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Original article

Synthesis and structure–activity relationship of 1- and 2-substituted-1,2,3-triazole letrozole-based analogues as aromatase inhibitors

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ABSTRACT

A series of bis- and mono-benzonitrile or phenyl analogues of letrozole **1**, bearing (1,2,3 and 1,2,5)-triazole or imidazole, were synthesized and screened for their anti-aromatase activities. The unsubstituted 1,2,3-triazole **10a** derivative displayed inhibitory activity comparable with that of the aromatase inhibitor, letrozole **1**. Compound **10a**, bearing a 1,2,3-triazole, is also 10000-times more tightly binding than the corresponding analogue **25** bearing a 1,2,5-triazole, which confirms the importance of a nitrogen atom at position 3 or 4 of the 5-membered ring needed for high activity. The effect on human epithelial adrenocortical carcinoma cell line (H295R) proliferation was also evaluated. The compound **10j** ($IC_{50} = 4.64$ μM), a letrozole **1** analogue bearing *para*-cyanophenoxymethylene-1,2,3-triazole decreased proliferation rates of H295R cells by 76 and 99% in 24 and 72 h respectively. Computer calculations, using quantum *ab initio* structures, suggest a possible correlation between anti-aromatase activity and the distance between the nitrogen in position 3 or 4 of triazole nitrogen and the cyano group nitrogen.

1. Introduction

The standard pharmacological treatment for hormone-dependent cancer is to block oestrogen binding to the oestrogen receptor (ER) with tamoxifen [1,2]. Unfortunately, this anti-oestrogen molecule has many drawbacks. First, as a partial ER agonist in many tissue types [3], its use has been correlated with an increase in the incidences of endometrial cancer [4]. Furthermore, resistance to tamoxifen therapy inevitably results [3]. An alternative approach to tamoxifen treatment is inhibition of oestrogen synthesis. The target for such therapy is aromatase. This key cytochrome P450 enzyme encoded by the CYP19 gene catalyzes the rate limiting step in the conversion (aromatization) of androgens to oestrogens [5].

To avoid inhibition of other steroidogenesis enzymes, inhibitor selectivity is crucial. However, non-selective aromatase inhibitors, like non-steroidal aminoglutethimide [6,7], which is a well known and long used therapeutic agent, could affect enzymes controlling the production of other steroids and induce significant side-effects. New aromatase inhibitors, including letrozole **1** and anastrozole **2** (Fig. 1), were found to be effective challengers of tamoxifen as oestrogen blocker and were highlighted in several recent publications [8–10]. They act through the aromatase pathway, to treat oestrogen-sensitive breast cancers by preventing oestrogen production in the first place. Unlike tamoxifen, that has mixed estrogen agonist and antagonist properties, the aromatase inhibitors have no oestrogenic agonist activity. There is now a strong case to be made for selectively inhibiting aromatase in order to achieve a more effective and selective endocrine therapy for hormone-dependent breast cancer.

Many studies have recently been undertaken to evaluate several new families of aromatase inhibitors [11–20]. Le Borgne et al. reported letrozole analogues having an arylindole moiety with imidazole or 1,2,4-triazole heterocycles [21–23]. Structure–activity relationships identified the importance of electron withdrawing groups at the para position of the phenyl with nitrile group being best [24]. This group mimics the carbonyl group of androstenedione as a hydrogen bond acceptor [25,26].

Farag et al. have recently reported new pyrazole-based letrozole and celecoxib analogues with interesting anti-aromatase activities [27,28]. Furthermore, Potter et al. have recently reported on the

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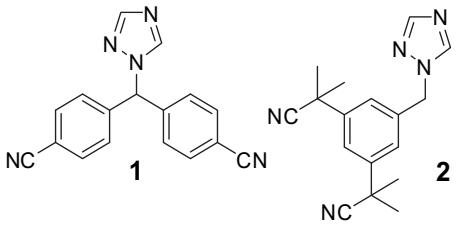


Fig. 1. Letrozole and anastrazole structures.

synthesis and *in vitro* and *in vivo* inhibitory activity of novel dual aromatase-sulfatase inhibitors based upon letrozole **1** and anastrozole **2** [29–32]. Ghosh et al. recently elucidated the crystallographic structure of aromatase with androstenedione [33]. This publically available structure will be essential for establishing the mechanism of the aromatization process, understanding the mode of action of known inhibitors, and is thus indispensable for future drug-discovery efforts for new inhibitors.

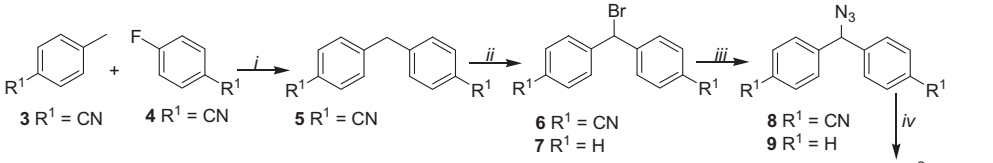
In an effort to develop more potent inhibitors of aromatase, letrozole **1** analogues were synthesized. In particular, our structure–activity relationship (SAR) study examines (1) the effect of 1,2,3-triazole instead of the 1,2,4-triazole present in the letrozole **1** structure (Fig. 1), the goal of which was to test various substituted 1,2,3-triazoles and (2) the requirement of one or two cyano or phenyl moieties together with various 1,2,3-; 1,2,4- and 1,2,5-triazoles. For comparison purposes, the corresponding imidazole analogues were synthesized. The effects of these changes were assayed against aromatase using an *in vitro* fluorimetric assay [34,35]. The effect on human epithelial adrenocortical carcinoma cell line (H295R) proliferation was also evaluated [36].

2. Results and discussion

2.1. Chemistry

Click chemistry has attracted much attention recently because of its high specificity, quantitative yield and tolerance to various groups [37]. The syntheses of letrozole **1** analogues with a 1,2,3-triazole heterocycle **10a**–**n** and **11a**–**n** are depicted in Scheme 1. Di(4-cyanophenyl)methane **5**, the key intermediate for **10a**–**n** synthesis, was obtained by cold base catalyzed (*t*-BuOK) condensation of *p*-tolunitrile **3** and *p*-flurobenzonitrile **4**. In order to introduce the azido group, necessary for copper catalyzed 1,3-dipolar cycloaddition, compound **5** was subjected to photochemical allylic bromination *via* *N*-bromosuccinimide (NBS) in CCl_4 under incandescent irradiation (250 W) to give the bromide **6** in good yields. Yields are given in the experimental section. Curiously, benzoyl peroxide catalyzed bromination with NBS failed both thermally and with UV irradiation. The novel azide **8** was thus obtained by conversion of brominated derivative **6** under nucleophilic substitution at 0 °C as all attempts to prepare **8** with heating or at room temperature failed. It should be noted that the synthesis of compounds **5**, **6** and **8** were undertaken in an oxygen free atmosphere, as the di(4-cyanophenyl)methyl framework of these compounds is prone to oxidation, producing di(4-cyanophenyl) ketone which is visible as a bright blue spot upon UV illumination of eluted TLC plates of the reaction mixture. As shown in Scheme 1, azide **9** [38] was efficiently synthesized by substitution of commercially available bromide **7** with sodium azide. Treatment of azide **8** or **9** under CuI-catalyzed click reaction conditions with aliphatic as well as substituted propargyl phenol ethers provided the final compounds, with or without *para*-cyano groups (**10a**–**n** or **11a**–**n** respectively), in good yields (Scheme 1). As described in the literature, substituted terminal alkynes used for the synthesis of **10h**–**n** and **11h**–**n** were obtained with treatment of propargyl bromide with desired substituted phenol under basic conditions (K_2CO_3, DMF) [39].

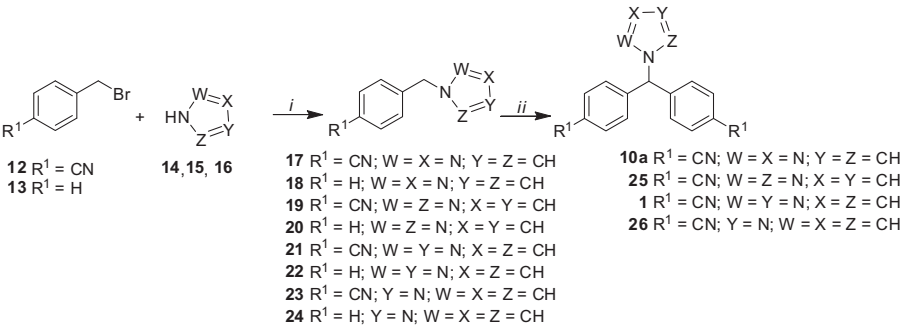
As shown in Scheme 2, mono-benzonitrile, monophenyl, and bis-benzonitrile letrozole **1** analogues in which the 1,2,4-triazole was substituted with 1,2,3-triazole (**17**–**22**, **25**) and imidazole (**23**, **24**, **26**) were also synthesized. Synthesis began with the nucleophilic substitution of brominated precursors **12** or **13** by the required five member heterocycles in acetone in the presence of potassium carbonate, affording the expected heterocyclic compounds with or without *para*-cyano groups (**17**,**19**,**21**,**23** or **18**,**20**,**22**,**24** respectively) [40,41]. Interestingly, compounds in which a 1H-1,2,3-triazole was to be tied to the aromatic frameworks afforded both the 1,2,3-triazole products (**17**,**18**) and the 1,2,5-triazole products (**19**,**20**) simultaneously. This phenomenon is most likely due to *in situ* base-induced tautomerisation of the nitrogenous heterocycle prior to the



10a R^1 = CN; R^2 = H
10b R^1 = CN; R^2 = n-Propyl
10c R^1 = CN; R^2 = n-Hexyl
10d R^1 = CN; R^2 = n-Heptyl
10e R^1 = CN; R^2 = n-Decyl
10f R^1 = CN; R^2 = Cyclohexyl
10g R^1 = CN; R^2 = Ph
10h R^1 = CN; R^2 = CH_2OPh
10i R^1 = CN; R^2 = CH_2O*p*-Cl-Ph
10j R^1 = CN; R^2 = CH_2O*p*-CN-Ph
10k R^1 = CN; R^2 = CH_2O*p*-NO_2-Ph
10l R^1 = CN; R^2 = CH_2O*p*-CH_3-Ph
10m R^1 = CN; R^2 = CH_2O*p*-OCH_3-Ph
10n R^1 = CN; R^2 = CH_2O*p*-Ph-Ph

11a R^1 = H; R^2 = H
11b R^1 = H; R^2 = n-Propyl
11c R^1 = H; R^2 = n-Hexyl
11d R^1 = H; R^2 = n-Heptyl
11e R^1 = H; R^2 = n-Decyl
11f R^1 = H; R^2 = Cyclohexyl
11g R^1 = H; R^2 = Ph
11h R^1 = H; R^2 = CH_2OPh
11i R^1 = H; R^2 = CH_2O*p*-Cl-Ph
11j R^1 = H; R^2 = CH_2O*p*-CN-Ph
11k R^1 = H; R^2 = CH_2O*p*-NO_2-Ph
11l R^1 = H; R^2 = CH_2O*p*-CH_3-Ph
11m R^1 = H; R^2 = CH_2O*p*-OCH_3-Ph
11n R^1 = H; R^2 = CH_2O*p*-Ph-Ph

Scheme 1. Reagents and conditions: (i) *t*-BuOK, DMF, −5 °C, 2 h, DMF; (ii) NBS, CCl_4, 250 W, 1 h; (iii) NaN_3, −5 °C, DMF, 1 hr for **8**; (vi) HC≡CR^2, NEt_3, CuI, rt, THF; 12 h or HC≡CH, NEt_3, CuI, rt, DMSO, 12 h for **10a** and **11a**.



Scheme 2. Reagents and conditions: (i) K_2CO_3, reflux, Acetone, 12 h; (ii) *t*-BuOK, 4-fluorobenzonitrile, rt, DMF 2.5 h.

substitution of the bromides [42]. These related compounds were easily separated and isolated by silica gel circular chromatography (see Experimental section). For the 1,2,3-triazoles, the triazole protons were observed as two singlets, each integrating for one proton, at 7.7 and 7.5 ppm. The structure of the 1,2,5-triazole isomers was confirmed by ^{1}H NMR, which gave a singlet, integrating for two protons, at 7.7 ppm for the symmetrical triazole protons. As for the synthesis of letrozole **1** [19] from compound **21**, mono-benzonitrile precursors **17**, **19** and **23** were subject to base-induced condensation with 4-fluorobenzonitrile **3** to afford the bis-benzonitrile analogues, **10a**, **25** and **26** respectively (Scheme 2) [19,43].

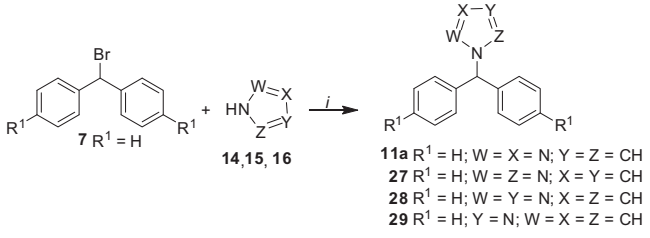
Since we were not able to obtain the corresponding bis-phenyl analogues of **18**, **20**, **22**, and **24** under basic condensation with fluorobenzene, commercially available bromide **7**, (1,2,4-; 1,2,3-) triazole, and imidazole were used for the synthesis of bis-phenyl derivatives **11a**, **27**, **28**, and **29** with good yields (Scheme 3) [44]. As for **17**, **18**, **19**, and **20** synthesis (Scheme 2), in addition to the 1,2,3-triazole isomer, the minor 1,2,5-triazole was also obtained. Compounds **11a** and **27** were isolated from the same reaction mixture after silica gel chromatography.

Following our interest to explore 1,2,3-triazole derivatives for aromatase inhibition, Scheme 4 describes the preparation of mono-aromatic 1,2,3-triazole bearing letrozole **1** analogues **34b**–**n** and **35b**–**n**. Their synthesis was initiated with the azides **32** [45] and **33** [46] which were prepared by the nucleophilic substitution of the respective benzyl bromide **30** and **31** with sodium azide. As for **10a**–**n** and **11a**–**n** synthesis, CuI-catalysed click reaction with aliphatic alkynes as well as substituted propargyl phenol ethers provided **34b**–**n** and **35b**–**n** in good yield (Scheme 4).

