Several therapeutically interesting 1,2,3-triazoles have been reported, including anti-HIV agents[ii], antimicrobial compounds[iii], β-3 selective adrenergic receptor agonists[iv], kinase inhibitors[v] and other enzyme inhibitors[vi]. The 1,2,3-triazole moiety is also present in a number of drugs such as Tazobactam[vii] and Cefatrizine[viii]. On the other hand, isoquinolines have demonstrated widespread biological activities and constitute a large number of naturally occurring alkaloids. Fused isoquinolines were used as anti-inflammatory, anti-pyretic and anti-cancer agents. Imidazole associated isoquinolines have been reported to have antitumor activity[ix]. Therapeutics like antimicrobial, anticancer, anti-inflammatory, antioxidant has been identified in many natural products in the

isoquinoline derivatives and α-methylene-γ-butyrolactones as bioactive ingredients [x-xii]. Tetrahydroisoquinolines have been observed as major structural designs within the natural products and pharmaceutical compounds which are biologically active [xiii,xiv].



Tazobactam

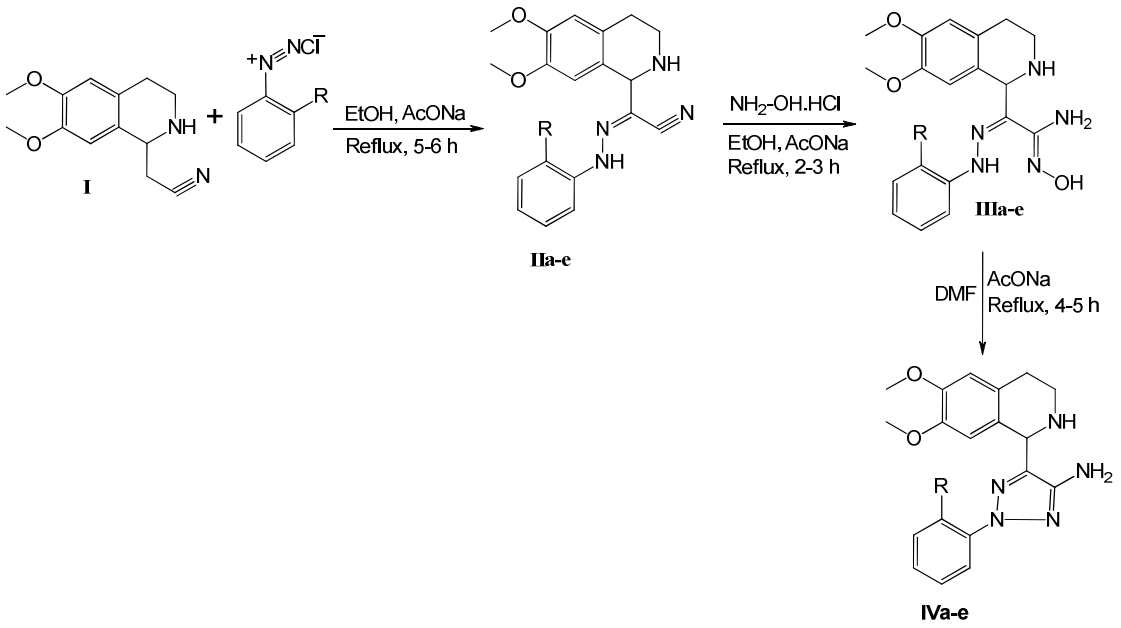


Cefatrizine

Results and discussion

Inspired by the biological profile of 1,2,3-triazoles and isoquinoline derivatives and in continuation of our interest to synthesize some novel heterocyclics, herein we are reporting the synthesis of 5-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline-1-yl)-2-phenyl-2*H*-1,2,3-triazol-4-amines **(IVa-e)** to find more potent antifungal agents. The synthetic protocol for the formation of title compounds is outlined in **Scheme 1**. Thus, the initial intermediates, (*Z*)-2-(2-phenylhydrazono)-2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1yl)-acetonitriles **(IIa-e)** were synthesized from the starting material, 2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1yl)acetonitrile **(I)** and different aryl diazonium salts in ethanol in the presence of sodium acetate at reflux temperature. Then these intermediates (**IIa-e)** have been turned into the next intermediates, (1*Z*, 2*Z*)-2-(2-phenylhydrazono)-2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1yl)-*N*′-hydroxyacetamides **(IIIa-e)** on reaction with hydroxylamine hydrochloride and sodium acetate in refluxing ethanol. Further, the title compounds, 5-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline-1-yl)-2-phenyl-2*H*-1,2,3-triazol-4-amine and its derivatives **(IVa-e)** were gained through cyclization of compounds (**IVa-e)** in good to excellent yields in the presence of sadium acetate in DMF under reflux.

