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ISOINDOLINOTRIAZOLE DERIVATIVES: SYNTHESIS BY THE AZIDE-ALKYNE CYCLOADDITION CLICK CHEMISTRY

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ABSTRACT

A novel series of isoindolinotriazole derivatives with different substituents in the triazole moiety were synthesized *via* copper-catalyzed cycloaddition (CuAAC) click chemistry between 2-(*meta*- or *para*-ethynylphenyl)-4,6-dimethoxyisoindolin-1-ones and several azides. The synthesized triazoles were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral techniques.

Indexing terms/Keywords

Isoindolinone; triazole; click chemistry.

Academic Discipline And Sub-Disciplines

Chemistry

SUBJECT CLASSIFICATION

Organic chemistry

TYPE (METHOD/APPROACH)

Synthesis, organic spectrometry

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INTRODUCTION

Isoindolinones are interesting heterocyclic compounds due to their presence in many naturally occurring substances [1,2] and because of their extensive biological properties such as antihypertensive [3], antipsychotic [4] anxiolytic [5] and antiviral [6].

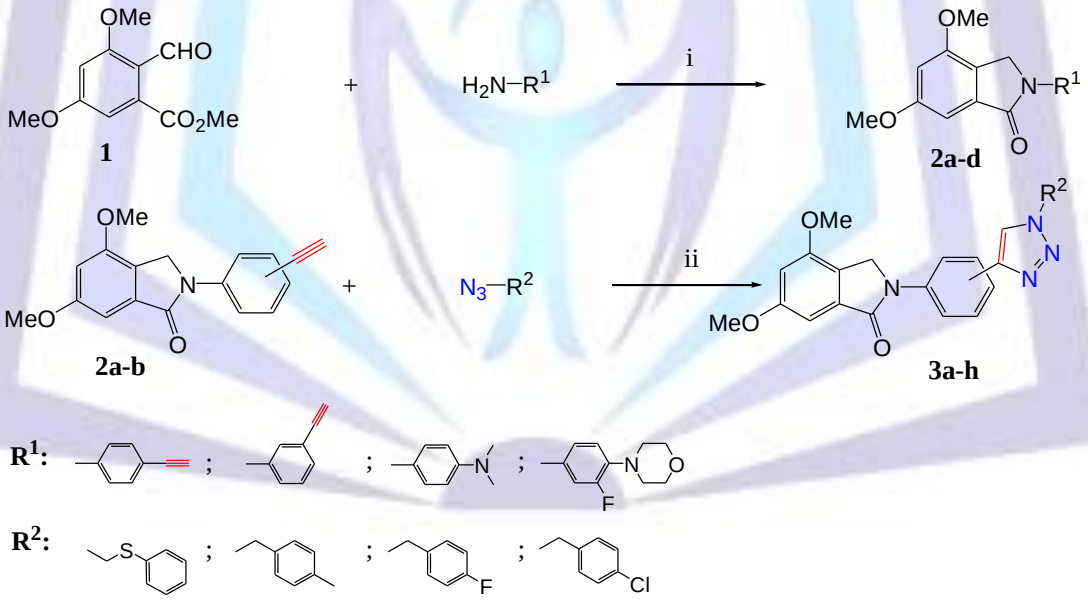
In medicinal chemistry, the triazoles are known to possess a number of desirable features including sufficient stability to acidic/basic hydrolysis and reductive/oxidative conditions, indicative of a high aromatic stabilization [7]. This moiety is relatively resistant to metabolic degradation. Tazobactam, a b-lactamase inhibitor is among the best-known examples of triazole containing structures with the broad-spectrum antibiotic piperacillin [8]. Also several members of the 1,2,3-triazole family have indeed shown interesting biological properties, such as anti-allergic, anti-bacterial and anti-HIV activity [9,10].

The coupling of two or more molecular entities with distinct properties to form novel conjugates with combined properties of parent components, has emerged as a fast growing technology in recent years [11,12]. Several new conjugates arising via such bioconjugation have been found to exhibit unusual biological properties and activities as the different molecular segments act cooperatively [13]. In this prospective, the 'Click'-chemistry [14] is a newer approach for the synthesis of drug-like molecules that can accelerate the drug discovery process by utilizing a few practical and reliable reactions [15]. Among the reactions comprising the click universe, the perfect example is the Huisgen 1,3-dipolar cycloaddition of terminal alkynes and organic azides to form 1,4-disubstituted-1,2,3-triazoles [16,17].