2.2. Biological evaluation

2.2.1. In vitro aromatase inhibitory activity

All compounds were evaluated for aromatase inhibitory activity using the CYP19 high-throughput screening kit (BD Biosciences),



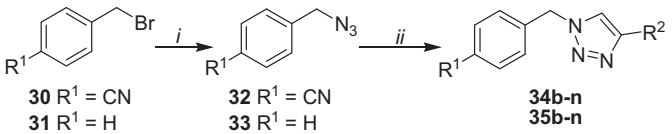
Scheme 3. Reagents and conditions: (i) K_2CO_3, reflux, Acetone, 12 h.

with 7-methoxy-4-trifluoromethyl coumarin (MFC) as the substrate and letrozole **1** as the standard for comparison (Tables 1–3). Letrozole **1** was determined to have an IC_{50} value of 0.008 μM.

Given the many reported successes of triazole use in aromatase lead discovery [12,20–23], a systematic series of unsubstituted and substituted 1,2,3-triazole and 1,2,4-triazole analogues of letrozole **1** (Fig. 1) were examined (Scheme 1). Several important trends emerged from the examination of this series (Table 1). As shown in Table 1, the 1,2,3-triazole derivatives **10a**–**n** were all relatively good inhibitors of aromatase (IC_{50}: 0.008–19.32 μM), with optimal activity obtained with the unsubstituted derivative **10a** (IC_{50}: 0.008 μM) which is equipotent with letrozole **1**. Substitution on carbon 4 of triazole of compound **10a**, results in a significant decrease of anti-aromatase activity. In the alkyl series (**10b**–**10f**), the more bulky cyclohexyl-substituted 1,2,3-triazole derivative **10f** was the least active (**10f**, IC_{50}: 19.3 μM). Introduction of phenyl (**10g**, IC_{50}: 10.3 μM) or phenoxymethyl (**10h**, IC_{50}: 10.9 μM) on carbon 4 of triazole of compound **10a** had no impact on the potency. Substituting the *para*-position of the phenyl ring of **10h** with electron withdrawing group, as in **10j** (IC_{50}: 4.6 μM) and **10k** (IC_{50}: 7.7 μM), enhanced the activity relative to the unsubstituted derivative **10h** (IC_{50}: 10.3 μM). Substitution with electron donating groups methyl and methoxy, as in **10l** and **10m**, had no impact on the activity, while the activity was decreased by the insertion of a chloride group (**10i**, IC_{50}: 16.1 μM) or a phenyl group (**10n**, IC_{50}: 13.3 μM).

As indicated by the series of 1,2,3-triazole derivatives **11a**–**n** (Table 1), the presence of the cyano groups appears to be essential for activity. Compound **10a** (IC_{50}: 0.008 μM), which bears two *para*-cyano groups is 500-fold more active than the corresponding cyano-free analogue **11a** (IC_{50}: 4.5 μM). The activity was not improved by substitution on carbon 4 of the triazole compound **11a**, as alkyl/aryl substituted derivatives (**11b**–**n**) were considerably less active than letrozole **1**, **10a**, and **11a** (Table 1). The lower IC_{50} value observed for **10b**–**n** and **11b**–**n** in comparison with **1**, **10a**, and **11a** could be attributed to an impediment of the coordination with the haeme iron of the aromatase by the bulky group (R2).

To investigate the influence of the presence of the two benzonitrile or phenyl moieties in **10a** and **11a**, mono-benzonitrile **17** and monophenyl **18** analogues were synthesized (Scheme 2). Interestingly, even when lacking one benzonitrile moiety, **17** (IC_{50}: 0.10 μM) exhibited a good inhibitory potency against aromatase and was 12.5-fold less active than **10a** and letrozole **1** (Table 2). In the same vein, **10a** analogues bearing asymmetrical (1,2,4-), symmetrical (1,2,5-) triazole and imidazole were investigated (Scheme 2). The presence of a nitrogen atom at position 3 or 4 of the five member ring seems to be crucial for activity. Asymmetrical (1,2,4- and 1,2,3-) triazole and imidazole-containing derivatives (**17**, IC_{50}: 0.10 μM **21**,



30 R^1 = CN
31 R^1 = H

32 R^1 = CN
33 R^1 = H

34b-n
35b-n

34b R^1 = CN; R^2 = n-Propyl
34c R^1 = CN; R^2 = n-Hexyl
34d R^1 = CN; R^2 = n-Heptyl
34e R^1 = CN; R^2 = n-Decyl
34f R^1 = CN; R^2 = Cyclohexyl
34g R^1 = CN; R^2 = Ph
34h R^1 = CN; R^2 = CH_2OPh
34i R^1 = CN; R^2 = CH_2O*p*-Cl-Ph
34j R^1 = CN; R^2 = CH_2O*p*-CN-Ph
34k R^1 = CN; R^2 = CH_2O*p*-NO_2-Ph
34l R^1 = CN; R^2 = CH_2O*p*-CH_3-Ph
34m R^1 = CN; R^2 = CH_2O*p*-OCH_3-Ph
34n R^1 = CN; R^2 = CH_2O*p*-Ph-Ph

35b R^1 = H; R^2 = n-Propyl
35c R^1 = H; R^2 = n-Hexyl
35d R^1 = H; R^2 = n-Heptyl
35e R^1 = H; R^2 = n-Decyl
35f R^1 = H; R^2 = Cyclohexyl
35g R^1 = H; R^2 = Ph
35h R^1 = H; R^2 = CH_2OPh
35i R^1 = H; R^2 = CH_2O*p*-Cl-Ph
35j R^1 = H; R^2 = CH_2O*p*-CN-Ph
35k R^1 = H; R^2 = CH_2O*p*-NO_2-Ph
35l R^1 = H; R^2 = CH_2O*p*-CH_3-Ph
35m R^1 = H; R^2 = CH_2O*p*-OCH_3-Ph
35n R^1 = H; R^2 = CH_2O*p*-Ph-Ph

Scheme 4. Reagents and conditions: (i) NaN_3, DMF, rt; (ii) $HC{\equiv}CR^2$, NEt_3, CuI, rt, THF, 12 h.

IC_{50}: 0.15 μM; **23**, IC_{50}: 0.007 μM) were more active than the symmetrical 1,2,5-triazole-containing derivative (**19**, IC_{50}: 12.2 μM). Compound **19**, bearing 1,2,5-triazole, was 81- and 122-fold less active than the corresponding 1,2,4-(**21**) and 1,2,3-(**17**) triazole, respectively. Compound **23**, bearing an imidazole five membered ring, was the most active in this series and was equipotent with letrozole **1** and **10a**. The importance of the presence of the nitrogen atom at position 3 or 4 of the five member ring was also confirmed by asymmetrical (1,2,4- and 1,2,3-) triazole and imidazole-containing **11a** analogues. Effectively, compounds **18**, **22**, and **24**, bearing asymmetrical triazole (1,2,3- and 1,2,4-) and imidazole, were 1.4-, 4-, and 108-fold more active than the 1,2,5-triazole-containing compound **20**, respectively (Table 2). In this fourth series, phenyl *para*-cyano substitution seems to be crucial for inhibition. Compounds **17**, **19**, **21**, and **23**, with a *para*-cyano substitution, were all more active than the corresponding free *para*-cyano substitution analogues **18**, **20**, **22**, and **24**, respectively (Table 2).

Encouraged by these latest results, symmetrical 1,2,5-triazole and imidazole-containing analogues of **1**, **10a**, and **11a** having the two benzonitrile or phenyl moieties were considered (Schemes 2 and 3). In this series our previous results were confirmed with symmetrical 1,2,5-triazole-containing compounds **25** (IC_{50}: 79.98 μM) being almost 10000-fold less active than **1** and **10a**. Imidazole-containing analogue **26** (IC_{50}: 0.004 μM), which is the most potent in this series, was 2- and 20000-fold more active than **1** (and **10a**) and **25**, respectively (Table 2). For **11a** analogues, symmetrical 1,2,5-triazole-containing compound **27** was less active than asymmetrical (1,2,4- and 1,2,3-) triazole and imidazole-containing **28**, **11a** and **29** respectively (Table 2). The imidazole-containing derivative **29** (IC_{50}: 0.02 μM) was also the most potent compound in comparison to **27**, **11a**, and **28** (Table 2). The phenyl *para*-substitution also seems to be beneficial for inhibition in this series. Except for compound **27** (IC_{50}: 12.01 μM), which was 6-fold more active than the corresponding phenyl *para*-cyano substitution-free derivative **25** (IC_{50}: 79.98 μM), **10a**, **1**, and **26** were more active than **11a**, **28** and **29** respectively (Table 2). In the last two series, the presence of two phenyl moieties seems to be crucial for inhibition. Except for compound **25** (IC_{50}: 79.98 μM), which was 6-fold less active than **19** (IC_{50}: 12.20 μM); **10a**, **1**, **26**, **11a**, **28**, and **29** were more active than **17**, **21**, **23**, **18**, **22**, and **24** respectively (Table 2).

Compound **17**, reporting an encouraging inhibitory activity (IC_{50}: 0.1 μM) prompted us to investigate whether introduction of various substituent groups at the triazole, using the classical click chemistry, would further improve the potency of aromatase inhibition. Hence, **34b**–**n** were prepared but, as shown in Table 3, the ability of these compounds to inhibit aromatase was low and did not reach the activities of letrozole **1**, **10a**, and **17** or other 1,2,3-triazoles (Table 3). Given IC_{50} values of 2–3 μM, the heptyl (**34d**, IC_{50}: 3.07 μM), phenyl (**34g**, IC_{50}: 3.38 μM), 4-chlorophenyl (**34j**, IC_{50}: 3.91 μM), and 4-methoxyphenyl (**34m**, IC_{50}: 2.34 μM) substituted compounds were the most potent. As shown with compounds **34b**–**n** (Table 3), the introduction of various substituent groups at the 1,2,3-triazole of compound **18** (IC_{50}: 11.88 μM) lead to an increase of activity in general. The *para*-cyanophenoxymethylene-containing analogue **35j** (IC_{50}: 1.36 μM), which is the most potent in this series, was 8-fold more active than **18** (Table 3). By comparison between Tables 1 and 3, compounds **34n**–**b** and **35b**–**n** are more active than their counterparts with two *para*-cyanophenyl (**10b**–**n**) or phenyl (**11b**–**n**), respectively. Unlike other series, the presence of the cyano group does not seem to influence

Table 1
IC_{50} data for analogues **10a**–**n** and **11a**–**n** using CYP19 high-throughput screening kit [47].

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)	Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
10a	0.008	**10h**	10.97	**11a**	4.58	**11h**	31.26
10b	4.70	**10i**	16.11	**11b**	10.96	**11i**	13.37
10c	5.07	**10j**	4.64	**11c**	14.83	**11j**	16.41
10d	10.60	**10k**	7.73	**11d**	19.36	**11k**	11.61
10e	16.02	**10l**	10.95	**11e**	13.54	**11l**	26.77
10f	19.32	**10m**	12.16	**11f**	13.72	**11m**	15.21
10g	10.33	**10n**	13.35	**11g**	12.94	**11n**	15.48

Table 2
IC_{50} data for analogues **17**–**29**, **1**, **10a**, and **11a** using CYP19 high-throughput screening kit [47].

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)	Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
17	0.10	**18**	11.88	**10a**	0.008	**11a**	4.58
19	12.20	**20**	16.31	**25**	79.98	**27**	12.01
21	0.15	**22**	4.11	**1**	0.008	**28**	1.10
23	0.007	**24**	0.15	**26**	0.004	**29**	0.02

Table 3
IC_{50} data for analogues **34b**–**n**, **35b**–**n**, **19**, and **20** using CYP19 high-throughput screening kit [47].

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)	Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
19	0.10	**34h**	6.09	**20**	11.88	**35h**	10.60
34b	4.37	**34i**	3.91	**35b**	12.63	**35i**	5.04
34c	5.26	**34j**	9.16	**35c**	7.47	**35j**	1.36
34d	3.07	**34k**	5.62	**35d**	9.53	**35k**	2.78
34e	7.88	**34l**	4.17	**35e**	6.40	**35l**	2.27
34f	10.70	**34m**	2.34	**35f**	7.98	**35m**	17.34
34g	3.38	**34n**	11.57	**35g**	9.77	**35n**	10.70

activity. Paradoxically, the best compound (**35j**, IC_{50}: 1.36 μM) in this series has a *para*-cyanophenoxymethylene at position 4 of the 1,2,3-triazole.

2.2.2. Antiproliferative activity

Some of the compounds from each series that showed the best biological activities in our first test, the triazoles (**10a**–**c**, **10j**, **35j**–**l**) and the imidazoles (**23**, **26**, **29**), were evaluated for their effects on the human epithelial adrenocortical carcinoma cell line (H295R) proliferation (see Fig. 2). The H295R cell line is a commonly used model for the study of aromatase activity [48–51]. The results showed that most of our compounds displayed an antiproliferative activity against H295R cells comparable with that of letrozole **1**. Furthermore, compound **10j** with a *para*-cyanophenoxymethylene-1,2,3-triazole moiety exhibits the most potent antiproliferative activity in comparison to letrozole **1**(Fig. 2), suggesting other effects in addition to aromatase inhibition. Previous studies have demonstrated that at a concentration of 10 nM, letrozole **1** inhibits nearly 10% of H295R proliferation [52]. While at the same concentration, **10j** inhibited 76% of cell proliferation in 24 h and 99% in 72 h. Compound **35j**, cyano-free group analogue, did not exhibit significant activity. Analogue **26** in which the 1,2,4-triazole was substituted with an imidazole inhibited 40% of H295R proliferation.