Structure elucidations of all the synthesized compounds were performed by IR, ^{1}H NMR, mass spectroscopic methods and elemental analysis. In the IR spectrum of the final compound **IVa**, the characteristic stretching bands were observed at 3258 cm^{-1} for N-H bond, 3048 cm^{-1} for C–H of aromatic ring and 2952 cm^{-1} for C-H bond of CH_3 group. The stretching frequency at 1622, 1458 and 1144 cm^{-1} has been identified for C=C of aromatic ring, C=N and C-O groups respectively. In the ^{1}H NMR spectrum of the same compound, protons of two CH_2 groups of isoquinoline ring were perceived as triplets at δ 2.25 and 2.36 ppm with same coupling constant (J = 5.0 Hz). The resonance frequancy at about δ 2.48 ppm as singlet is obtained from CH group of same ring. Six protons of two methyl groups were assigned both as singlets at δ 2.75 and 2.77 ppm. The shielded and deshielded protons as singlets of NH and NH_2 groups were resonated at upfield and downfield regions with δ-chemical shifts δ 3.56 and 6.28 ppm. Finally, the protons of aromatic rings were resonated at a large area between δ 7.38 and 7.71 ppm. Regarding to the mass spectrum, compound **IVa** exhibited similar behaviour in their fragmentation pattern, showing the molecular ion peak at m/z 351. Furthermore, the chemical structures of all other compounds of this study have been investigated with the same procedure.



Scheme 1: Synthesis of compounds IVa-e; R (a) = H, (b) = CH_3, (c) = Cl, (d) = Br, (e) = NO_2

Antifungal activity

All the newly synthesized title compounds, 5-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline-1-yl)-2-phenyl-2*H*-1,2,3-triazol-4-amines **(IVa-e)** have used to screen their *in vitro* antifungal activity against four representative fungal organisms such as *Candida albicans, Aspergillus flavus, Aspergillus ficuum* and *Aspergillus niger* using tube dilution method by using Ketoconazole as standard. The minimum inhibitory concentration (MIC) and was measured by visual comparison with the positive and negative control tubes [xv]. A stock solution of the compound was prepared using dimethyl sulfoxide. To 2 mL of sterile Sabourauds dextrose broth taken in a test tube, 10 to 80 µL of the stock solution was added, followed by a loopful of an authentic culture of Candida albicans. This corresponds to a concentration range of 12.5, 25, 37.5, 50, 75, 100, 125, 150 and 200 µg/mL of the compounds. The tests were carried out in duplicate. The tubes were incubated at 37 ± 1OC and observed for growth at the end of 24 and 48 h. The activity of the compounds was determined by visual observation of the presence or absence of turbidity, used as a marker indicating the growth of the organism. The MIC was taken as the minimum concentration of the compound at which the clarity of the medium in the tube was the same as the negative control indicating complete inhibition of growth. According to the screening results of the compounds disclosed Figure 1, product **IVd** against *C. albicans*, **IVe** towards *A. flavus* and both compounds **IVb** and **IVe** in the direction of *A. ficuum* and **IVe** against *A. niger* disclosed highest activity with growth inhibition 50.0, 25.0, 50.0 and 37.5 µg/mL respectively. In the remaining study, all the compounds **IVa-e** exhibited moderate to good activity against all organisms employed with a degree of variation. It is interesting to note that none of the title compound is inactive against any fungal strain compare with standard in the present study.