In this study, we report the high-yielding synthesis of novel isoindolinotriazoles **3a-h** using 1,3-dipolar cycloaddition reaction of ethynylisoindolinones **2a-b** with several azides in the presence of Cu(I) catalyst at room temperature. All the synthesized isoindolinones and 1,4-disubstituted-1*H*-1,2,3-triazoles were characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy and mass spectrometry.

RESULTS AND DISCUSSION

Isoindolinone derivatives were obtained using methods developed by Yoo *et al.* [18] (Scheme 1). The reaction between methyl 2-formyl-3,5-dimethoxybenzoate **1** with the appropriate amines in methanol was carried at room temperature over 1 h. The resulting solution was mixed with sodium borohydride at 0 °C and reacted overnight at room temperature to produce isoindolinone compounds **2a-d** (Table 1).



Scheme 1. Synthesis of isoindolinones 2a-d and 1*H*-1,2,3-triazoles 3a-h. Reagents and conditions: (i) $NaBH_4$, MeOH, 0 °C-r.t., 20 h. (ii) Na-ascorbate (0.45 equiv), $CuSO_4.5H_2O$ (0.1 equiv), THF/*t*-BuOH/H_2O (3 :1 :1, v/v/v), r.t., 2 d**.**

The (3 + 2) cycloaddition of 2-(*meta*- or *para*-ethynylphenyl)-4,6-dimethoxyisoindolin-1-ones with different azides (Scheme 1) in the presence of Na-ascorbate, THF/*t*-BuOH/H_2O and $CuSO_4$**.**$5H_2O$, at room temperature resulted in the corresponding 1,4-disubstituted-1,2,3-triazole compounds **3a-h** in good yields (Table 1).

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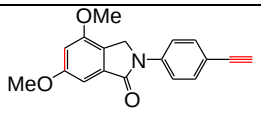
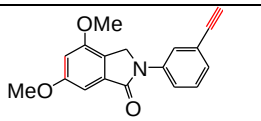
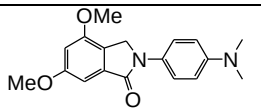
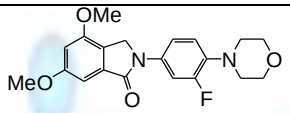
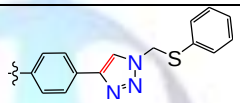
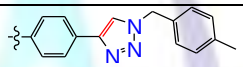
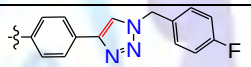
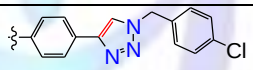
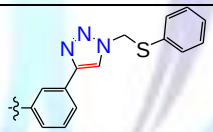
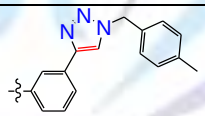
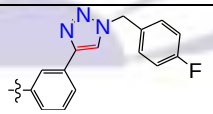
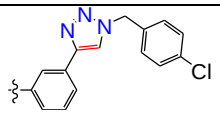
Table 1: Synthesis of isoindolinones **2a-d** and 1,4-disubstituted-1,2,3-triazoles **3a-h**.

Entry	Compounds	Structure	Yields[a]
1	2a		51
2	2b		59
3	2c		64
4	2d		52
5	3a		70
6	3b		68
7	3c		76
8	3d		75
9	3e		80
10	3f		60
11	3g		65
12	3h		71

[a] isolated yield

The structures of the isoindolinones were determined primarily from spectroscopic data. The IR spectra showed bands in the range of 1700-1680 cm^{-1} which confirmed the presence of a C=O function. The ^{13}C-NMR spectra confirmed the formation of the isoindolinone ring with signals of the *C=O* function at δ = 166-168 ppm and CH_2 at the δ = 47.80 – 48.26 ppm. The mass spectra showed the respective $[M + H]^+$ peaks.

The formation of triazole was confirmed by the presence of absorption band in the region 3188-3105 cm^{-1} in IR spectra due to =C-H stretching of triazole ring. The presence of characteristic singlet in ^{1}H NMR due to triazolyl protons in the region of δ 7.64-8.71 and δ 119.1-121.3 in ^{13}C NMR due to C-5 of the triazole ring confirmed the formation of triazole ring. The results obtained from mass spectral analysis were found in accordance to their molecular weights.