2.3. Computer modelling

Comparison of the IC_{50} data for **10a** and **25** (0.008 μM *vs* 79.98 μM) clearly shows the importance of carbon substitution at position 3 or 4 of the five member ring by nitrogen (Table 2)). At the same time, experimental analysis of the interaction between aromatase cytochrome P450 and its substrate androstenedione shows the importance of hydrogen bonding in positioning and stabilization of the substrate [33]. Hydrogen bond acceptors in androstenedione are the two oxygen atoms of carbonyl functions at 10.25 Å separation [33]. Finally, virtual screening and analysis of known, strong, aromatase inhibitors resulted in recommendations for the necessary requirements for a pharmacophore including the need for two hydrogen bond acceptors [54]. Similarly the work of Neves et al. [55] points also to the importance of hydrogen bonding in aromatase inhibitor binding. Geometric differences of the studied compounds particularly related to hydrogen bonding potential have been explored by using quantum chemical structure and electronic structure simulations. From theoretically obtained

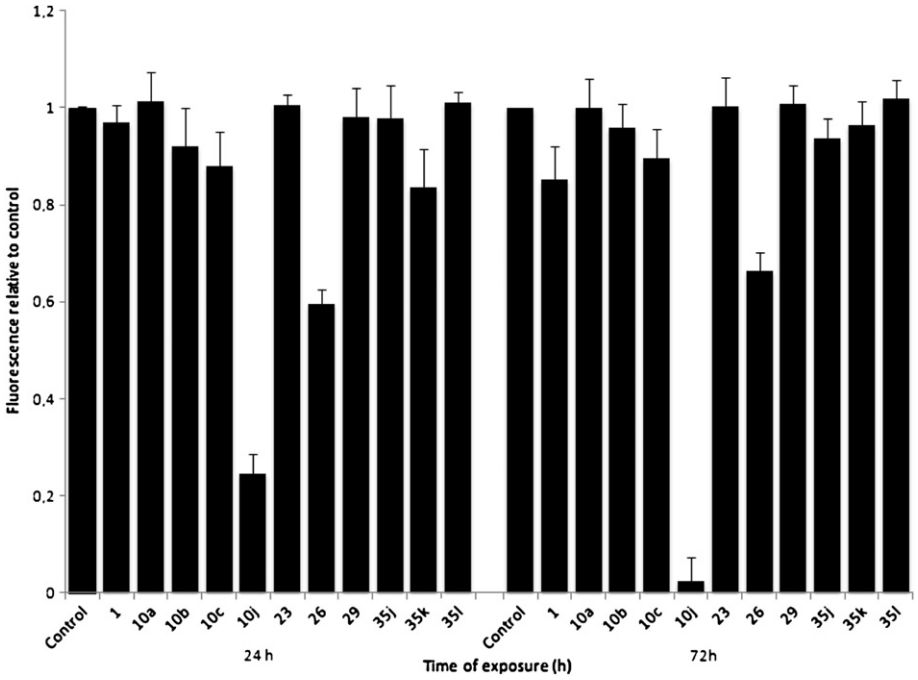


Fig. 2. Relative growth rates of the human epithelial adrenocortical carcinoma cell line (H295R) treated with different test compounds (10 nM) [53].

structures for these compounds (Fig. 2), the geometric differences in the orientation of the asymmetrical 1,2,3-triazole and the symmetrical 1,2,5-triazole rings are apparent (Figure S1: see supplementary material). Theoretical calculations revealed a correlation between the inter-nitrogen distances, as shown for **10a** and **25** (Table S1: see supplementary material), and biological activity. As a cyano group in the *para* position of the phenyl ring is an essential structural requirement for inhibitory activity with azole-type aromatase inhibitors [24,56], the presence of another nitrogen on the heterocyclic ring, at a particular position and distance, seems to be also crucial for inhibition with such compounds [26,55]. Nitrogens in the studied compounds are expected to be hydrogen bond acceptors as was confirmed by the HOMO and LUMO analysis (data not shown). The distance between the nitrogens in computationally analyzed structures of androstenedione, **1**, **10a**, and **25** are provided in Table S1 (see supplementary material) [57]. It can be observed that in compound **10a** and letrozole **1** distances between the nitrogen of the cyano group and the nitrogen at position 3 or 4 of the triazole are similar to the distance between oxygens in the natural substrate (Figure S1: see supplementary material). At the same time, nitrogens at position 2 of the triazole and that of the second cyano group in compounds **1**, **10a** and **25** could possibly provide an additional hydrogen bond with another binding partner in the target protein which might explain the observed difference in the IC_{50} values.

3. Conclusions

In summary, we have described the synthesis of a systematic series of unsubstituted and substituted 1,2,3-triazole, 1,2,4-triazole and imidazole analogues of letrozole **1**. The key step of the synthesis of 1,2,3-triazole analogues is a copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition (click) onto azides (**8**, **9**, **32**, or **33**) with selected aliphatic alkynes or substituted propargyl phenol ethers. Mono-benzonitrile and monophenyl letrozole **1** analogues in which the 1,2,4-triazole was substituted with (1,2,3 or 1,2,5)-triazole and imidazole were also synthesized by nucleophilic substitution onto brominated precursors by the required five member heterocycles. Base-induced condensation with 4-fluorobenzonitrile onto mono-benzonitrile precursors afforded the bis-benzonitrile analogues.

From the structure–activity point of view, the synthesized and tested molecules in this study allowed us to conclude that the nitrogen atom in position 3 or 4 of 1,2,4-triazole is crucial for inhibition of aromatase. Analogues with a 1,2,3-triazole or imidazole are more active than the corresponding 1,2,5-triazole analogue. The presence of a *para*-cyano group and two aryl groups also seems important for good activity. Moreover, among our analogues with 1,2,3-triazole, synthesized *via* click chemistry, compounds bearing a *para*-cyanophenoxymethylene (**10j** and **35j**) could serve as potential lead compounds. With IC_{50}'s of 4.6 and 1.36 μM, respectively (**10j** and **35j**) and with excellent inhibition of cell proliferation for **10j**, these compounds will be the starting point of another series of molecules in which the cyano group position, the nature, as well as the length of the linker between the phenyl and the triazole can be investigated.

4. Experimental section

4.1. Chemistry

All chemicals used were purchased from Aldrich (CA). Purification of compounds was carried out by silica gel circular chromatography (chromatotron®, model 7924, Harrison Research). TLC was run on silica gel coated aluminium sheets (SiliaPlate TLC, Silicycle®) with detection by UV light (254 nm, UVS-11, Mineralight® shortwave UV lamp). Melting points were obtained using a MEL-TEMP® (model 1001D) melting point apparatus. FTIR spectra were recorded on a Nicolet® Impact 400 spectrometer. NMR spectra were recorded on a Bruker® Avance III 400 MHz spectrometer. High resolution mass measurements were performed on an Agilent® LC-MSD-TOF instrument (model 6210) in positive electrospray. Protonated ions (M + nH)n+ were used for empirical formula confirmation.

4.1.1. 4,4′-Dicyanodiphenylmethane (*5*)

At −5 °C and under inert atmosphere, 7.68 g (69 mmol) of *t*-BuOK are suspended in 20 mL anhydrous DMF with vigourous stirring. Over a period of 1 h, 2.34 g (19.9 mmol) of 4-methylbenzonitrile dissolved in 5 mL DMF are added dropwise to the reaction mixture, followed by dropwise addition of 3.66 g (30.3 mmol) of 4-fluorobenzonitrile dissolved in 5 mL DMF over 30 min. After 30 min the solution is quenched with 120 mL water, which is then extracted with 4 × 40 mL AcOEt. The organic fraction is dried over $MgSO_4$, filtered and concentrated under vacuum to give a yellow oil which slowly crystallizes. The resulting solid is recrystallized in 20 mL tertbutyl ether to give 2.25 g (5.64 mmol, yield = 52%) of 4,4′-dicycanodiphenylmethane **5** as fluffy beige crystals. Mp = 166–167 °C (lit. 168 °C), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.62 (d, 4H, *J* = 8.2 Hz, N≡CC(CH)), 7.29 (d, 4H, *J* = 8.2 Hz, N≡CC(CHCH)), 4.11 (s, 2H, Ar–CH_2–Ar), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm) = 144.82, 132.58, 129.72, 118.66, 110.78, 41.90; HRMS *m*/*z* calc. for $C_{15}H_{10}N_2$ + (H^+): 219.0917; found: 219.0913.

4.1.2. 4,4′-Dicyanodiphenylbromomethane (*6*)

Under nitrogen and with stirring, 2.027 g (9.29 mmol) of 4,4′-dicyanodiphenylmethane **5** and 1.689 g (9.29 mmol) of NBS are dissolved in 10 mL CCl_4. A 250 W incandescent lamp is then placed 10–15 cm from the reaction vessel, which quickly comes to reflux. After 1hr, TLC analysis (30% AcOEt/Hex) shows disappearance of the starting material. The resulting mixture is cooled, filtered and the residual solid washed with CH_2Cl_2 until no more solid dissolves to give an orange solution which is then evaporated under vacuum. The resulting oil is diluted with 40 mL CH_2Cl_2, washed twice with water, twice with brine, dried over $MgSO_4$, filtered and concentrated. The oily residue is then recrystallized from 60% AcOEt/Hex to give 1.739 g (5.85 mmol, yield = 63%) of the desired bromide **6** as a white solid. Mp = 118–119 °C, R_f = 0.55 (30% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.68 (d, 4H, *J* = 8.3 Hz, N≡CC(CH)), 7.55 (d, 4H, *J* = 8.3 Hz, N≡CC(CHCH)), 6.25 (s, 1H, CHBr), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm) = 144.65, 132.69, 129.15, 118.07, 112.59, 51.61; HRMS *m*/*z* calc. for $C_{15}H_9BrN_2$ + (H^+): 297.0022; found: 297.0021.

4.1.3. 4,4′-Dicyanodiphenylazidomethane (*8*)

To a stirred solution of 1.404 g (21.6 mmol) NaN_3 in anhydrous DMF at −5 °C and under N_2 was added 1.727 g (5.81 mmol) of 4,4′-dicyanodiphenylbromomethane **6**. After 1 h the reaction is quenched with 75 mL H_2O and extracted with 3 × 25 mL diethyl ether. The combined organic fractions were then washed with water, brine, dried over $MgSO_4$ and concentrated. The resulting translucent oil is purified by silica gel circular chromatography using 10% AcOEt/Hex to afford 1.450 g (5.60 mmol, yield = 96%) of the desired azido derivative **8** as a white solid. Mp = 63–64 °C, R_f = 0.67 (100% CH_2Cl_2), I.R. 2232 cm^{-1}, 2117 cm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.71 (d, 4H, *J* = 8.3 Hz, N≡CC(CH)), 7.45 (d, 4H, *J* = 8.3 Hz, N≡CC(CHCH)), 5.82 (s, 1H, CHN_3), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm) = 143.44, 132.87, 128.03, 118.11, 112.73, 62.23; HRMS *m*/*z* calc. for $C_{15}H_9N_5$ + (H^+): 260.0931; found: 260.0930.

4.1.4. 1-(4,4′-Dicyanodiphenylmethyl)-1H-1,2,3-triazole (**10a**)

To a stirred solution of 180 mg (0.7 mmol) 4,4′-dicyanodiphenylazidomethane **8** in 6 mL DMSO was added 13 mg (0.07 mmol) CuI. The reaction vessel was then purged with acetylene gas, after which 85 mg (0.84 mmol) triethylamine were added. The reaction mixture was left under acetylene atmosphere (balloon pressure) with stirring overnight before being quenched with 125 mL saturated sodium chloride solution. The resulting mixture was extracted with 4 × 25 mL AcOEt after which the organic phases were combined and washed with 2 × 25 mL concentrated NH_4Cl and 2 × 25 mL brine, dried over $MgSO_4$ and concentrated to yield a yellow oil which, after silica gel circular chromatography (0–40% AcOEt/Hex) afforded the desired triazole as a white powder, yield = 29% Mp = 210 °C (dec.), R_f = 0.49 (2% MeOH/CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.83 (s, 1H, =CHN), 7.73 (d, 4H, J = 8.3 Hz, H_{Ar}), 7.52 (s, 1H, =CHN), 7.27 (d, 4H, J = 8.3 Hz, H_{Ar}), 7.16 (s, 1H, Ph–CH–Ph); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm): 141.79, 134.37, 133.02, 128.87, 123.70, 117.81, 113.41, 66.91; HRMS m/z calc. for $C_{17}H_{11}N_5 + (H^+)$: 286.1087; found: 286.1084.

4.2. General procedure for the preparation of 1,2,3-triazoles (**10b–10n**, **11b–11n**)

To a stirred solution of the azido precursor **8** (0.5 mmol) in 4 mL THF at room temperature are sequentially added 1.5 eq of the desired alkyne (0.75 mmol), 0.1 eq. of copper (I) iodide (0.05 mmol) and 1.2 eq. of triethylamine (0.6 mmol). The solution is stirred for 12 h then diluted with 30 mL ethyl acetate, washed twice with a saturated solution of NH_4Cl, twice with brine, dried over $MgSO_4$, filtered and evaporated. The residue is purified by silica gel circular chromatography (eluent: EtOAc/Hex or MeOH/CH_2Cl_2).

4.2.1. 1-(4,4′-Dicyanodiphenylmethyl)-4-propyl-1H-1,2,3-triazole (**10b**)

From azide **8** and 1-pentyne. Dark brown oil after silica gel circular chromatography (0–40% AcOEt/Hex), yield = 58%. R_f = 0.19 (30% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.71 (d, 4H, J = 8.4 Hz, N≡CC(CH)), 7.26 (d, 4H, J = 8.4 Hz, N≡CC(CHC<u>H</u>)), 7.20 (s, 1H, =CHN), 7.09 (s, 1H, Ph–CH–Ph), 2.73–2.70 (t, 2H, J = 7.6 Hz, <u>CH_2</u>CH_2CH_3), 1.75–1.70 (m, 2H, CH_2<u>CH_2</u>CH_3), 0.99–0.95 (t, 3H, J = 7.4 Hz, CH_3), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm) = 148.97, 142.07, 132.96, 128.87, 120.73, 117.89, 113.23, 66.84, 27.67, 22.56, 13.79; HRMS m/z calc. for $C_{20}H_{17}N_5 + (H^+)$: 328.1557; found: 328.1556.

4.2.2. 1-(4,4′-Dicyanodiphénylméthyl)-4-hexyl-1H-1,2,3-triazole (**10c**)

From azide **8** and 1-octyne. Translucent oil after silica gel circular chromatography (0–25% AcOEt/Hex), yield = 80%. R_f = 0.41 (35% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.72 (d, 4H, J = 8.5 Hz, N≡CC(CH)), 7.22 (d, 4H, J = 8.5 Hz, N≡CC(CHC<u>H</u>)), 7.19 (s, 1H, =CHN), 7.08 (s, 1H, Ph–CH–Ph), 2.73 (t, 2H, J = 7.8 Hz, <u>CH_2</u>$CH_2(CH_2)_3CH_3$), 1.67 (m, 2H, CH_2<u>CH_2</u>$(CH_2)_3CH_3$), 1.41–1.25 (m, 6H, CH_2CH_2(<u>CH_2</u>$)_3CH_3$), 0.89 (t, 3H, J = 6.9 Hz, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm) = 149.24, 142.06, 132.95, 128.87, 120.60, 117.87, 113.25, 66.85, 31.47, 29.25, 28.91, 25.71, 22.52, 14.02; HRMS m/z calc. for $C_{23}H_{23}N_5 + (H^+)$: 370.2020; found: 370.2019.