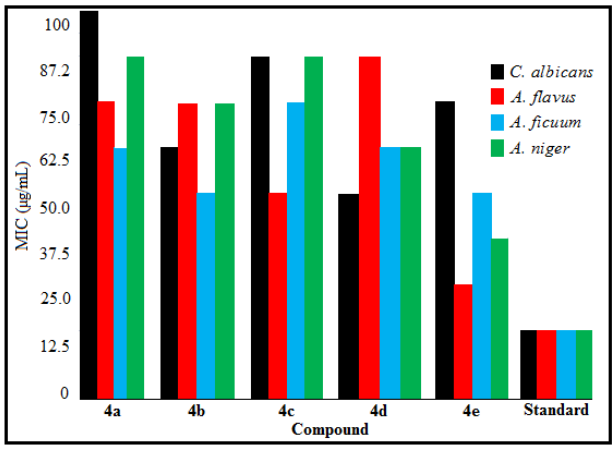


Figure 1: Antifungal activity of compounds 4a-e

Experimental

Starting materials were commercially available. Melting points of the synthesized compounds were determined by using electrothermal melting point apparatus and uncorrected. ^{1}H NMR spectra were recorded with a Bruker 300MHz digital FT-NMR spectrometer in DMSO-d_6 solvent including TMS as an internal standard. Coupling constants (J) are reported as Hertz. IR spectra were obtained on a PerkinElmer BX series FT-IR 5000 spectrometer using KBr pellet. Mass spectra were recorded on a VG-Micromass 7070H spectrometer operating at 70 eV. The purities of compounds were checked by TLC on silica gel 60 F_{254}.

Synthesis of (*Z*)-2-(2-phenylhydrazono)-2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1yl)-acetonitriles (IIa-e)

A suspension of 2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1yl)acetonitrile **(I)** (0.01 mol) in ethyl alcohol (10 ml) in the presence of sodium acetate (0.01 mol) was heated at reflux temperature on uniform stirring for 5-6 h. After achievement of the reaction (examined by TLC), the mixture is precipitated after poured in ice-cold water. The crude product was filtered off and washed with hexane and recrystallized from ethyl acetate to get corresponding pure (*Z*)-2-(2-phenylhydrazono)-2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1yl)-acetonitriles **(IIa-e)**.

Synthesis of (1*Z*, 2*Z*)-2-(2-phenylhydrazono)-2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1yl)-*N*′-hydroxyacetam-ides (IIIa-e)

A mixture of (*Z*)-2-(2-phenylhydrazono)-2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1yl)-acetonitriles **(IIa-e)** (0.01 ml) and hydroxyl amine hydrochloride (0.02 mol) was refluxed in ethanol (20 ml) in presence of sodium acetate (0.01 mol) for 2-3 h on water bath with steady stirring. After realization of the reaction (scanned by TLC), the solvent was evaporated under *vacuum* and the crude product was poured in crushed ice, thus obtained solid was filtered, dried and crystallized from ethanol to get (1*Z*, 2*Z*)-2-(2-phenylhydrazono)-2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1yl)-*N*′-hydroxyacetamides **(IIIa-e)** in pure form.

Synthesis of 5-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline-1-yl)-2-phenyl-2*H*-1,2,3-triazol-4-amines (IVa-e)

A mixture of (1*Z*, 2*Z*)-2-(2-phenylhydrazono)-2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-1yl)-*N*′-hydroxyacetamides **(IIIa-e)** (0.01 mol) and anhydrous sodium

acetate (0.01 mol) in DMF (20 ml) was refluxed on water bath with uniform stirring for 4-5 h. After completion of the reaction (monitored by TLC), solvent was evaporated under *vacuum* and the crude product was collected and recrystallized from ethyl acetate to offer pure 5-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline-1-yl)-2-phenyl-2*H*-1,2,3-triazol-4-amines **(IVa-e)**.