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CONCLUSION

In summary, various isoindolinones were synthesized and utilized as starting materials in the 'click' reaction to attach azido residues. Consequently, we have employed these, in house synthesized precursors, to prepare a new class of hybrid molecules 1,4-disubstituted-1*H*-1,2,3-triazoles employing already known chemistry of (3 + 2) cycloaddition of azides and alkynes in good to very good yields. All products that we have obtained were hitherto unknown. A number of them are presently under pharmacological screening.

EXPERIMENTAL

General

Melting points were determined with an Electrothermal 9300 capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer PARAGON 1000 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on an AC Bruker spectrometer at 300 MHz (^{1}H) and 75 MHz (^{13}C) using $(CD_3)_2SO$ or $CDCl_3$ as solvents. High resolution mass spectra (HRMS) were recorded on a Bruker Maxis spectrometer (Service Commun Toulouse, France). Silica Gel 60 (Merck 70–230) was used for column chromatography. The progress of the reactions was monitored by thin layer chromatography (TLC) on Kieselgel 60 F254 (Merck) plates. Compound purity was determined by an LC-PDA-MS method and was found to be in the range 96-99%.

General experimental procedure for preparation of 2-substitued-4,6-dimethoxyisoindolin-1-ones

To a solution of methyl 2-formyl-3,5-dimethoxybenzoate **1** (2.5 mmol) in methanol (20 mL) was added the appropriate amine (2.5 mmol). The mixture was stirred at room temperature until the appearance of a suspension. $NaBH_4$ (5 mmol) was then added at 0 °C and the mixture allowed to react at room temperature for 20 h with stirring. The precipitate thus formed was filtered through a glass filter to give a solid compound.

*2-(4-ethynylphenyl)-4,6-dimethoxyisoindolin-1-one (**2a**)*

White solid, yield (51%), mp 186-188 °C. IR (KBr) cm^{-1}: 3271 (C≡H), 2915, 2834, 1697 (C=O), 1627, 1607, 1504, 1448, 1384, 1362, 1320, 1294, 1201, 1141, 1118, 1048, 934, 830, 762, 635, 518. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.85 (s, 3H, CH_3), 3,89 (s, 3H, CH_3), 4.15 (s, 1H, CH), 4.84 (s, 2H, CH_2), 6.82-6.83 (d, *J*= 3 Hz, 1H), 6.86-6.87 (d, *J*= 3 Hz, 1H), 7.51-7.54 (m, 2H), 7.93-7.96 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 48.3 (CH_2), 56.2 (CH_3), 56.2 (CH_3), 80.8 (CH), 83.8 (C), 98.4 (CH), 103.7 (CH), 117.3 (C), 119.3 (2 CH), 121.88 (C), 132.9 (2 CH), 134.7 (C), 140.4 (C), 155.4 (C), 162.0 (C); 167.2 (C). MS-(+)ESI: m/z (%): 294 ($[M+H]^+$, 100). HR-MS (ESI) m/z calcd for $C_{18}H_{16}NO_3$ $[M+H]^+$ 294.1130. Found 294.1137.

*2-(3-ethynylphenyl)-4,6-dimethoxyisoindolin-1-one (**2b**)*

White solid, yield (59%), mp 191-193 °C. IR (KBr) cm^{-1}: 3240 (C≡H), 2960, 2833, 1686 (C=O), 1615, 1577, 1504, 1429, 1384, 1329, 1239, 1208, 1140, 1120, 1061, 945, 815, 788, 682. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.85 (s, 3H, CH_3), 3,90 (s, 3H, CH_3), 4.24 (s, 1H, CH), 4.87 (s, 2H, CH_2), 6.83-6.84 (d, *J*= 3 Hz, 1H), 6.87-6.88 (d, *J*= 3 Hz, 1H), 7.26-7.29 (m, 1H), 7.41-7.47 (t, *J*= 9 Hz, 1H), 7.90-7.94 (m, 1H), 8.08-8.09 (t, *J*= 3 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 48.3 (CH_2), 56.2 (CH_3), 56.2 (CH_3), 81.4 (CH), 83.8 (C), 98.4 (CH), 103.7 (CH), 120.2 (CH), 121.9 (C), 122.5 (CH), 122.7 (C), 127.6 (CH), 129.8 (CH), 134.7 (C), 140.2 (C), 155.5 (C), 162.0 (C); 167.2 (C); MS-(+)ESI m/z: 294 ($[M+H]^+$, 100%). HRMS-ESI (m/z): calcd for $C_{18}H_{16}NO_3$ $[M+H]^+$ 294.1130 found: 294.1139.