4.2.3. 1-(4,4′-Dicyanodiphenylmethyl)-4-heptyl-1H-1,2,3-triazole (**10d**)

From azide **8** and 1-nonyne. Translucent oil after silica gel circular chromatography (0–30% AcOEt/Hex), yield = 69%. R_f = 0.38 (35% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.71 (d, 4H, J = 8.5 Hz, N≡CC(CH)), 7.26 (d, 4H, J = 8.5 Hz, N≡CC(CHC<u>H</u>)), 7.19 (s, 1H, =CHN), 7.08 (s, 1H, Ph–CH–Ph), 2.73 (t, 2H, J = 7.8 Hz, <u>CH_2</u>$CH_2(CH_2)_4CH_3$), 1.67 (m, 2H, CH_2<u>CH_2</u>$(CH_2)_4CH_3$), 1.34–1.22 (m, 8H, CH_2CH_2(<u>CH_2</u>$)_4CH_3$), 0.88 (t, 3H, J = 6.9 Hz, CH_3), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm) = 149.23, 142.08, 132.95, 128.88, 120.62, 117.88, 113.23, 66.84, 31.70, 29.29, 29.21, 28.94, 25.71, 22.59, 14.07; HRMS m/z calc. for $C_{24}H_{25}N_5 + (H^+)$: 384.2180; found: 384.2180.

4.2.4. 1-(4,4′-Dicyanodiphenylmethyl)-4-decyl-1H-1,2,3-triazole (**10e**)

From azide **8** and 1-dodecyne. Translucent oil after silica gel circular chromatography (0–25% AcOEt/Hex), yield = 79%. R_f = 0.43 (35% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.71 (d, 4H, J = 8.3 Hz, N≡CC(CH)), 7.26 (d, 4H, J = 8.3 Hz, N≡CC(CHC<u>H</u>)), 7.19 (s, 1H, =CHN), 7.08 (s, 1H, Ph–CH–Ph), 2.73 (t, 2H, J = 7.8 Hz, <u>CH_2</u>$CH_2(CH_2)_7CH_3$), 1.67 (m, 2H, CH_2<u>CH_2</u>$(CH_2)_7CH_3$), 1.40–1.23 (m, 14H, CH_2CH_2(<u>CH_2</u>$)_7CH_3$), 0.89 (t, 3H, J = 6.9 Hz, CH_3), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm) = 149.25, 142.07, 132.95, 128.87, 120.60, 117.87, 113.25, 66.85, 31.89, 29.56, 29.53, 29.30, 25.72, 22.67, 14.11; HRMS m/z calc. for $C_{27}H_{31}N_5 + (H^+)$: 426.2652; found: 426.2648.

4.2.5. 1-(4,4′-Dicyanodiphenylmethyl)-4-cyclohexyl-1H-1,2,3-triazole (**10f**)

From azide **8** and ethynylcyclohexane. White solid after silica gel circular chromatography (0–35% AcOEt/Hex), yield = 63%. Mp = 150–152 °C, R_f = 0.34 (35% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.71 (d, 4H, J = 8.1 Hz, N≡CC(CH)), 7.25 (d, 4H, J = 8.1 Hz, N≡CC(CHC<u>H</u>)), 7.15 (s, 1H, =CHN), 7.07 (s, 1H, Ph–CH–Ph), 2.80–2.75 (m, 1H, cyclohexyl), 2.11–2.00 (m, 2H, cyclohexyl), 1.84–1.65 (m, 3H, cyclohexyl), 1.48–1.33 (m, 4H, cyclohexyl), 1.33–1.19 (m, 1H, cyclohexyl), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm) = 154.42, 142.12, 132.94, 128.89, 119.32, 117.89, 113.21, 66.89, 35.31, 32.91, 26.04, 25.93; HRMS m/z calc. for $C_{23}H_{21}N_5 + (H^+)$: 368.1870; found: 368.1865.

4.2.6. 1-(4,4′-Dicyanodiphenylmethyl)-4-phenyl-1H-1,2,3-triazole (**10g**)

From azide **8** and 1-ethynylbenzene. White solid after silica gel circular chromatography (0–0.3% MeOH/CH_2Cl_2), yield = 91%. Mp = 82–85 °C, R_f = 0.52 (2% MeOH/CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.83 (m, 2H, H_{Ar}), 7.74 (d, 4H, J = 8.4 Hz, N≡CC(CH)), 7.68 (s, 1H, =CHN), 7.46–7.42 (m, 2H, H_{Ar}), 7.40–7.35 (m, 1H, H_{Ar}), 7.32 (d, 4H, J = 8.4 Hz, N≡CC(CHC<u>H</u>)), 7.18 (s, 1H, Ph–CH–Ph), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm) = 148.38, 141.76, 133.06, 129.75, 128.97, 128.93, 128.73, 125.78, 119.50, 117.83, 113.42, 67.10; HRMS m/z calc. for $C_{23}H_{15}N_5 + (H^+)$: 362.1400; found: 362.1393.

4.2.7. 1-(4,4′-Dicyanodiphenylmethyl)-4-(phenoxymethyl)-1H-1,2,3-triazole (**10h**)

From azide **8** and 1-(prop-2-ynyloxy)benzene. White solid after silica gel circular chromatography (0–0.3% MeOH/CH_2Cl_2), yield = 71%. Mp = 55–59 °C, R_f = 0.27 (1.5% MeOH/CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.72 (d, 4H, J = 8.5 Hz, N≡CC(CH)), 7.56 (s, 1H, =CHN), 7.33–7.29 (m, 2H, H_{Ar}), 7.26 (d, 4H, J = 8.5 Hz, N≡CC(CHC<u>H</u>)), 7.12 (s, 1H, Ph–CH–Ph), 7.03–6.99 (m, 3H, H_{Ar}), 5.25 (s, 2H, CH_2–O–Ph), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm) = 157.96, 145.09, 141.64, 133.03, 129.62, 128.89, 122.81, 121.55, 117.82, 114.80, 113.41, 67.14, 62.00; HRMS m/z calc. for $C_{24}H_{17}N_5O + (H^+)$: 392.1506; found: 392.1503.

4.2.8. 1-(4,4′-Dicyanodiphenylmethyl)-4-((4-chlorophenoxy)methyl)-1H-1,2,3-triazole (**10i**)

From azide **8** and 1-chloro-4-(prop-2-ynyloxy)benzene. White solid after silica gel circular chromatography (0–0.3% MeOH/CH_2Cl_2), yield = 60%. Mp = 59–63 °C, R_f = 0.27 (1.5% MeOH/

CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.72 (d, 4H, J = 8.4 Hz, N≡CC(CH)), 7.55 (s, 1H, =CHN), 7.27–7.24 (m, 6H, N≡CC(CHC<u>H</u>) + ClC(CH)), 7.12 (s, 1H, Ph–CH–Ph), 6.91 (m, 2H, ClC(CHC<u>H</u>)), 5.20 (s, 2H, CH_2–O–Ph), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm) = 156.58, 144.57, 141.56, 133.05, 129.49, 128.87, 126.48, 122.90, 117.79, 116.14, 113.47, 67.18, 62.25; HRMS m/z calc. for $C_{24}H_{16}ClN_5O$ + (H^+): 426.1116; found: 426.1111.

4.2.9. 1-(4,4′-Dicyanodiphenylmethyl)-4-((4-cyanophenoxy) methyl)-1H-1,2,3-triazole (**10j**)

From azide **8** and 4-(prop-2-ynyloxy)benzonitrile. White solid after silica gel circular chromatography (0–0.4% MeOH/CH_2Cl_2), yield = 97%. Mp = 72–75 °C, R_f = 0.32 (2% MeOH/CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.73 (d, 4H, J = 8.5 Hz, N≡CC(CH)), 7.63–7.59 (m, 3H, H_{Ar} + =CHN), 7.28 (d, 4H, J = 8.5 Hz, N≡CC(CHC<u>H</u>)), 7.13 (s, 1H, Ph–CH–Ph), 7.07 (m, 2H, H_{Ar}), 5.27 (s, 2H, CH_2–O–Ph), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm) = 161.24, 143.68, 141.48, 134.11, 133.08, 128.89, 123.18, 118.91, 117.75, 115.46, 113.53, 104.89, 67.26, 62.00; HRMS m/z calc. for $C_{25}H_{16}N_6O$ + (H^+): 417.1458; found: 417.1449.

4.2.10. 1-(4,4′-Dicyanodiphenylmethyl)-4-((4-nitrophenoxy) methyl)-1H-1,2,3-triazole (**10k**)

From azide **8** and 1-nitro-4-(prop-2-ynyloxy)benzene. White solid after silica gel circular chromatography (0–0.4% MeOH/CH_2Cl_2), yield = 71%. Mp = 72–76 °C, R_f = 0.21 (1% MeOH/CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 8.22 (dt, 2H, J = 7.0 Hz, 2.8 Hz, NO_2C(CH)), 7.73 (d, 4H, J = 8.5 Hz, N≡CC(CH)), 7.63 (s, 1H, =CHN), 7.29 (d, 4H, J = 8.5 Hz, N≡CC(CHC<u>H</u>)), 7.13 (s, 1H, Ph–CH–Ph), 7.08 (dt, 2H, J = 7.0 Hz, 2.8 Hz, NO_2C(CHC<u>H</u>)), 5.32 (s, 2H, CH_2–O–Ph), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm) = 162.90, 143.48, 142.06, 141.44, 133.09, 128.88, 125.98, 123.24, 117.74, 114.77, 113.56, 67.30, 62.33; HRMS m/z calc. for $C_{24}H_{16}N_6O_3$ + (H^+): 437.1357; found: 437.1351.

4.2.11. 1-(4,4′-Dicyanodiphenylmethyl)-4-((p-tolyloxy)methyl)-1H-1,2,3-triazole (**10l**)

From azide **8** and 1-methyl-4-(prop-2-ynyloxy)benzene. White solid after silica gel circular chromatography (0–0.4% MeOH/CH_2Cl_2), yield = 77%. Mp = 55–64 °C, R_f = 0.47 (2% MeOH/CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.71 (d, 4H, J = 8.4 Hz, N≡CC(CH)), 7.56 (s, 1H, =CHN), 7.26 (d, 4H, J = 8.4 Hz, N≡CC(CHC<u>H</u>)), 7.12–7.09 (m, 3H, H_{Ar} + Ph–CH–Ph), 6.87 (m, 2H, H_{Ar}), 5.20 (s, 2H, CH_2–O–Ph), 2.31 (s, 3H, CH_3), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm) = 155.90, 145.23, 141.68, 133.02, 130.86, 130.04, 128.90, 122.82, 117.84, 114.67, 113.37, 67.12, 62.19, 20.50; HRMS m/z calc. for $C_{15}H_{19}N_5O$ + (H^+): 416.1662; found: 406.1659.

4.2.12. 1-(4,4′-Dicyanodiphenylmethyl)-4-((4-methoxyphenoxy) methyl)-1H-1,2,3-triazole (**10m**)

From azide **8** and 1-methoxy-4-(prop-2-ynyloxy)benzene. White solid after silica gel circular chromatography (0–0.4% MeOH/CH_2Cl_2), yield = 70%. Mp = 55–63 °C, ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.72 (d, 4H, J = 8.4 Hz, N≡CC(CH)), 7.53 (s, 1H, =CHN), 7.26 (d, 4H, J = 8.4 Hz, N≡CC(CHC<u>H</u>)), 7.11 (s, 1H, Ph–CH–Ph), 6.92–6.89 (m, 2H, H_{Ar}), 6.87–6.83 (m, 2H, H_{Ar}), 5.19 (s, 2H, CH_2–O–Ph), 3.79 (s, 3H, OCH_3), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm) = 154.41, 152.06, 145.26, 141.64, 133.03, 128.88, 122.75, 117.81, 115.97, 114.70, 113.43, 67.13, 62.82, 55.70; HRMS m/z calc. for $C_{25}H_{19}N_5O_2$ + (H^+): 422.1612; found: 422.1603.

4.2.13. 1-(4,4′-Dicyanodiphenylmethyl)-4-((4-phenylphenoxy) methyl)-1H-1,2,3-triazole (**10n**)

From azide **8** and 1-phenyl-4-(prop-2-ynyloxy)benzene. White solid after silica gel circular chromatography (0–0.25% MeOH/CH_2Cl_2), yield = 80%. Mp = 66–70 °C, R_f = 0.28 (1% MeOH/CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.72 (d, 4H, J = 8.3 Hz, N≡CC(CH)), 7.58–7.53 (m, 5H, H_{Ar} + =CHN), 7.47–7.42 (m, 2H, H_{Ar}), 7.36–7.32 (m, 1H, H_{Ar}), 7.27 (d, 4H, J = 8.3 Hz, N≡CC(CHC<u>H</u>)), 7.12 (s, 1H, Ph–CH–Ph), 7.08–7.04 (m, 2H, H_{Ar}), 5.29 (s, 2H, CH_2O), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm) = 157.53, 145.00, 141.62, 140.44, 134.64, 133.04, 128.89, 128.83, 128.26, 126.94, 126.71, 122.86, 117.80, 115.11, 113.44, 67.18, 62.15; HRMS m/z calc. for $C_{30}H_{21}N_5O$ + (H^+): 468.1819; found: 468.1813.

4.2.14. 1-(Diphenylmethyl)- 1H-1,2,3-triazole (**11a**)

Compound **11a** was prepared from azide **9** [32] and acetylene using the general procedure for the synthesis of **10a**. Purification by chromatography (0–20% AcOEt/Hex) gave **11a** as a white solid; yield = 92%. Mp = 119–120 °C, R_f = 0.27 (40% AcOEt/hexane), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.75 (s, 1H, =CHN=), 7.45 (s, 1H, =CHN–Ph), 7.40–7.37, (m, 6H, H_{Ar}), 7.17 (s, 1H, CH–Ph), 7.14–7.12 (m, 4H, H_{Ar}), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm): 138.19, 133.65, 128.94, 128.59, 128.08, 123.56, 67.94; HRMS m/z calc. for $C_{15}H_{13}N_3$ + (H^+): 236.1182; found: 236.1178.

4.2.15. 1-(Diphenylmethyl)-4-propyl-1H-1,2,3-triazole (**11b**)

From azide **9** and 1-pentyne and using the general procedure for the synthesis of **10b**–**n**. White solid after silica gel circular chromatography (0–20% AcOEt/Hex), yield = 40%. Mp = 89–90 °C, R_f = 0.25 (30% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.40–7.34 (m, 6H, H_{Ar}), 7.15 (s, 1H, =CHN), 7.14–7.11 (m, 4H, H_{Ar}), 7.10 (s, 1H, Ph–CH–Ph), 2.70 (t, 2H, J = 7.4 Hz, <u>CH_2</u>CH_2CH_3), 1.69 (sext., 2H, J = 7.4 Hz, CH_2<u>CH_2</u>CH_3), 0.96 (t, 3H, J = 7.4 Hz, CH_3), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 148.10, 138.44, 128.87, 128.45, 128.09, 120.66, 67.88, 27.81, 22.70, 13.80. HRMS m/z calc. for $C_{18}H_{19}N_3$ + (H^+): 278.1652; found: 278.1645.