Physical and spectral data

(*Z*)-2-(2-Phenylhydrazono)-2-(1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinolin-1yl)-acetonitrile (IIa)

Yield: 87 %, mp: 131-133 ^{0}C, IR (KBr): 3258 (N-H), 3065 (C-H, Ar), 2961 (C-H, CH_3), 2236 (C≡N), 1552 (C=C), 1424 (C=N), 1131 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.26 (t, 2H, J = 4.8 Hz, CH_2), 2.38 (t, 2H, J = 4.8 Hz, CH_2), 2.53 (s, 1H, CH), 2.85 (s, 3H, CH_3), 2.92 (s, 3H, CH_3), 3.59 (s, 1H, NH), 7.52-7.76 (m, 5H, Ar-H), 7.58 (s, 1H, Ar-H), 7.65 (s, 1H, Ar-H), 11.32 (s, 1H, NH). MS: 336 m/z (M^+); Elemental analysis: Calculated for $C_{19}H_{20}N_4O_2$: C-67.84, H-5.99, N-16.66, O-9.51. Found: C-66.89, H-5.98, N-16.59, O-9.49.

(*Z*)-2-(2-*o*-Tolylhydrazono)-2-(1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinolin-1yl)-acetonitrile (IIb)

Yield: 85 %, mp: 120-122 ^{0}C, IR (KBr): 3265 (N-H), 3061 (C-H, Ar), 2958 (C-H, CH_3), 2241 (C≡N), 1581 (C=C), 1448 (C=N), 1136 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.23 (t, 2H, J = 4.6 Hz, CH_2), 2.33 (t, 2H, J = 4.6 Hz, CH_2), 2.55 (s, 1H, CH), 2.72 (s, 3H, CH_3), 2.89 (s, 3H, CH_3), 2.95 (s, 3H, CH_3), 3.62 (s, 1H, NH), 7.55 (s, 1H, Ar-H), 7.58-7.72 (m, 4H, Ar-H), 7.62 (s, 1H, Ar-H), 11.21 (s, 1H, NH). MS: 350 m/z (M^+); Elemental analysis: Calculated for $C_{20}H_{22}N_4O_2$: C-68.55, H-6.33, N-15.99, O-9.13. Found: C-67.68, H-6.32, N-15.92, O-9.12.

(*Z*)-2-(2-(2-Chlorophenyl)hydrazono)-2-(1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinolin-1yl)- acetonitrile (IIc)

Yield: 88 %, mp: 128-130 ^{0}C, IR (KBr): 3255 (N-H), 3065 (C-H, Ar), 2952 (C-H, CH_3), 2248 (C≡N), 1592 (C=C), 1457 (C=N), 1130 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.20 (t, 2H, J = 4.9 Hz, CH_2), 2.28 (t, 2H, J = 4.9 Hz, CH_2), 2.51 (s, 1H, CH), 2.68 (s, 3H, CH_3), 2.88 (s, 3H, CH_3), 3.65 (s, 1H, NH), 7.52-7.77 (m, 4H, Ar-H), 7.55 (s, 1H, Ar-H), 7.60 (s, 1H, Ar-H), 11.26 (s, 1H, NH). MS: 370 m/z (M^+); Elemental analysis: Calculated for $C_{19}H_{19}ClN_4O_2$: C-61.54, H-5.16, Cl-9.56, N-15.11, O-8.63. Found: C-60.65, H-5.15, Cl-9.55, N-15.09, O-8.62.

(*Z*)-2-(2-(2-Bromophenyl)hydrazono)-2-(1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinolin-yl)- acetonitrile (IId)

Yield: 84 %, mp: 137-139 ^{0}C, IR (KBr): 3262 (N-H), 3068 (C-H, Ar), 2958 (C-H, CH_3), 2252 (C≡N), 1581 (C=C), 1452 (C=N), 1138 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.18 (t, 2H, J = 4.7 Hz, CH_2), 2.31 (t, 2H, J = 4.7 Hz, CH_2), 2.47 (s, 1H, CH), 2.65 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 3.69 (s, 1H, NH), 7.50 (s, 1H, Ar-H), 7.55 (s, 1H, Ar-H), 7.57-7.70 (m, 4H, Ar-H), 11.22 (s, 1H, NH). MS: 414 m/z (M^+); Elemental analysis: Calculated for $C_{19}H_{19}BrN_4O_2$: C-54.95, H-4.61, Br-19.24, N-13.49, O-7.71. Found: C-53.98, H-4.60, Br-19.21, N-13.47, O-7.70.