*2-(4-(dimethylamino)phenyl)-4,6-dimethoxyisoindolin-1-one (**2c**)*

White solid, yield 64%, mp: 152-153 °C. IR (KBr) cm^{-1}: 1692, 1683 (C=O), 1614, 1522, 1326, 1270, 1207, 1146, 1110, 1050, 944, 808. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.89 (s, 6H, CH_3), 3.84 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 4.74 (s, 2H, CH_2), 6.76-6.79 (m, 3H), 6.83 (d, *J* = 3 Hz, 1H), 7.64-7.67 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 40.8 (2 CH_3), 48.8 (CH_2), 56.1 (CH_3), 56.2 (CH_3), 98.3 (CH), 102.9 (CH), 113.1 (2 CH), 121.5 (C), 121.6 (2 CH), 129.6 (C), 135.4 (C), 148.1 (C), 155.4 (C), 161.9 (C), 166.3 (C). MS-(+)ESI m/z: 313 ($[M+H]^+$, 100%). HRMS-ESI (m/z): calcd for $C_{18}H_{21}N_2O_3$ $[M+H]^+$ 313.1552 found: 313.1551.

*2-(3-fluoro-4-morpholinophenyl)-4,6-dimethoxyisoindolin-1-one (**2d**)*

White solid, yield 79%, mp: 204-205 °C. IR (KBr) cm^{-1}: 2949, 2840, 1688 (C=O), 1627, 1512, 1363, 1328, 1270, 1204, 1146, 1129, 1118, 1054, 1042, 935, 824. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.10 (t, *J* = 3 Hz, 4H, CH_2), 3.88 (t, *J* = 3 Hz, 4H, CH_2), 3.89 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 4.67 (s, 2H, CH_2), 6.64 (d, *J* = 3 Hz, 1H), 6.95-7.01 (m, 2H), 7.48 (dd, *J* = 3, 9 Hz,1H), 7.79 (dd, *J* = 3, 9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 48.4 (CH_2), 51.0 (CH_2), 51.1 (CH_2), 55.6 (CH_3), 55.9 (CH_3), 67.0 (2 CH_2), 97.9 (CH), 103.0 (CH), 108.4 (CH), 114.7 (CH), 118.8 (CH), 121.1 (C), 135.1 (C), 136.4 (C), 153.9 (C), 155.1 (C), 157.1 (C), 162.0 (C), 167.3 (C); MS-(+)ESI m/z: 373 ($[M+H]^+$, 100%). HRMS-ESI m/z: calcd for $C_{20}H_{22}FN_2O_4$ $[M+H]^+$ 373.1564 found: 373.1555.

General experimental procedure for preparation of 1,4-disubstituted-1,2,3-triazoles

The mixture of alkyne **2a** or **2b** (1 mmol) and azides (1 mmol) was suspended in a mixture of THF/*t*-BuOH/H2O (3:1:1, v/v/v, 6/2/2 mL). Sodium ascorbate (89 mg, 0.45 equiv) was added followed by addition of $CuSO_4.5H_2O$ (16 mg, 0.1 equiv.). The heterogeneous mixture was stirred vigorously for 2 days, at which time TLC showed complete conversion.

The reaction mixture was concentrated under vacuum and the residue was treated with H_2O (50 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to give a crude mass. Column chromatography purification using ethyl acetate/dichloromethane as eluent gave the clicked product [16,17].

*4,6-dimethoxy-2-(4-(1-(phenylthiomethyl)-1H-1,2,3-triazol-4-yl)phenyl)isoindolin-1-one (**3a**)*