4.2.16. 1-(Diphenylmethyl)-4-hexyl-1H-1,2,3-triazole (**11c**)

From azide **9** and 1-octyne and using the general procedure for the synthesis of **10b**–**n**. White solid after silica gel circular chromatography (0–13% AcOEt/Hex), yield = 68%. Mp = 70–72 °C, R_f = 0.11 (30% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.40–7.35 (m, 6H, H_{Ar}), 7.162–7.109 (m, 5H, H_{Ar} + =CHN), 7.10 (s, 1H, Ph–CH–Ph), 2.71 (t, 2H, J = 7.7 Hz, <u>CH_2</u>$CH_2(CH_2)_3CH_3$), 1.66 (quint., 2H, J = 7.7 Hz, CH_2<u>CH_2</u>$(CH_2)_3CH_3$), 1.39–1.27 (m, 6H, CH_2CH_2(<u>CH_2</u>)$_3CH_3$), 0.88 (m, 3H, CH_3), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C δ (ppm): 148.35, 138.45, 128.86, 128.44, 128.09, 120.56, 67.87, 31.51, 29.39, 28.92, 25.83, 22.54, 14.03. HRMS m/z calc. for $C_{21}H_{25}N_3$ + (H^+): 320.2121; found 320.2116.

4.2.17. 1-(Diphenylmethyl)-4-heptyl-1H-1,2,3-triazole (**11d**)

From azide **9** and 1-nonyne and using the general procedure for the synthesis of **10b**–**n**. White solid after silica gel circular chromatography (0–15% AcOEt/Hex), yield = 66%. Mp = 70–71 °C, R_f = 0.29 (30% AcOEt/Hex). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.40–7.34 (m, 6H, H_{Ar}), 7.16–7.11 (m, 5H, H_{Ar} + =CHN), 7.10 (s, 1H, Ph–CH–Ph), 2.71 (t, 2H, J = 7.6 Hz, <u>CH_2</u>$CH_2(CH_2)_4CH_3$), 1.66 (quit., 2H, J = 7.6 Hz, CH_2<u>CH_2</u>$(CH_2)_4CH_3$), 1.36–1.27 (m, 8H, CH_2CH_2(<u>CH_2</u>)$_4CH_3$), 0.88 (m, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 148.35, 138.46, 128.86, 128.44, 128.09, 120.56, 67.88, 31.74, 29.43, 29.22, 28.97, 25.82, 22.59, 14.08. HRMS m/z calc. for $C_{22}H_{27}N_3$ + (H^+): 334.2278; found: 334.2270.

4.2.18. 1-(Diphenylmethyl)-4-decyl-1H-1,2,3-triazole (**11e**)

From azide **9** and 1-dodecyne and using the general procedure for the synthesis of **10b**–**n**. White solid after silica gel circular chromatography (0–25% AcOEt/Hex), yield = 88%. Mp = 83–84 °C, R_f = 0.52 (30% AcOEt/Hex). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C)

δ (ppm): 7.41–7.35 (m, 6H, H_{Ar}), 7.15–7.11 (m, 5H, H_{Ar} + =CHN), 7.09 (s, 1H, Ph–CH–Ph), 2.71 (t, 2H, J = 7.6 Hz, $\underline{CH_2}CH_2(CH_2)_7CH_3$), 1.64 (quit., 2H, J = 7.6 Hz, $CH_2\underline{CH_2}(CH_2)_7CH_3$), 1.33–1.29 (m, 14H, $CH_2CH_2(\underline{CH_2})_7CH_3$), 0.89 (m, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 148.36, 138.46, 128.85, 128.43, 128.09, 120.55, 67.88, 31.90, 29.56, 29.44, 29.32, 25.83, 22.68, 14.11. HRMS m/z calc. for $C_{25}H_{33}N_3$ + (H^+): 376.2747; found: 375.2740.

*4.2.19. 1-(Diphenylmethyl)-4-cyclohexyl-1H-1,2,3-triazole (**11f**)*

From azide **9** and ethynylcyclohexane and using the general procedure for the synthesis of **10b**–**n**. White solid after silica gel circular chromatography (0–15% AcOEt/Hex), yield = 51%. Mp = 160–162 °C, R_f = 0.31 (30% AcOEt/Hex). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.40–7.33 (m, 6H, H_{Ar}), 7.15–7.10 (m, 5H, H_{Ar} + =CHN), 7.09 (s, 1H, Ph–CH–Ph), 2.80–2.74 (m, 1H, cyclohexyl), 2.07–2.05 (m, 2H, cyclohexyl), 1.81–1.69 (m, 3H, cyclohexyl), 1.44–1.29 (m, 4H, cyclohexyl), 1.29–1.23 (m, 1H, cyclohexyl). ^{13}C NMR (101 MHz, $CDCl_3$, 25 C) δ (ppm): 153.60, 138.50, 128.85, 128.42, 128.11, 119.20, 67.90, 35.42, 33.02, 26.15, 26.06. HRMS m/z calc. for $C_{21}H_{23}N_3$ + (H^+): 318.1965; found: 318.1958.

*4.2.20. 1-(Diphenylmethyl)-4-phenyl-1H-1,2,3-triazole (**11g**)*

From azide **9** and 1-ethynylbenzene and using the general procedure for the synthesis of **10b**–**n**. White solid after silica gel circular chromatography (0–15% AcOEt/Hex), yield = 78%. Mp = 176–178 °C, R_f = 0.35 (30% AcOEt/Hex). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.84–7.82 (m, 2H, H_{Ar}), 7.63 (s, 1H, =CHN), 7.43–7.38 (m, 8H, H_{Ar}), 7.37–7.31 (m, 1H, H_{Ar}), 7.20–7.19 (m, 4H, H_{Ar}), 7.18 (s, 1H, Ph–CH–Ph), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 147.58, 138.15, 130.57, 128.97, 128.79, 128.62, 128.16, 128.13, 125.73, 119.58, 68.16. HRMS m/z calc. for $C_{21}H_{17}N_3$ + (H^+): 312.1495; found: 312.1489.

*4.2.21. 1-(Diphenylmethyl)-4-phenoxymethyl-1H-1,2,3-triazole (**11h**)*

From azide **9** and 1-(prop-2-ynyloxy)benzene and using the general procedure for the synthesis of **10b**–**n**. Pale yellow solid after silica gel circular chromatography (0–15% AcOEt/Hex), yield = 72%. Mp = 153–154 °C, R_f = 0.28 (30% AcOEt/Hex). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.50 (s, 1H, =CHN), 7.41–7.36 (m, 5H, H_{Ar}), 7.32–7.28 (m, 3H, H_{Ar}), 7.14–7.12 (m, 5H, H_{Ar} + Ph–CH–Ph), 7.01–6.97 (m, 3H, H_{Ar}), 5.22 (s, 2H, CH_2–O–Ph), ^{13}C NMR, (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 158.21, 144.08, 138.02, 129.51, 128.97, 128.63, 128.10, 122.79, 121.30, 114.90, 68.23, 62.23. HRMS m/z calc. for $C_{22}H_{19}N_3O$ + (H^+): 342.1601; found: 342.1597.

*4.2.22. 1-(Diphenylmethyl)-4-chloro-phenoxymethyl-1H-1,2,3-triazole (**11i**)*

From azide **9** and 1-chloro-4-(prop-2-ynyloxy)benzene and using the general procedure for the synthesis of **10b**–**n**. White solid after silica gel circular chromatography (0–20% AcOEt/Hex), yield = 70%. Mp = 137–138 °C, R_f = 0.47 (30% AcOEt/Hex). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.48 (s, 1H, =CHN), 7.42–7.36 (m, 6H, H_{Ar}), 7.26–7.22 (m, 2H, H_{Ar}), 7.17–7.10 (m, 5H, H_{Ar} + Ph–CH–Ph), 6.94–6.90 (m, 2H, H_{Ar}), 5.18 (s, 2H, CH_2–O–Ph), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 156.78, 143.57, 137.95, 129.39, 128.99, 128.68, 128.07, 126.22, 122.91, 116.27, 68.25, 62.48. HRMS m/z calc. for $C_{22}H_{18}N_3OCl$ + (H^+): 376.1211; found: 376.1207.

*4.2.23. 1-(Diphenylmethyl)-4-cyano-phenoxymethyl-1H-1,2,3-triazole (**11j**)*

From azide **9** and 4-(prop-2-ynyloxy)benzonitrile and using the general procedure for the synthesis of **10b**–**n**. White solid after silica gel circular chromatography (0–15% AcOEt/Hex), yield = 78%. Mp = 116–117 °C, R_f = 0.37 (30% AcOEt/Hex). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.61–7.52 (m, 2H, H_{Ar}), 7.51 (s, 1H, =CHN), 7.42–7.37 (m, 6H, H_{Ar}), 7.15–7.11 (m, 5H, H_{Ar} + Ph–CH–Ph), 7.07–7.04 (m, 2H, H_{Ar}), 5.25 (s, 2H, CH_2–O–Ph), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 161.42, 142.73, 137.84, 134.03, 129.03, 128.75, 128.06, 123.15, 119.06, 115.60, 104.61, 68.33, 62.23. HRMS m/z calc. for $C_{23}H_{19}N_4O$ + (H^+): 367.1553, found: 367.1547.

*4.2.24. 1-(Diphenylmethyl)-4-nitro-phenoxymethyl-1H-1,2,3-triazole (**11k**)*

From azide **9** and 1-nitro-4-(prop-2-ynyloxy)benzene and using the general procedure for the synthesis of **10b**–**n**. White solid after silica gel circular chromatography (0–13% AcOEt/Hex), yield = 88%. Mp = 134–135 °C, R_f = 0.17 (30% AcOEt/Hex). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 8.24–8.20 (m, 2H, H_{Ar}), 7.53 (1H, s, =CHN), 7.41–7.37 (6H, m, H_{Ar}), 7.16–7.12 (5H, m, H_{Ar} + Ph–CH–Ph), 7.10–7.06 (2H, m, H_{Ar}), 5.30 (2H, s, CH_2–O–Ph), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 163.12, 142.53, 141.91, 137.82, 129.04, 128.77, 128.06, 125.93, 123.22, 114.89, 68.36, 62.57. HRMS m/z calc. for $C_{22}H_{18}N_4O_3$ + (H^+): 387.1452; found: 387.1442.

*4.2.25. 1-(Diphenylmethyl)-4-methyl-phenoxymethyl-1H-1,2,3-triazole (**11l**)*

From azide **9** and 1-methyl-4-(prop-2-ynyloxy)benzene and using the general procedure for the synthesis of **10b**–**n**. White solid after silica gel circular chromatography (0–25% AcOEt/Hex), yield = 99%. Mp = 121–122 °C, R_f = 0.58 (30% AcOEt/Hex). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.49 (s, 1H, =CHN), 7.41–7.36 (m, 6H, H_{Ar}), 7.16–7.09 (m, 7H, H_{Ar} + Ph–CH–Ph), 6.90–6.87 (m, 2H, H_{Ar}), 5.19 (s, 2H, CH_2–O–Ph), 2.31 (s, 3H, CH_3), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 156.14, 144.24, 138.04, 130.57, 129.95, 128.96, 128.62, 128.11, 122.77, 114.80, 68.21, 62.46, 20.50. HRMS m/z calc. for $C_{23}H_{21}N_3O$ + (H^+): 356.1757; found: 356.1749.

*4.2.26. 1-(Diphenylmethyl)-4-methoxy-phenoxymethyl-1H-1,2,3-triazole (**11m**)*

From azide **9** and 1-methoxy-4-(prop-2-ynyloxy)benzene and using the general procedure for the synthesis of **10b**–**n**. White solid after silica gel circular chromatography (0–25% AcOEt/Hex), yield = 40%. Mp = 122–123 °C, R_f = 0.53 (30% AcOEt/Hex). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.48 (s, 1H, =CHN), 7.41–7.28 (m, 6H, H_{Ar}), 7.14–7.11 (m, 5H, H_{Ar} + Ph–CH–Ph), 6.94–6.90 (m, 2H, H_{Ar}), 6.86–6.82 (m, 2H, H_{Ar}) 5.17 (s, 2H, CH_2–O–Ph), 3.73 (s, 3H, CH_3), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 154.25, 152.33, 144.23, 138.03, 128.96, 128.62, 128.10, 122.79, 116.09, 114.63, 68.20, 63.06, 55.69. HRMS m/z calc. for $C_{23}H_{21}N_3O_2$ + (H^+): 372.1707; found: 372.1698.

*4.2.27. 1-(Diphenylmethyl)-4-phenyl-phenoxymethyl-1H-1,2,3-triazole (**11n**)*

From azide **9** and 1-phenyl-4-(prop-2-ynyloxy)benzene and using the general procedure for the synthesis of **10b**–**n**. Grey solid after silica gel circular chromatography (0–25% AcOEt/Hex), yield = 80%. Mp = 180–182 °C, R_f = 0.51 (30% AcOEt/Hex). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.58–7.53 (m, 5H, H_{Ar} + =CHN), 7.46–7.28 (m, 9H, H_{Ar}), 7.16–7.13 (m, 5H, H_{Ar} et Ph–CH–Ph), 7.08–7.06 (m, 2H, H_{Ar}), 5.27 (s, 2H, CH_2–O–Ph), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 157.79, 143.98, 140.66, 138.01, 134.37, 128.99, 128.75, 128.66, 128.19, 128.11, 126.78, 126.76, 122.88, 115.21, 68.26, 62.38. HRMS m/z calc. for $C_{28}H_{23}N_3O$ + (H^+): 418.1914; found: 418.1903.

*4.3. General procedure for the preparation of compounds **17**–**24***

To a stirred solution of 500 mg of the appropriate bromide **12** or **13** in 25 mL anhydrous acetone, under N_2 at room temperature, is

added 1.5 eq. of the desired nitrogenous heterocycle followed by 1.5 eq. of K_2CO_3 and 0.05 eq. of KI. The reaction mixture is left to react overnight at reflux temperature. The resulting solution is diluted with 100 mL of water and extracted with 3 × 30 mL EtOAc. The organic fractions are combined, washed twice with 30 mL KOH 1 M, twice with brine, dried over $MgSO_4$, filtered and concentrated. The residue is purified by silica gel circular chromatography (eluent: EtOAc/Hex or MeOH/CH_2Cl_2) to yield the pure heterocyclic compounds. 1-substituted-1H-1,2,3-triazoles and 2-substituted-2H-1,2,3-triazoles (**17**/**18**, **19**/**20**) were obtained simultaneously. These isomers were separated by silica gel circular chromatography.