(*Z*)-2-(2-(2-Nitrophenyl)hydrazono)-2-(1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinolin-1yl)- acetonitrile (IIe)

Yield: 89 %, mp: 115-117 ^{0}C, IR (KBr): 3255 (N-H), 3061 (C-H, Ar), 2965 (C-H, CH_3), 2258 (C≡N), 1588 (C=C), 1455 (C=N), 1144 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.25 (t, 2H, J = 4.7 Hz, CH_2), 2.33 (t, 2H, J = 4.7 Hz, CH_2), 2.51 (s, 1H, CH), 2.62 (s, 3H, CH_3), 2.83 (s, 3H, CH_3), 3.62 (s, 1H, NH), 7.40 (s, 1H, Ar-H), 7.48-7.71 (m, 4H, Ar-H), 7.52

(s, 1H, Ar-H), 11.18 (s, 1H, NH). MS: 381 m/z (M^+); Elemental analysis: Calculated for $C_{19}H_{19}BrN_4O_2$: C-54.95, H-4.61, Br-19.24, N-13.49, O-7.71. Found: C-59.84, H-5.02, N-18.36, O-16.78.

(1*Z*,2*Z*)-2-(2-Phenylhydrazono)-2-(1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinolin-1yl)-*N′*-hydroxyacetamide (IIIa)

Yield: 83 %, mp: 109-111 ^{0}C, IR (KBr): 3312 (O-H), 3282 (N-H), 3072 (C-H, Ar), 2958 (C-H, CH_3), 1612 (C=C), 1455 (C=N), 1132 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 2.31 (t, 2H, J = 5.2 Hz, CH_2), 2.37 (t, 2H, J = 5.2 Hz, CH_2), 2.55 (s, 1H, CH), 2.67 (s, 3H, CH_3), 2.91 (s, 3H, CH_3), 3.67 (s, 1H, NH), 5.82 (s, 2H, NH_2), 7.42-7.78 (m, 5H, Ar-H), 7.49 (s, 1H, Ar-H), 7.52 (s, 1H, Ar-H), 9.92 (s, 1H, OH), 11.36 (s, 1H, NH). MS: 369 m/z (M^+); Elemental analysis: Calculated for $C_{19}H_{23}N_5O_2$: C-61.77, H-6.28, N-18.96, O-12.99. Found: C-60.36, H-6.27, N-18.85, O-12.97.

(1*Z*,2*Z*)-2-(2-*o*-Tolylhydrazono)-2-(1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinolin-1yl)-*N′*-hydroxyacetamide (IIIb)

Yield: 87 %, mp: 135-137 ^{0}C, IR (KBr): 3325 (O-H), 3275 (N-H), 3068 (C-H, Ar), 2960 (C-H, CH_3), 1647 (C=C), 1450 (C=N), 1137 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 2.29 (t, 2H, J = 5.0 Hz, CH_2), 2.35 (t, 2H, J = 5.0 Hz, CH_2), 2.51 (s, 1H, CH), 2.62 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 2.88 (s, 3H, CH_3), 3.62 (s, 1H, NH), 5.87 (s, 2H, NH_2), 7.43 (s, 1H, Ar-H), 7.50-7.72 (m, 4H, Ar-H), 7.55 (s, 1H, Ar-H), 9.90 (s, 1H, OH), 11.31 (s, 1H, NH). MS: 383 m/z (M^+); Elemental analysis: Calculated for $C_{20}H_{25}N_5O_3$: C-62.65, H-6.57, N-18.26, O-12.52. Found: C-61.35, H-6.56, N-18.23, O-12.50.

(1*Z*, 2*Z*)-2-(2-(2-Chlorophenylhydrazono)-2-(1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinolin-1yl)-*N′*-hydroxyacetamide (IIIc)

Yield: 82 %, mp: 121-123 ^{0}C, IR (KBr): 3328 (O-H), 3281 (N-H), 3071 (C-H, Ar), 2963 (C-H, CH_3), 1621 (C=C), 1454 (C=N), 1142 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 2.33 (t, 2H, J = 5.2 Hz, CH_2), 2.37 (t, 2H, J = 5.2 Hz, CH_2), 2.53 (s, 1H, CH), 2.65 (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 3.60 (s, 1H, NH), 5.84 (s, 2H, NH_2), 7.46 (s, 1H, Ar-H), 7.55-7.76 (m, 4H, Ar-H), 7.58 (s, 1H, Ar-H), 9.87 (s, 1H, OH), 11.36 (s, 1H, NH). MS: 403 m/z (M^+); Elemental analysis: Calculated for $C_{19}H_{22}ClN_5O_3$: C-56.51, H-5.49, Cl-8.78, N-17.34, O-11.88. Found: C-55.69, H-5.48, Cl-8.77, N-17.30, O-11.86.