White solid, yield (70%), mp: 194-196 °C. IR (KBr) cm^{-1}: 3140, 3055, 2942, 2841, 1688 (C=O), 1629, 1612, 1502, 1453, 1384, 1361, 1322, 1267, 1202, 1145, 1120, 1074, 1041, 972, 929, 832, 802, 764, 738, 689, 515, 472. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.86 (s, 3H, CH_3), 3,90 (s, 3H, CH_3), 4.87 (s, 2H, CH_2), 6.00 (s, 2H, CH_2), 6.82-6.83 (d, *J*= 3 Hz, 1H), 6.87-6.88 (d, *J*= 3 Hz, 1H), 7.30-7.39 (m, 2H), 7.44-7.47 (m, 3H), 7.86-7.89 (m, 2H) 7.98-8.01 (m, 2H), 8.55 (s, 1H, $CH_{triazole}$). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 48.4 (CH_2), 52.41 (CH_2), 56.2 (CH_3), 56.2 (CH_3), 98.4 (CH), 103.6 (CH), 119.8 (2 CH), 121.1 ($CH_{triazole}$), 121.8 (C), 126.2 (2 CH), 126.5 (C), 128.2 (CH), 129.8 (2 CH), 131.1 (2 CH), 132.9 (C), 134.9 (C), 139.7 (C), 146.8 ($C_{q\ triazole}$), 155.5 (C), 162.0 (C); 167.0 (C). MS-(+)ESI m/z: 459 ($[M+H]^+$, 100%). HRMS-ESI (m/z): calcd for $C_{25}H_{23}N_4O_3S$ $[M+H]^+$ 459.1491 found: 459.1490.

*4,6-dimethoxy-2-(4-(1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)phenyl)isoindolin-1-one (**3b**)*

White solid, yield (68%), mp 223-224 °C. IR (KBr) cm^{-1}: 3162, 1697 (C=O), 1629, 1613, 1503, 1451, 1196, 1141, 1047, 1037, 817, 761. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.38 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 3,90 (s, 3H, CH_3), 4.74 (s, 2H, CH_2), 5.54 (s, 2H, CH_2), 6,63-6,64 (d, *J*= 3 Hz, 1H), 6.99-7.00 (d, *J*= 3 Hz, 1H), 7.20-7.26 (m, 4H), 7.64 (s, 1H, $CH_{triazole}$), 7.83-7.86 (m, 2H), 7.93-7.96 (m, 2H). ^{13}C NMR (75MHz, $CDCl_3$) δ: 21.2 (CH_3), 48.3 (CH_2), 54.1 (CH_2), 55.6 (CH_3), 55.9 (CH_3), 97.9 (CH), 103.0 (CH), 119.1 ($CH_{triazole}$), 119.2 (2 CH), 121.3 (C), 126.4 (2 CH), 126.5 (C), 128.2 (2 CH), 129.8 (2 CH), 131.6 (C), 135.2 (C), 138.8 (C), 139.5 (C), 147.7 ($C_{q\ triazole}$), 155.1 (C), 162.0 (C), 167.6 (C); MS-(+)ESI m/z: 441 ($[M+H]^+$, 100%). HRMS-ESI m/z: calcd for $C_{26}H_{25}N_4O_3$ $[M+H]^+$ 441.1927 found: 441.1924.

*2-(4-(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)phenyl)-4,6-dimethoxyisoindolin-1-one (**3c**)*

White solid, yield (76%), mp 229-230 °C. IR (KBr) cm^{-1}: 3188, 1685 (C=O), 1623, 1606, 1504, 1360, 1221, 1143, 1122, 1045, 842, 767. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.86 (s, 3H, CH_3), 3,90 (s, 3H, CH_3), 4.88 (s, 2H, CH_2), 5.64 (s, 2H, CH_2), 6,83-6,84 (d, *J*= 3 Hz, 1H), 6.87-6.88 (d, *J*= 3 Hz, 1H), 7.21-7.27 (m, 2H), 7.42-7.47 (m, 2H), 7.87-7.90 (m, 2H), 7.99-7.02 (m, 2H), 8.61 (s, 1H, $CH_{triazole}$). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 48.4 (CH_2), 52.7 (CH_2), 56.2 (CH_3), 56.2 (CH_3), 98.4 (CH), 103.6 (CH), 115.9 (CH), 116.6 (CH), 119.8 (2 CH), 121.6 ($CH_{triazole}$), 121.8 (C), 126.2 (2 CH), 126.8 (C), 130.7 (CH), 130.8 (CH), 132.72 (C), 132.71 (C), 134.9 (C), 139.6 (C), 146.8 ($C_{q\ triazole}$), 155.5 (C), 162.0 (C), 167.0 (C); MS-(+)ESI m/z: 445 ($[M+H]^+$, 100%). HRMS-ESI m/z: calcd for $C_{25}H_{22}FN_4O_3$ $[M+H]^+$ 445.1676 found: 445.1672.