4.3.1. 1-(4-Cyanophenylmethyl)-1H-1,2,3-triazole (17) and 2-(4-cyanophenylmethyl)-2H-1,2,3-triazole (**19**)

From bromide **12** and 1H-1,2,3-triazole **14**, white solid after silica gel circular chromatography (0–80% AcOEt/Hex), yield (**17**) = 52%. Mp = 82–83 °C, R_f = 0.40 (2% MeOH/CH_2Cl_2). (**17**): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.77 (s, 1H, =CHN=), 7.70 (d, 2H, J = 8.1 Hz, H_{Ar}), 7.62 (s, 1H, =CHN–Ph), 7.35 (d, 2H, J = 8.1 Hz, H_{Ar}), 5.66 (s, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm) = 199.75, 139.98, 134.59, 132.87, 128.32, 123.71, 118.14, 112.72, 53.18; HRMS m/z calc. for $C_{10}H_8N_4$ + (H^+): 185.0822; found: 185.0823. Yield (**19**) = 35%. Mp = 80–81 °C, R_f = 0.83 (2% MeOH/CH_2Cl_2). (**19**): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.70 (s, 2H, NCHCHN), 7.66 (d, 2H, J = 8.1 Hz, H_{Ar}), 7.38 (d, 2H, J = 8.1 Hz, H_{Ar}), 5.69 (s, 2H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm) = 140.36, 135.04, 132.61, 128.49, 118.38, 112.34, 57.79; HRMS m/z calc. for $C_{10}H_8N_4$ + (H^+): 185.0822; found: 185.0819.

4.3.2. 1-(Phenylmethyl)-1H-1,2,3-triazole (**18**) and 2-(phenylmethyl)-2H-1,2,3-triazoles (**20**)

From bromide **13** and 1H-1,2,3-triazole **14**, white solid after silica gel circular chromatography (0–50% AcOEt/Hex), yield (**18**) = 75%. Mp = 56–57 °C, R_f = 0.17 (40% AcOEt/hexane). (**18**): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.75 (s, 1H, =CH–N=), 7.49 (s, 1H, =CH–N–Ph), 7.42–7.35, (m, 3H, H_{Ar}), 7.29–7.27 (m, 2H, H_{Ar}), 5.59 (s, 2H, CH_2–Ph), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm): 134.70, 134.27, 129.12, 128.75, 128.02, 123.30, 53.98. HRMS m/z calc. for $C_9H_9N_3$ + (H^+): 160.0869; found: 160.0868. Yield (**20**) = 23%. Mp = 39–41 °C, R_f = 0.63 (40% AcOEt/hexane). (**20**) ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.65 (s, 2H, =CHCH=), 7.39–7.32, (5H, m, H_{Ar}), 5.63 (s, 2H, CH_2–Ph), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm): 135.25, 134.53, 128.80, 128.33, 128.01, 58.59; HRMS m/z calc. for $C_9H_9N_3$ + (H^+): 160.0869; found: 160.0868.

4.3.3. 1-(4-Cyanophenylmethyl)-1H-1,2,4-triazole (**21**)

From bromide **12** and 1H-1,2,4-triazole **15**, white solid after silica gel circular chromatography (0–80% AcOEt/Hex), yield = 56%. Mp = 66–68 °C, R_f = 0.14 (70% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 8.17 (s, 1H, NCHN), 8.02 (s, 1H, NCHN), 7.68 (d, 2H, J = 8.1 Hz, H_{Ar}), 7.35 (d, 2H, J = 8.1 Hz, H_{Ar}), 5.44 (s, 2H, CH_2), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm): 152.70, 143.46, 139.91, 132.84, 128.31, 116.16, 112.67, 52.74; HRMS m/z calc. for $C_{10}H_{18}N_4$ + (H^+): 185.0822; found: 185.0821.

4.3.4. 1-(Phenylmethyl)-1H-1,2,4-triazole (**22**)

From bromide **13** and 1H-1,2,4-triazole **15**, yellow solid after silica gel circular chromatography (0–50% AcOEt/Hex), yield = 63%. Mp = 90 °C, R_f = 0.45 (50% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 8.05 (s, 1H, NCHN), 7.95 (s, 1H, NCHN), 7.45–7.23 (m, 5H, H_{Ar}), 5.34 (s, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm) = 153.10, 144.00, 135.50, 130.04, 129.64, 128.98, 54.57; HRMS m/z calc. for $C_9H_9N_3$ + (H^+): 160.0869; found: 160.0870.

4.3.5. 1-(4-Cyanophenylmethyl)-1H-imidazole (**23**)

From bromide **12** and imidazole **16**, white solid after silica gel circular chromatography (0–1% MeOH/CH_2Cl_2), yield = 50%. Mp = 89–90 °C, R_f = 0.10 (1% MeOH/CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.71–7.65 (d, 2H, J = 8.1 Hz, H_{Ar}), 7.58 (s, 1H, NCH=N), 7.27–7.21 (d, 2H, J = 8.1 Hz, H_{Ar}), 7.18 (s, 1H, NCHCHN), 6.95 (s, 1H, NCHCHN), 5.24 (s, 1H, CH_2–Ph); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm): 141.63, 137.55, 132.78, 130.40, 127.59, 119.28, 118.25, 112.22, 50.11; HRMS m/z calc. for $C_{11}H_9N_3$ + (H^+): 184.0869; found: 184.0867.

4.3.6. 1-(Phenylmethyl)-1H-imidazole (**24**)

From bromide **13** and imidazole **16**, yellow solid after silica gel circular chromatography (0–50% AcOEt/Hex), yield = 67%. Mp = 68–70 °C, R_f = 0.21 (50% AcOEt/Hex), ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.52 (s, 1H, NCHN), 7.45–7.00 (m, 5H, H_{Ar}), 6.97 (s, 1H, NCHCHN), 6.89 (s, 1H, NCHCHN), 5.00 (s, 2H, CH_2), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm) = 137.45, 136.21, 129.82, 128.98, 128.25, 127.27, 119.29, 50.78; HRMS m/z calc. for $C_{10}H_{10}N_2$ + (H^+): 159.0917; found: 159.0914.

4.4. General procedure for the preparation of compounds **10a**, **25**, and **26**

At −5 °C and under inert atmosphere, 2.0 mmol of *t*-BuOK are suspended in 3.5 mL anhydrous DMF with vigourous stirring. Over a period of 1 h, 0.75 mmol of **17** (**19**, or **23**) dissolved in 1 mL DMF is added dropwise to the reaction mixture, followed by dropwise addition of 133 mg (1.09 mmol) of 4-fluorobenzonitrile over 30 min. After 1hr the mixture is quenched with 3 M HCl until acidic (pH < 5), neutralized with $NaHCO_3$, diluted with 100 mL water then extracted with 4 × 25 mL EtOAc. The organic fraction is washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue is purified by silica gel circular chromatography (eluent: EtOAc/Hex) to yield the pure compounds.

4.4.1. 1-(4,4′-Dicyanodiphenylmethyl)-1H-1,2,3-triazole (**10a**)

From **17** and 4-fluorobenzonitrile, white powder after silica gel circular chromatography (0–40% AcOEt/Hex), yield = 26%. Mp = 210 °C (dec.), R_f = 0.49 (2% MeOH/CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.83 (s, 1H, =CHN), 7.73 (d, 4H, J = 8.3 Hz, H_{Ar}), 7.52 (s, 1H, =CHN), 7.27 (d, 4H, J = 8.3 Hz, H_{Ar}), 7.16 (s, 1H, Ph–CH–Ph); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm): 141.79, 134.37, 133.02, 128.87, 123.70, 117.81, 113.41, 66.91; HRMS m/z calc. for $C_{17}H_{11}N_5$ + (H^+): 286.1087; found: 286.1084.

4.4.2. 2-(4,4′-Dicyanodiphenylmethyl)-2H-1,2,3-triazoles (**25**)

From **19** and 4-fluorobenzonitrile, yellow crystals after silica gel circular chromatography (0–25% AcOEt/Hex), yield = 58%. Mp = 154–156 °C, R_f = 0.82 (2% MeOH/CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.76 (s, 2H, NCHCHN), 7.69 (d, 4H, J = 8.3 Hz, H_{Ar}), 7.33 (d, 4H, J = 8.3 Hz, H_{Ar}), 7.15 (s, 1H, Ph–CH–Ph); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm): 142.38, 135.37, 132.66, 129.03, 118.11, 112.88, 70.91; HRMS m/z calc. for $C_{17}H_{11}N_5$ + (H^+): 286.1087; found: 286.1083.

4.4.3. 1-(4,4′-Dicyanodiphenylmethyl)-1H-imidazole (**26**)

From **23** and 4-fluorobenzonitrile, yellow syrup after silica gel circular chromatography (0–25% AcOEt/Hex), yield = 66%. R_f = 0.30 (2% MeOH/CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.72 (d, 4H, J = 8.1 Hz, H_{Ar}), 7.49 (s, 1H, NCH=N), 7.22 (d, 4H, J = 8.1 Hz, H_{Ar}), 7.16 (s, 1H, Ph–CH–Ph), 6.89 (s, 1H, NCHCHN), 6.72 (s, 1H, NCHCHN); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm): 142.87, 137.15, 132.97, 130.33, 128.81, 118.88, 117.93, 113.01, 63.83; HRMS m/z calc. for $C_{18}H_{12}N_4$ + (H^+): 285.1135; found: 285.1133.

4.4.4. 2-(Diphenylmethyl)-2H-1,2,3-triazoles (**27**) and 1-(diphenylmethyl)-1H-1,2,3-triazole (**11a**)

Compound **27** and **11a** were simultaneously prepared from bromide **7** (400 mg, 1.6 mmol) and 1H-1,2,3-triazole **14** (223.5 mg, 3.23 mmol) using the general procedure for the synthesis of **17**–**24**. Purification by chromatography (0–20% AcOEt/Hex) gave **27** as a white solid; yield = 22%. Mp = 89–91 °C, R_f = 0.67 (40% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.71 (s, 2H, =CHCH=), 7.40–7.34, (m, 6H, H_{Ar}), 7.25–7.23 (m, 4H, H_{Ar}), 7.11 (s, 1H, Ph–CH–Ph), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm): 138.67, 134.49, 128.59, 128.27, 128.22, 72.26; HRMS *m*/*z* calc. for $C_{15}H_{13}N_3$ + (H^+): 236.1182; found: 236.1178. Purification by chromatography (0–20% AcOEt/Hex) gave **11a** as a white solid; yield = 71%. Mp = 119–120 °C, R_f = 0.27 (40% AcOEt/hexane), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.75 (s, 1H, =CHN=), 7.45 (s, 1H, CHN–Ph), 7.40–7.37, (m, 6H, H_{Ar}), 7.17 (s, 1H, CH–Ph), 7.14–7.12 (m, 4H, H_{Ar}), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm): 138.19, 133.65, 128.94, 128.59, 128.08, 123.56, 67.94; HRMS *m*/*z* calc. for $C_{15}H_{13}N_3$ + (H^+): 236.1182; found: 236.1178.

4.4.5. 1-(Diphenylmethyl)-1H-1,2,4-triazole (**28**)

Compound **28** was prepared from bromide **7** (500 mg, 2.03 mmol) and 1H-1,2,4-triazole **15** (209 mg, 3.04 mmol) using the general procedure for the synthesis of **17**–**24**. Purification by chromatography (0–20% AcOEt/Hex) gave **27** as a white solid; yield = 51%. Mp = 89–91 °C, R_f = 0.71 (50% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 8.02 (s, 1H, NCHN), 7.91 (s, 1H, NCHN), 7.50–7.00 (m, 10H, H_{Ar}), 6.72 (s, 1H, Ph–CH–Ph), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm) = 152.30, 143.56, 137.95, 128.97, 128.63, 128.15, 67.89; HRMS *m*/*z* calc. for $C_{15}H_{13}N_3$ + (H^+): 236.1182; found: 236.1182.

4.4.6. 1-(Diphenylmethyl)-1H-imidazole (**29**)

Compound **29** was prepared from bromide **7** (500 mg, 2.03 mmol) and imidazole **16** (206 mg, 3.03 mmol) using the general procedure for the synthesis of **17**–**24**. Purification by chromatography (0–20% AcOEt/Hex) gave **29** as a yellow solid; yield = 55%. Mp = 83–84 °C, R_f = 0.47 (50% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm) = 7.40 (s, 1H, NCHN), 7.38–7.12 (m, 11H, NCHCHN + H_{Ar}), 6.89 (s, 1H, NCHCHN), 6.54 (s, 1H, Ph–CH–Ph), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C), δ (ppm) = 139.15, 137.44, 129.39, 128.88, 128.38, 128.08, 119.39, 65.04; HRMS *m*/*z* calc. for $C_{16}H_{14}N_2$ + (H^+): 235.1230; found: 236.1228.

4.5. General CuAAC procedure for the preparation of 1,2,3-triazoles (**34b**–**n**, **35b**–**n**)

To a stirred solution of the appropriate azido precursor **32** [39], or **33** [40] (0.5 mmol) in 4 mL THF at room temperature are sequentially added 1.5 eq of the desired alkyne (0.75 mmol), 0.1 eq. of copper (I) iodide (0.05 mmol) and 1.2 eq. of triethylamine (0.6 mmol). The solution is stirred for 12 h then diluted with 30 mL ethyl acetate, washed twice with a saturated solution of NH_4Cl, twice with brine, dried over $MgSO_4$, filtered and evaporated. The residue is purified by silica gel circular chromatography (eluent: EtOAc/Hex or MeOH/CH_2Cl_2).

4.5.1. 1-(4-Cyanophenylmethyl)-4-propyl-1H-1,2,3-triazole (**34b**)

From azide **32** and pent-1-yne. Yellow crystals after silica gel circular chromatography (0–30% AcOEt/Hex), yield = 40%. Mp = 80–82 °C, R_f = 0.57 (50% AcOEt/Hex), ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.67 (d, 2H, *J* = 8.4 Hz, N≡CC(CH)), 7.45–7.35 (m, 3H, =CHN + N≡CC(CHCH)), 5.60 (s, 2H, CH_2–Ph), 2.72 (m, 2H, $-\underline{CH_2}CH_2CH_3$), 1.70 (m, 2H, $-CH_2\underline{CH_2}CH_3$), 0.95 (m, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 149.12, 140.34, 132.79, 128.26, 120.92, 118.21, 112.51, 53.15, 27.64, 22.57, 13.74. HRMS *m*/*z* calc. for $C_{13}H_{14}N_4$ + (H^+): 227.1291; found: 227.1290.