(1*Z*, 2*Z*)-2-(2-(2-Bromophenylhydrazono)-2-(1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinolin-1yl)-*N′*-hydroxyacetamide (IIId)

Yield: 87 %, mp: 135-137 ^{0}C, IR (KBr): 3318 (O-H), 3276 (N-H), 3066 (C-H, Ar), 2958 (C-H, CH_3), 1625 (C=C), 1459 (C=N), 1148 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 2.30 (t, 2H, J = 5.1 Hz, CH_2), 2.34 (t, 2H, J = 5.1 Hz, CH_2), 2.50 (s, 1H, CH), 2.62 (s, 3H, CH_3), 2.84 (s, 3H, CH_3), 3.63 (s, 1H, NH), 5.81 (s, 2H, NH_2), 7.43 (s, 1H, Ar-H), 7.53 (s, 1H, Ar-H), 7.58-7.72 (m, 4H, Ar-H), 9.85 (s, 1H, OH), 11.32 (s, 1H, NH). MS: 447 m/z (M^+); Elemental analysis: Calculated for $C_{19}H_{22}BrN_5O_3$: C-50.90, H-4.95, Br-17.82, N-15.62, O-10.71. Found: C-49.58, H-4.94, Br-17.78, N-15.58, O-10.69.

(1*Z*, 2*Z*)-2-(2-(2-Nitrophenylhydrazono)-2-(1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinolin-1yl)-*N′*-hydroxyacetamide (IIIe)

Yield: 89 %, mp: 119-121 ^{0}C, IR (KBr): 3327 (O-H), 3281 (N-H), 3059 (C-H, Ar), 2962 (C-H, CH_3), 1629 (C=C), 1463 (C=N), 1152 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 2.28 (t, 2H, J = 5.4 Hz, CH_2), 2.32 (t, 2H, J = 5.4 Hz, CH_2), 2.54 (s, 1H, CH), 2.65 (s, 3H, CH_3), 2.81 (s, 3H, CH_3), 3.67 (s, 1H, NH), 5.85 (s, 2H, NH_2), 7.46 (s, 1H, Ar-H), 7.51 (s, 1H, Ar-H), 7.55-7.76 (m, 4H, Ar-H), 9.82 (s, 1H, OH), 112.35 (s, 1H, NH). MS: 414 m/z (M^+); Elemental analysis: Calculated for $C_{19}H_{22}N_6O_5$: C-55.07, H-5.35, N-20.28, O-19.30. Found: C-54.12, H-5.3, N-20.21, O-19.22.

5-(1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinoline-1-yl)-2-phenyl-2*H*-1,2,3-triazol-4-amine (IVa)

Yield: 82 %, mp: 108-110 ^{0}C, IR (KBr): 3258 (N-H), 3048 (C-H, Ar), 2952 (C-H, CH_3), 1622 (C=C), 1458 (C=N), 1144 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.25 (t, 2H, J = 5.0 Hz, CH_2), 2.36 (t, 2H, J = 5.0 Hz, CH_2), 2.48 (s, 1H, CH), 2.75 (s, 3H, CH_3), 2.77 (s, 3H, CH_3), 3.56 (s, 1H, NH), 6.28 (s, 2H, NH_2), 7.38 (s, 1H, Ar-H), 7.47 (s, 1H, Ar-H), 7.50-7.71 (m, 5H, Ar-H). MS: 351 m/z (M^+); Elemental analysis: Calculated for $C_{19}H_{21}N_5O_2$: C-64.94, H-6.02, N-19.93, O-9.11. Found: C-63.98, H-6.01, N-19.89, O-9.10.