*2-(4-(1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)phenyl)-4,6-dimethoxyisoindolin-1-one (**3d**)*

White solid, yield (75%), mp 209-210 °C. IR (KBr) cm^{-1}: 3105, 1694 (C=O), 1626, 1608, 1500, 1363, 1272, 1143, 1123, 1045, 839, 764. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.90 (s, 3H, CH_3), 3,91 (s, 3H, CH_3), 4.75 (s, 2H, CH_2), 5.56 (s, 2H, CH_2), 6,64-6,65 (d, *J*= 3 Hz, 1H), 6.99-7.00 (d, *J*= 3 Hz, 1H), 7.26-7.30 (m, 2H), 7.36-7.41 (m, 2H), 7.68 (s, 1H, $CH_{triazole}$), 7.84-7.87 (m, 2H), 7.94-7.98 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 48.3 (CH_2), 53.5 (CH_2), 55.6 (CH_3), 55.9 (CH_3), 97.9 (CH), 103.1 (CH), 119.2 ($CH_{triazole}$), 119.2 (2 CH), 121.3 (C), 126.3 (C), 126.4 (2 CH), 129.4 (4 CH), 129.8 (C), 133.2 (C), 135.2 (C), 139.7 (C), 147.9 ($C_{q\ triazole}$), 155.1 (C), 162.0 (C), 167.6 (C). MS-(+)ESI m/z: 461 ($[M+H]^+$, 100%), 463 ($[M+H]^+$, 35%). HRMS-ESI m/z: calcd for $C_{25}H_{22}ClN_4O_3$ $[M+H]^+$ 461.1380 found: 461.1382.

*4,6-dimethoxy-2-(3-(1-(phenylthiomethyl)-1H-1,2,3-triazol-4-yl)phenyl)isoindolin-1-one (**3e**)*

White solid, yield (80%), mp 179-181 °C. IR (KBr) cm^{-1}: 3145, 2965, 2945, 2843, 1713 (C=O), 1624, 1611, 1578, 1506, 1491, 1436, 1371, 1359, 1345, 1301, 1210, 1148, 1111, 1073, 1046, 1006, 932, 844, 815, 789, 753, 690, 634, 490. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.86 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 4.91 (s, 2H, CH_2), 6.01 (s, 2H, CH_2), 6.83-6.84 (d, *J*= 3 Hz, 1H), 6.88-6.89 (d, *J*= 3 Hz, 1H), 7.33-7.37 (m, 3H), 7.44-7.48 (m, 3H), 7.62-7.65 (m, 1H), 7.97-8.01 (m, 1H), 8.26-8.28 (t, *J* = 3 Hz, 1H), 8.67 (s, 1H, $CH_{triazole}$). ^{13}C NMR (300 MHz, DMSO-d_6) δ: 48.5 (CH_2), 52.5 (CH_2), 56.2 (CH_3), 56.2 (CH_3), 98.4 (CH), 103.6 (CH), 116.3 (CH), 119.3 (CH), 121.3 ($CH_{triazole}$), 121.8 (CH), 121.9 (C), 128.3 (CH), 129.8 (2 CH), 130.0 (CH), 131.1 (2 CH), 131.6 (C), 132.8 (C), 134.9 (C), 140.6 (C), 147.0 ($C_{q\ triazole}$), 155.5 (C), 162.0 (C), 167.1 (C). MS-(+)ESI m/z: 459 ($[M+H]^+$, 100%). HRMS- ESI m/z: calcd for $C_{25}H_{23}N_4O_3S$ $[M+H]^+$ 459.1491 found: 459.1483.

*4,6-dimethoxy-2-(3-(1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)phenyl)isoindolin-1-one (**3f**)*