4.5.2. 1-(4-Cyanophenylmethyl)-4-hexyl-1H-1,2,3-triazole (**34c**)

From azide **32** and oct-1-yne. White powder after silica gel circular chromatography (0–30% AcOEt/Hex), yield = 76%. Mp = 84–86 °C, R_f = 0.74 (50% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.68 (d, 2H, *J* = 8.4 Hz, N≡CC(CH)), 7.32 (d, 2H, *J* = 8.4 Hz, N≡CC(CHCH)), 7.28 (s, 1H, =CHN), 5.60 (s, 2H, CH_2–Ph), 2.75 (m, 2H, $-\underline{CH_2}CH_2(CH_2)_3CH_3$), 1.82–1.60 (m, 2H, $-CH_2\underline{CH_2}(CH_2)_3CH_3$), 1.55–1.20 (m, 6H, $-CH_2CH_2(\underline{CH_2})_3CH_3$), 0,89 (m, 3H, CH_3), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 149.47, 140.30, 132.83, 128.25, 120.73, 118.18, 112.63, 53.20, 31.52, 29.31, 28.89, 25.68, 22.53, 14.04. HRMS *m*/*z* calc. for $C_{16}H_{20}N_4$ + (H^+): 269.1761; found: 269.1758.

4.5.3. 1-(4-Cyanophenylmethyl)-4-heptyl-1H-1,2,3-triazole (34d)

From azide **32** and non-1-yne. White solid after silica gel circular chromatography (0–20% AcOEt/Hex), yield = 71%. Mp = 70–72 °C, R_f = 0.18 (50% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.68 (d, 2H, *J* = 8.4, N≡CC(CH)), 7.35 (d, 2H, *J* = 8.4 Hz, N≡CC(CHCH)), 7.25 (s, 1H, =CHN), 5.56 (s, 2H, CH_2–Ph), 2.72 (m, 2H, $\underline{CH_2}CH_2(CH_2)_4CH_3$), 1.80–1.58 (m, 2H, $CH_2\underline{CH_2}(CH_2)_4CH_3$), 1.55–1.10 (m, 8H, $CH_2CH_2(\underline{CH_2})_4CH_3$), 0.86 (m, 3H, CH_3).^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 149.43, 140.31, 132.80, 128.25, 120.74, 118.17, 112.59, 53.18, 31.703, 29.33, 29.17, 28.97, 25.67, 22.59, 14.05. HRMS *m*/*z* calc. for $C_{17}H_{22}N_4$ + (H^+): 283.1917; found: 283.1914.

4.5.4. 1-(4-Cyanophenylmethyl)-4-decyl-1H-1,2,3-triazole (**34e**)

From azide **32** and dodec-1-yne. White solid after silica gel circular chromatography (0–20% AcOEt/Hex), yield = 58%. Mp = 98–100 °C, R_f = 0.19 (50% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.68 (d, 2H, *J* = 8.4 Hz, N≡CC(CH)), 7.35 (d, 2H, *J* = 8.4, N≡CC(CHCH)), 7.30 (s, 1H, =CHN), 5.60 (s, 2H, CH_2–Ph), 2.72 (m, 2H, $\underline{CH_2}CH_2(CH_2)_7CH_3$), 1.80–1.60 (m, 2H, $CH_2\underline{CH_2}(CH_2)_7CH_3$), 1.60–1.15 (m, 14H, $CH_2CH_2(\underline{CH_2})_7CH_3$), 0.90 (m, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 149.46, 140.30, 132.81, 128.24, 120.73, 118.18, 112.60, 53.18, 31.88, 29.56, 29.52, 29.33, 29.24, 25.68, 22.66, 14.10. HRMS *m*/*z* calc. for $C_{20}H_{28}N_4$ + (H^+): 325.2387; found: 325.2381.

4.5.5. 1-(4-Cyanophenylmethyl)-4-cyclohexyl-1H-1,2,3-triazole (**34f**)

From azide **32** and ethynylcyclohexane. White powder after silica gel circular chromatography (0–20% AcOEt/Hex), yield = 86%. Mp = 159–160 °C, R_f = 0.17 (30% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.68 (d, 2H, *J* = 8.4 Hz, N≡CC(CH)), 7.34 (d, 2H, *J* = 8.4 Hz, N≡CC(CHCH)), 7.22 (s, 1H, =CHN), 5.57 (s, 2H, CH_2–Ph), 2.78–2.75 (m, 1H, cyclohexyl), 2.07–2.04 (m, 2H, cyclohexyl), 1.82–1.67 (m, 4H, cyclohexyl), 1.45–1.34 (m, 2H, cyclohexyl), 1.29–1.22 (m, 2H, cyclohexyl). ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 154.72, 140.27, 132.85, 128.29, 119.41, 118.21, 112.63, 53.23, 35.30, 32.96, 26.09, 25.99. HRMS *m*/*z* calc. for $C_{16}H_{18}N_4$ + (H^+): 267.1604; found: 267.1597.

4.5.6. 1-(4-Cyanophenylmethyl)-4-phenyl-1H-1,2,3-triazole (**34g**)

From azide **32** and 1-ethynylbenzene. White solid after silica gel circular chromatography (0–20% AcOEt/Hex), yield = 63%. Mp = 120–124 °C, R_f = 0.68 (50% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.95–7.62 (5H, m, H_{Ar} + =CHN), 7.60–7.36 (5H, m, H_{Ar}), 5.65 (2H, s, CH_2–Ph). ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 148.70, 139.90, 132.94, 130.12, 128.92, 128.49, 128.36, 125.75, 119.64, 118.13, 112.85, 53.48. HRMS *m*/*z* calc. for $C_{16}H_{12}N_4$ + (H^+): 261.1135; found: 261.1132.

4.5.7. 1-(4-Cyanophenylmethyl)-4-phenoxymethyl-1H-1,2,3-triazole (**34h**)

From azide **32** and 1-(prop-2-ynyloxy)benzene. White solid after silica gel circular chromatography (0–30% AcOEt/Hex), yield = 77%. Mp = 78–80 °C, R_f = 0.20 (50% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.75–7.65 (m, 3H, H_{Ar} + =CHN), 7.45–7.30 (m, 4H, H_{Ar}), 7.05–6.98 (m, 3H, H_{Ar}), 5.62 (s, 2H, CH_2–Ph), 5.25 (s, 2H, CH_2–O–Ph). ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 158.07, 145.27, 139.69, 132.91, 129.58, 128.40, 122.80, 121.40, 114.76, 112.84, 61.97, 53.45. HRMS *m*/*z* calc. for $C_{17}H_{14}N_4O$ + (H^+): 291.1240; found: 291.1236.

4.5.8. 1-(4-Cyanophenylmethyl)-4-((4-chlorophenoxy)methyl)-1H-1,2,3-triazole (**34i**)

From azide **32** and 1-chloro-4-(prop-2-ynyloxy)benzene. White powder after silica gel circular chromatography (0–40% AcOEt/Hex), yield = 78%. Mp = 124–128 °C, R_f = 0.44 (50% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.61 (d, 2H, *J* = 8.4 Hz, N≡CC(CH)), 7.60 (s, 1H, =CHN), 7.38 (d, 2H, *J* = 8.4 Hz, N≡CC(CHCH)), 7.30–7.42 (m, 2H, H_{Ar}), 7.00–6.90 (m, 2H, H_{Ar}), 5.61 (s, 2H, CH_2–Ph), 5.20 (s, 2H, CH_2–O–Ph). ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 156.67, 144.76, 139.59, 132.93, 129.45, 128.43, 126.32, 122.88, 118.08, 116.12, 112.91, 62.24, 53.49. HRMS *m*/*z* calc. for $C_{17}H_{13}ClN_4O$ + (H^+): 325.0851; found: 325.0844.

4.5.9. 1-(4-Cyanophenylmethyl)-4-((4-cyanophenoxy)methyl)-1H-1,2,3-triazole (**34j**)

From azide **32** and 4-(prop-2-ynyloxy)benzonitrile. White solid after silica gel circular chromatography (0–2% MeOH/CH_2Cl_2), yield = 98%. Mp = 142–144 °C, R_f = 0.60 (5% MeOH/CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.80–7.55 (d, 5H, H_{Ar} + =CHN), 7.48–7.40 (m, 2H, H_{Ar}), 7.15–7.05 (m, 2H, H_{Ar}), 5.62 (s, 2H, CH_2–Ph), 5.27 (s, 2H, CH_2–O–Ph). ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 161.34, 143.82, 139.51, 134.06, 132.93, 128.50, 123.22, 119.00, 118.06, 115.52, 112.91, 104.64, 62.02, 53.54. HRMS *m*/*z* calc. for $C_{18}H_{13}N_5O$ + (H^+): 316.1193; found: 316.1189.

4.5.10. 1-(4-Cyanophenylmethyl)-4-((4-nitrophenoxy)methyl)-1H-1,2,3-triazole (**34k**)

From azide **32** and 1-nitro-4-(prop-2-ynyloxy)benzene. White flakes after silica gel circular chromatography (0–1% MeOH/CH_2Cl_2), yield = 76%. Mp = 108–110 °C, R_f = 0.20 (5% MeOH/CH_2Cl_2), ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ (ppm): 8.42 (s, 1H, =CHN), 8.22 (d, 2H, *J* = 8.6 Hz, NO_2C(CH)), 7.88 (d, 2H, *J* = 8.4 Hz, N≡CC(CH)) 7.55 (d, 2H, *J* = 8.4 Hz, N≡CC(CHCH)), 7.29 (d, 2H, *J* = 8.6 Hz, NO_2C(CHCH)), 5.75 (s, 2H, CH_2–Ph), 5.36 (s, 2H, CH_2–O–Ph). ^{13}C NMR (101 MHz, DMSO-d_6, 25 °C) δ (ppm): 163.28, 142.25, 141.39, 141.12, 132.80, 128.79, 125.89, 125.41, 118.54, 115.372, 111.05, 61.93, 52.31. HRMS *m*/*z* calc. for $C_{17}H_{13}N_5O_3$ + (H^+): 336.1091; found: 336.1086.

4.5.11. 1-(4-Cyanophenylmethyl)-4-((4-methylphenoxy)methyl)-1H-1,2,3-triazole (**34l**)

From azide **32** and 1-methyl-4-(prop-2-ynyloxy)benzene. White powder after silica gel circular chromatography (0–30% AcOEt/Hex), yield = 71%. Mp = 112–114 °C, R_f = 0.20 (50% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.69 (d, 2H, *J* = 8.4 Hz, N≡CC(CH)), 7.60 (s, 1H, =CHN), 7.36 (d, 2H, *J* = 8.4 Hz, N≡CC(CHCH)), 7.10 (d, 2H, *J* = 8.3 Hz, CH_3C(CH)), 6.88 (d, 2H, *J* = 8.3 Hz, CH_3C(CHCH)), 5.62 (s, 2H, CH_2–Ph), 5.21 (s, 2H, CH_2–O–Ph), 2.31 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 155.97, 145.48, 139.69, 132.92, 130.70, 130.01, 128.40, 122.72, 118.11, 114.62, 112.87, 62.17, 53.46, 20.48. HRMS *m*/*z* calc. for $C_{18}H_{16}N_4O$ + (H^+): 305.1397; found: 305.1392.

4.5.12. 1-(4-Cyanophenylmethyl)-4-((4-methoxyphenoxy)methyl)-1H-1,2,3-triazole (**34m**)

From azide **32** and 1-methoxy-4-(prop-2-ynyloxy)benzene. Beige powder after silica gel circular chromatography (0–2% MeOH/CH_2Cl_2), yield = 95%. Mp = 168–170 °C, R_f = 0.77 (5% MeOH/CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.67 (d, 2H, *J* = 8.4 Hz, N≡CC(CH)), 7.58 (s, 1H, =CHN), 7.32 (d, 2H, *J* = 8.4 Hz, N≡CC(CHCH)), 6.97–6.80 (m, 4H, H_{Ar}), 5.60 (s, 2H, CH_2–Ph), 5.15 (s, 2H, CH_2–O–Ph), 3.76 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 154.30, 152.19, 145.45, 139.71, 132.90, 128.40, 122.77, 115.88, 114.70, 62.76, 55.70, 53.44. HRMS *m*/*z* calc. for $C_{18}H_{16}N_4O_2$ + (H^+): 321.1346; found: 321.1341.

4.5.13. 1-(4-Cyanophenylmethyl)-4-((4-phenylphenoxy)methyl)-1H-1,2,3-triazole (**34n**)

From azide **32** and 1-phenyl-4-(prop-2-ynyloxy)benzene. White powder after silica gel circular chromatography (0–50% AcOEt/Hex), yield = 88%. Mp = 154–156 °C, R_f = 0.48 (5% MeOH/CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.75–7.29 (m, 12H, =CHN + H_{Ar}), 7.12–7.02 (m, 2H, H_{Ar}), 5.63 (s, 2H, CH_2–Ph), 5.25 (s, 2H, CH_2–O–Ph). ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 157.62, 145.20, 139.64, 134.50, 132.94, 128.79, 128.43, 128.25, 126.86, 126.73, 122.83, 118.10, 115.07, 112.89, 62.12, 53.49. HRMS *m*/*z* calc. for $C_{23}H_{18}N_4O$ + (H^+): 367.1553; found: 367.1546.

4.5.14. 1-(Phenylmethyl)-4-propyl-1H-1,2,3-triazole (35b)

From azide **33** and pent-1-yne. Yellow oil after silica gel circular chromatography (0–13% AcOEt/Hex), yield = 77%. R_f = 0.11 (30% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.41–7.35 (m, 3H, H_{Ar}), 7.28–7.25 (m, 2H, H_{Ar}), 7.20 (s, 1H, =CHN), 5.50 (s, 2H, CH_2–Ph), 2.68 (t, 2H, *J* = 7.4 Hz, $-CH_2CH_2CH_3$), 1.68 (sext., 2H, *J* = 7.4 Hz, $-CH_2CH_2CH_3$), 0.95 (t, 3H, *J* = 7.4, CH_3), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 148.76, 135.03, 129.05, 128.59, 127.95, 120.54, 53.96, 27.73, 22.66, 13.78. HRMS *m*/*z* calc. for $C_{12}H_{15}N_3$ + (H^+): 202.1339; found: 202.1336.

4.5.15. 1-(Phenylmethyl)-4-hexyl-1H-1,2,3-triazole (**35c**)

From azide **33** and oct-1-yne. White powder after silica gel circular chromatography (0–20% AcOEt/Hex), yield = 82%. Mp = 51–53 °C, R_f = 0.36 (30% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.38–7.36 (m, 3H, H_{Ar}), 7.27–7.26 (m, 2H, H_{Ar}), 7.25 (s, 1H, =CHN), 5.50 (s, 2H, CH_2–Ph), 2.69 (m, 2H, $-CH_2CH_2(CH_2)_3CH_3$), 1.66–1.62 (m, 2H, $-CH_2CH_2(CH_2)_3CH_3$), 1.34–1.27 (m, 6H, $-CH_2CH_2(CH_2)_3CH_3$), 0.88 (m, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 149.00, 135.05, 129.04, 128.57, 127.94, 120.45, 53.96, 31.54, 29.37, 28.91, 25.74, 14.04. HRMS *m*/*z* calc. for $C_{15}H_{21}N_3$ + (H^+): 244.1808; found: 244.1801.