5-(1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinoline-1-yl)-2-*o*-tolyl-2*H*-1,2,3-triazol-4-amine (IVb)

Yield: 82 %, mp: 120-132 ^{0}C, IR (KBr): 3247 (N-H), 3044 (C-H, Ar), 2945 (C-H, CH_3), 1628 (C=C), 1447 (C=N), 1138 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.21 (t, 2H, J = 5.4 Hz, CH_2), 2.39 (t, 2H, J = 5.4 Hz, CH_2), 2.52 (s, 1H, CH), 2.55 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 3.59 (s, 1H, NH), 6.32 (s, 2H, NH2), 7.41 (s, 1H, Ar-H), 7.45 (s, 1H, Ar-H), 7.55-7.69 (m, 4H, Ar-H). MS: 365 m/z (M^+); Elemental analysis: Calculated for $C_{20}H_{23}N_5O_2$: C-65.73, H-6.34, N-19.16, O-8.76. Found: C-64.82, H-6.33, N-19.10, O-8.75.

2-(2-Chlorophenyl)-5-(1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinoline-1-yl)-2*H*-1,2,3-triazol-4-amine (IVc)

Yield: 87 %, mp: 135-137 ^{0}C, IR (KBr): 3242 (N-H), 3052 (C-H, Ar), 2952 (C-H, CH_3), 1628 (C=C), 1445 (C=N), 1135 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.24 (t, 2H, J = 5.1 Hz, CH_2), 2.35 (t, 2H, J = 5.1 Hz, CH_2), 2.55 (s, 1H, CH), 2.65 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 3.55 (s, 1H, NH), 6.28 (s, 2H, NH2), 7.38 (s, 1H, Ar-H), 7.42 (s, 1H, Ar-H), 7.48-7.62 (m, 4H, Ar-H). MS: 385 m/z (M^+); Elemental analysis: Calculated for $C_{19}H_{20}ClN_5O_2$: C-59.14, H-5.22, Cl-9.19, N-18.15, O-8.29. Found: C-58.65, H-5.21, Cl-9.18, N-18.12, O-8.27.

2-(2-Bromophenyl)-5-(1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinoline-1-yl)-2*H*-1,2,3-triazol-4-amine (IVd)

Yield: 81 %, mp: 112-14 ^{0}C, IR (KBr): 3239 (N-H), 3048 (C-H, Ar), 2963 (C-H, CH_3), 1641 (C=C), 1440 (C=N), 1130 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.22 (t, 2H, J = 5.5 Hz, CH_2), 2.31 (t, 2H, J = 5.5 Hz, CH_2), 2.52 (s, 1H, CH), 2.68 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 3.51 (s, 1H, NH), 6.22 (s, 2H, NH2), 7.42 (s, 1H, Ar-H), 7.47 (s, 1H, Ar-H), 7.52-7.67 (m, 4H, Ar-H). MS: 430 m/z (M^+); Elemental analysis: Calculated for $C_{19}H_{20}BrN_5O_2$: C-53.03, H-4.68, Br-18.57, N-16.28, O-7.44. Found: C-52.08, H-4.67, Br-18.51, N-16.23, O-7.43.

2-(2-Nitrophenyl)-5-(1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinoline-1-yl)-2*H*-1,2,3-triazol-4-amine (IVe)

Yield: 84 %, mp: 127-129 ^{0}C, IR (KBr): 3234 (N-H), 3052 (C-H, Ar), 2956 (C-H, CH_3), 1638 (C=C), 1447 (C=N), 1138 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.27 (t, 2H, J = 5.3 Hz, CH_2), 2.33 (t, 2H, J = 5.3 Hz, CH_2), 2.55 (s, 1H, CH), 2.63 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 3.55 (s, 1H, NH), 6.25 (s, 2H, NH2), 7.47 (s, 1H, Ar-H), 7.51 (s, 1H, Ar-H), 7.55-7.69 (m, 4H, Ar-H). MS: 396 m/z (M^+); Elemental analysis: Calculated for $C_{19}H_{20}N_6O_4$: C-57.57, H-5.09, N-21.20, O-16.14. Found: C-56.85, H-5.08, N-21.09, O-16.09.

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