White solid, yield (60%), mp 176-177 °C. IR (KBr) cm^{-1}: 3142, 1695 (C=O), 1627, 1608, 1508, 1448, 1386, 1362, 1203, 1147, 1119, 1053, 887, 756. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.38 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 3,91 (s, 3H, CH_3), 4.79 (s, 2H, CH_2), 5.55 (s, 2H, CH_2), 6,64-6,65 (d, *J*= 3 Hz, 1H), 6.98-6.99 (d, *J*= 3 Hz, 1H), 7.20-7.26 (m, 4H), 7.43-7.49 (t, *J*= 9 Hz, 1H), 7.63-7.64 (m, 1H), 7.73 (s, 1H, $CH_{triazole}$), 7.94-7.96 (m, 1H), 8.25-8.27 (t, *J*= 3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.2 (CH_3), 48.48 (CH_2), 54.1 (CH_2), 55.6 (CH_3), 55.9 (CH_3), 97.9 (CH), 103.1 (CH), 116,1 (CH), 118.9 (CH), 119.7 (CH), 121.5 (C), 121.5 ($CH_{triazole}$), 128.2 (2 CH), 129.6 (CH), 129.9 (2 CH), 131.5 (C), 131.5 (C), 135,2 (C), 138.8 (C), 140.2 (C), 147.9 ($C_{q\ triazole}$), 155.2 (C), 162.0 (C), 167.7 (C). MS-(+)ESI m/z: 441 ($[M+H]^+$, 100%). HRMS-ESI m/z: calcd for $C_{26}H_{25}N_4O_3$ $[M+H]^+$ 441.1927 found: 441.1921.

*2-(3-(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)phenyl)-4,6-dimethoxyisoindolin-1-one (**3g**)*

White solid, yield (65%), mp 189-190 °C. IR (KBr) cm^{-1}: 3180, 1702 (C=O), 1629, 1611, 1508, 1365, 1224, 1143, 1114, 1046, 832, 774. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.86 (s, 3H, CH_3), 3,90 (s, 3H, CH_3), 4.90 (s, 2H, CH_2), 5.75 (s, 2H, CH_2), 6,83-6.84 (d, *J*= 3 Hz, 1H), 6.87 -6,88 (d, *J*= 3 Hz, 1H), 7.20-7.28 (m, 2H), 7.42-7.51 (m, 3H), 7.65-7.67 (m, 1H), 7.96-8.00 (m, 1H), 8.26-8.28 (m, 1H), 8.70 (s, 1H, $CH_{triazole}$). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 48.5 (CH_2), 52.7 (CH), 56.2 (CH_3), 56.2 (CH_3), 98.4 (CH), 103.5 (CH), 116,3 (CH), 119.2 (CH), 121.3 ($CH_{triazole}$), 121.9 (C), 122.3 (CH), 129.9 (CH), 130.7 (2 CH), 130.8 (2 CH), 131.8 (C), 132.7 (C), 132,7 (C), 134.9 (C), 140.5 (C), 147.0 ($C_{q\ triazole}$), 155.5 (C), 162.0 (C), 167.1 (C). MS-(+)ESI m/z: 445 ($[M+H]^+$, 100%). HRMS-ESI m/z: calcd for $C_{25}H_{22}FN_4O_3$ $[M+H]^+$ 445.1676 found: 445.1668.

*2-(3-(1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)phenyl)-4,6-dimethoxyisoindolin-1-one (**3h**)*

White solid, yield (71%), mp 176-177 °C. IR (KBr) cm^{-1}: 3145, 1688 (C=O), 1626, 1609, 1492, 1449, 1362, 1202, 1146, 1118, 1053, 762. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.86 (s, 3H, CH_3), 3,90 (s, 3H, CH_3), 4.90 (s, 2H, CH_2), 5.75 (s, 2H, CH_2), 6,83-6.84 (d, *J*= 3 Hz, 1H), 6.87-6,88 (d, *J*= 3 Hz, 1H), 7.38-7.51 (m, 5H), 7.65-7.68 (m, 1H), 7.97-8.01 (m, 1H), 8.26-8.28 (m, 1H), 8.71 (s, 1H, $CH_{triazole}$). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 48.5 (CH_2), 52.7 (CH), 56.2 (CH_3), 56.2 (CH_3), 98.4 (CH), 103.5 (CH), 116,3 (CH), 119.2 (CH), 121.3 ($CH_{triazole}$), 121.9 (C), 122.4 (CH), 129.3 (2 CH), 130.0 (CH), 130.4 (2 CH), 131.8 (C), 133,4 (C), 134.9 (C), 135.4 (C), 140.5 (C), 147.0 ($C_{q\ triazole}$), 155.5 (C), 162.0 (C), 167.1 (C); MS-(+)ESI m/z: 461 ($[M+H]^+$, 100%), 463 ($[M+H]^+$, 35%). HRMS-ESI m/z: calcd for $C_{25}H_{22}ClN_4O_3$ $[M+H]^+$ 461.1380 found: 461.1371.

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