4.5.16. 1-(Phenylmethyl)-4-heptyl-1H-1,2,3-triazole (**35d**)

From azide **33** and non-1-yne. White powder after silica gel circular chromatography (0–20% AcOEt/Hex), yield = 84%. Mp = 61–62 °C, R_f = 0.30 (30% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.36–7.34 (m, 3H, H_{Ar}), 7.29–7.25 (m, 2H, H_{Ar}), 7.19 (s, 1H, =CHN), 5.51 (s, 2H, CH_2–Ph), 2.69 (m, 2H, $-CH_2CH_2(CH_2)_4CH_3$), 1.72–1.63 (m, 2H, $-CH_2CH_2(CH_2)_4CH_3$), 1.35–1.27 (m, 8H, $-CH_2CH_2(CH_2)_4CH_3$), 0.88 (t, 3H, *J* = 7.0 Hz, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 149.01, 135.04, 129.04, 128.58, 127.95, 120.44, 53.97, 31.73, 29.41, 29.20, 29.00, 25.74, 22.61, 14.08. HRMS *m*/*z* calc. for $C_{16}H_{23}N_3$ + (H^+): 258.1965; found: 258.1960.

4.5.17. 1-(Phenylmethyl)-4-decyl-1H-1,2,3-triazole (**35e**)

From azide **33** and dodec-1-yne. White powder after silica gel circular chromatography (0–20% AcOEt/Hex), yield = 29%. Mp = 78–79 °C, R_f = 0.32 (30% AcOEt/Hex), ^{1}H NMR (400 MHz,

$CDCl_3$, 25 °C) δ (ppm): 7.40–7.35 (m, 3H, H_{Ar}), 7.28–7.25 (m, 2H, H_{Ar}), 7.19 (s, 1H, =CHN), 5.51 (s, 2H, CH_2–Ph), 2.69 (m, 2H, $-\underline{CH_2}CH_2(CH_2)_7CH_3$), 1.66–1.61 (m, 2H, $-CH_2\underline{CH_2}(CH_2)_7CH_3$), 1.31–1.26 (m, 14H, $-CH_2CH_2(\underline{CH_2})_7CH_3$), 0.89 (m, 3H, CH_3), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 149.02, 135.05, 129.04, 128.58, 127.95, 120.44, 53.97, 31.89, 29.57, 29.54, 29.42, 29.35, 29.32, 29.27, 25.75, 22.68, 14.12. HRMS *m*/*z* calc. for $C_{19}H_{29}N_3 + (H^+)$: 300.2434; found: 300.2427.

4.5.18. 1-(Phenylmethyl)-4-cyclohexyl-1H-1,2,3-triazole (**35f**)

From azide **33** and ethynylcyclohexane. Grey powder after silica gel circular chromatography (0–20% AcOEt/Hex), yield = 94%. Mp = 105–108 °C, R_f = 0.32 (30% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.41–7.35 (m, 3H, H_{Ar}), 7.29–7.26 (m, 2H, H_{Ar}), 7.16 (s, 1H, =CHN), 5.50 (s, 2H, CH_2–Ph), 2.76–2.73 (m, 1H, cyclohexyl), 2.05–2.02 (m, 2H, cyclohexyl), 1.81–1.69 (m, 2H, cyclohexyl), 1.43–1.35 (m, 4H, cyclohexyl), 1.28–1.22 (m, 2H, cyclohexyl), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 154.23, 135.04, 129.04, 128.57, 128.00, 119.14, 53.98, 35.35, 33.00, 26.14, 26.03. HRMS *m*/*z* calc. for $C_{15}H_{19}N_3 + (H^+)$: 242.1652; found: 242.1647.

4.5.19. 1-(Phenylmethyl)-4-phenyl-1H-1,2,3-triazole (**35g**)

From azide **33** and 1-ethynylbenzene. Yellow powder after silica gel circular chromatography (0–15% AcOEt/Hex), yield = 64%. Mp = 128–130 °C, R_f = 0.20 (30% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.83–7.81 (m, 2H, H_{Ar}), 7.68 (s, 1H, =CHN), 7.43–7.36 (m, 5H, H_{Ar}), 7.35–7.31 (m, 3H, H_{Ar}), 5.59 (s, 2H, CH_2–Ph), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 148.25, 134.70, 130.55, 129.17, 128.81, 128.17, 128.07, 125.71, 119.48, 54.24. HRMS *m*/*z* calc. for $C_{15}H_{13}N_3 + (H^+)$: 236.1182; found: 236.1177.

4.5.20. 1-(Phenylmethyl)-4-phenoxymethyl-1H-1,2,3-triazole (**35h**)

From azide **33** and 1-(prop-2-ynyloxy)benzene. Grey powder after silica gel circular chromatography (0–25% AcOEt/Hex), yield = 87%. Mp = 119–120 °C, R_f = 0.40 (30% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.55 (s, 1H, =CHN), 7.41–7.37 (m, 3H, H_{Ar}), 7.32–7.28 (m, 4H, H_{Ar}), 7.00–6.96 (m, 3H, H_{Ar}), 5.55 (s, 2H, CH_2–Ph), 5.21 (s, 2H, CH_2–O–Ph), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 158.20, 144.73, 134.73, 129.53, 129.16, 128.82, 128.13, 122.55, 121.25, 114.17, 62.07, 54.26. HRMS *m*/*z* calc. for $C_{16}H_{15}N_3O + (H^+)$: 266.1288; found: 266.1283.

4.5.21. 1-(Phenylmethyl)-4-chloro-phenoxymethyl-1H-1,2,3-triazole (**35i**)

From azide **33** and 1-chloro-4-(prop-2-ynyloxy)benzene. Grey powder after silica gel circular chromatography (0–15% AcOEt/Hex), yield = 81%. Mp = 98–99 °C, R_f = 0.20 (30% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.53 (s, 1H, =CHN), 7.39 (s, 3H, H_{Ar}), 7.29–7.23 (m, 4H, H_{Ar}), 6.92–6.90 (m, 2H, H_{Ar}), 5.55 (s, 2H, CH_2–Ph), 5.17 (s, 2H, CH_2–O–Ph), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 156.77, 144.24, 134.38, 129.40, 129.18, 128.87, 128.13, 126.18, 122.63, 116.13, 62.33, 54.29. HRMS *m*/*z* calc. for $C_{16}H_{14}N_3OCl + (H^+)$: 300.0898; found: 300.0893.

4.5.22. 1-(Phenylmethyl)-4-cyano-phenoxymethyl-1H-1,2,3-triazole (**35j**)

From azide **33** and 4-(prop-2-ynyloxy)benzonitrile. White powder after silica gel circular chromatography (0–15% AcOEt/Hex), yield = 88%. Mp = 109–110 °C, R_f = 0.12 (30% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25) δ (ppm): 7.60–7.57 (m, 2H, H_{Ar}), 7.55 (s, 1H, =CHN), 7.42–7.38 (m, 3H, H_{Ar}), 7.31–7.28 (m, 2H, H_{Ar}), 7.07–7.04 (m, 2H, H_{Ar}), 5.56 (s, 2H, CH_2–Ph), 5.24 (s, 2H, CH_2–O–Ph), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 161.40, 143.39, 134.25, 134.04, 129.22, 128.96, 128.17, 122.85, 119.05, 115.54, 104.59, 62.14, 54.37. HRMS *m*/*z* calc. for $C_{17}H_{14}N_4O + (H^+)$: 291.1240; found: 291.1232.

4.5.23. 1-(Phenylmethyl)-4-nitro-phenoxymethyl-1H-1,2,3-triazole (**35k**)

From azide **33** and 1-nitro-4-(prop-2-ynyloxy)benzene. White powder after silica gel circular chromatography (0–10% AcOEt/Hex), yield = 99%. Mp = 100–101 °C, R_f = 0.15 (30% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 8.23–8.19 (m, 2H, H_{Ar}), 7.57 (s, 1H, =CHN), 7.42–7.39, (m, 3H, H_{Ar}), 7.31–7.28 (m, 2H, H_{Ar}), 7.09–7.05 (m, 2H, H_{Ar}), 5.57 (s, 2H, CH_2–Ph), 5.29 (s, 2H, CH_2–O–Ph), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 163.10, 143.19, 141.89, 134.22, 129.24, 128.98, 128.19, 125.93, 122.92, 114.85, 62.48, 54.39. HRMS *m*/*z* calc. for $C_{16}H_{14}N_4O_3 + (H^+)$: 311.1139; found: 311.1131.

4.5.24. 1-(Phenylmethyl)-4-methyl-phenoxymethyl-1H-1,2,3-triazole (**35l**)

From azide **33** and 1-methyl-4-(prop-2-ynyloxy)benzene. White powder after silica gel circular chromatography (0–25% AcOEt/Hex), yield = 91%. Mp = 107–108 °C, R_f = 0.38 (30% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.53 (s, 1H, =CHN), 7.42–7.35, (m, 3H, H_{Ar}), 7.32–7.28 (m, 2H, H_{Ar}), 7.10–7.08 (m, 2H, H_{Ar}), 6.90–6.86 (m, 2H, H_{Ar}), 5.54 (s, 2H, CH_2–Ph), 5.18 (s, 2H, CH_2–O–Ph), 2.30 (s, 3H, CH_3), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 156.11, 144.91, 134.50, 130.53, 129.96, 129.15, 128.81, 128.13, 122.50, 114.66, 62.27, 54.24, 20.48. HRMS *m*/*z* calc. for $C_{17}H_{17}N_3O + (H^+)$: 280.1444; found: 280.1439.

4.5.25. 1-(Phenylmethyl)-4-methoxy-phenoxymethyl-1H-1,2,3-triazole (**35m**)

From azide **33** and 1-methoxy-4-(prop-2-ynyloxy)benzene. White powder after silica gel circular chromatography (0–15% AcOEt/Hex), yield = 96%. Mp = 91–92 °C, R_f = 0.12 (30% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.53 (s, 1H, =CHN), 7.42–7.37, (m, 3H, H_{Ar}), 7.30–7.27 (m, 2H, H_{Ar}), 6.94–7.90 (m, 2H, H_{Ar}), 6.85–6.81 (m, 2H, H_{Ar}), 5.55 (s, 2H, CH_2–Ph), 5.15 (s, 2H, CH_2–O–Ph), 3.78 (s, 3H, CH_3–O–Ph), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 154.20, 152.33, 144.90, 134.49, 129.15, 128.81, 128.12, 122.53, 115.88, 114.65, 62.85, 55.70, 54.24. HRMS *m*/*z* calc. for $C_{17}H_{17}N_3O_2 + (H^+)$: 296.1394; found: 296.1386.

4.5.26. 1-(Phenylmethyl)-4-phenyl-phenoxymethyl-1H-1,2,3-triazole (**35n**)

From azide **33** and 1-phenyl-4-(prop-2-ynyloxy)benzene. White powder after silica gel circular chromatography (0–20% AcOEt/Hex), yield = 49%. Mp = 194–196 °C, R_f = 0.22 (30% AcOEt/Hex), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 7.57 (s, 1H, =CHN), 7.55–7.52 (m, 4H, H_{Ar}), 7.45–7.38 (m, 5H, H_{Ar}), 7.35–7.28 (m, 3H, H_{Ar}), 7.08–7.04 (m, 2H, H_{Ar}), 5.56 (s, 2H, CH_2–Ph), 5.25 (s, 2H, CH_2–O–Ph), ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ (ppm): 157.76, 144.65, 140.65, 134.46, 134.35, 129.18, 128.85, 128.74, 128.21, 128.15, 126.77, 126.75, 122.60, 115.08, 62.22, 54.29 HRMS *m*/*z* calc. for $C_{22}H_{19}N_3O + (H^+)$: 342.1601; found: 342.1592.

4.6. Aromatase inhibition assay

Inhibition of aromatase (CYP19) by synthesized compounds (IC_{50}) was determined using the P450 Inhibition Kit CYP19/MFC (BD Biosciences, Two Oak Park Bedford, MA, USA) according to the manufacturer's instructions. Briefly, 100 μl of each compound was diluted in NADPH-cofactor mix for every concentration tested (10000, 3333, 1111, 370, 123, 41, 13, 4 and 0 nM) and placed in duplicate on a 96-well plate. The plate was then incubated at 37 °C

for 10 min. After incubation, 100 μl of the enzyme/substrate mix was added to the treated conditions and the plate was then incubated at 37 °C for 30 min. After incubation, 75 μl of Stop Reagent was added to the entirety of the plate and 100 μl of the enzyme/substrate mix was added in the blank columns. Thereafter, the plate was subjected to a colorimetric analysis and read on a fluorescence microplate reader (FLUOstar Optima, BMG Labtechnologies, λexc = 410 nm/λem = 520 nm). IC_{50} values were determined using the colorimetric data analyzed through normalized non-linear regression using the GraphPad Prism 5 software. The less active molecules ($IC_{50} > 10$ μM) were assayed by two independent experiments ($n = 2$), each being run in technical triplicate. The most active compounds ($IC_{50} \leq 10$ μM) were assayed by three independent experiments ($n = 3$), each being run in technical triplicate.

4.7. Cell proliferation assay

Human epithelial adrenocortical carcinoma cell line (NCI-H295R) was obtained from American Type Culture Collection (Manassas, VA, USA). Cells were maintained in DMEM/F12 media supplemented with 10% Nu-Serum Serum Replacements, 1% ITS+ Universal Culture Supplement Premix, 2 L equivalent (BD Biosciences), L-glutamine (2 mM), penicillin G (100 U mL^{-1}), and streptomycin (100 mg mL^{-1}) (Invitrogen). During experiments, cells were either left untreated, treated with DMSO (0.01%) or were incubated with 10 nM of synthesized compounds (reconstituted in DMSO) in DMEM/F12 phenol red free media supplemented with 1.5% Nu-Serum (minimum concentration for cells to proliferate), 1% ITS, L-glutamine (2 mM), penicillin G (100 U mL^{-1}), and streptomycin (100 mg mL^{-1}) for 24 and 72 h prior to analysis of cell proliferation. Cell proliferation assays were performed on seeded cells (2×10^4 cells/well) in 96-well plates and analyzed for cellular viability using a multiplexed assay of CellTiter Blue (Promega, Madison, WI) kit according to the manufacturer's instructions. Briefly, 20 μl of the CellTiter Blue substrate was added to 100 μl of cell suspension and incubated for 1 h at 37 °C. Thereafter, the plate was subjected to a colorimetric analysis and read on a fluorescence microplate reader (FLUOstar Optima, BMG Labtechnologies, λexc = 560 nm/λem = 590 nm).

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Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2011.05.074.

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