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Non-Steroidal Aromatase Inhibitors Based on a Biphenyl Scaffold: Synthesis, in vitro SAR, and Molecular Modelling

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The synthesis and in vitro biological evaluation (JEG-3 cells) of a series of novel and potent aromatase inhibitors, prepared by microwave-enhanced Suzuki cross-coupling methodology, are reported. These compounds possess a biphenyl template incorporated with the haem-ligating triazolylmethyl moiety, either on its own or in combination with other substituent(s) at various positions on the phenyl rings. The most potent aromatase inhibitor reported herein has an IC_{50} value of 0.12 nM, although seven of its congeners are also highly potent ($IC_{50} \leq 0.5$ nM). They all bear the (5-triazolylmethyl-2-cyano)biphenyl structural motif. Docking of representative compounds into a homology model of human aromatase assists in the rationalisation of the SAR derived from the in vitro biological results and supports a crucial role for a cyano group on the "A" phenyl ring, which is accessible to hydrogen bond interactions with Ser478. Further development of these compounds as potential therapeutic agents for the treatment of hormone-dependent breast cancer is warranted given the high level of potency observed for this class of aromatase inhibitor in vitro.

Introduction

Breast cancer is one of the most high-profile malignant diseases in modern society. Among postmenopausal women affected by the disease, a substantial portion has breast tumours that are oestrogen-receptor positive and hence are classified as hormone-dependent. For decades, tamoxifen, a selective oestrogen receptor modulator, has been the gold standard endocrine therapy for the primary treatment of this type of breast cancer. Tamoxifen antagonises the binding of oestrogens to the oestrogen receptor in the breast tumour and thus blocks the resulting biological response. However, there is an alternative form of endocrine therapy available. The oestrogenic stimulation to a breast tumour can be attenuated or abolished through oestrogen ablation produced by agents such as aromatase inhibitors (AIs).

Aromatase, a cytochrome P450 enzyme, converts androgens to oestrogens in the final step of oestrogen biosynthesis. Clearly, the inhibition of this enzyme should be advantageous for the control and regression of a tumour that requires oestrogenic stimulation to develop and grow. Indeed, extensive research to this end over the last three decades has led to the development of some highly effective AIs.[1–3] Two significant non-steroidal aromatase inhibitors (NSAIs), anastrozole and letrozole, were recently shown to have improved efficacies and superior toxicity profiles relative to tamoxifen.[4,5] Evidently, the recent success of AIs in the clinic has not only enhanced their status as anti-endocrine agents but has also broadened their application in the treatment of hormone-dependent breast cancer as first-line therapy for advanced breast cancer and as adjuvant therapy for primary breast cancer.

A common pharmacophore for NSAIs is a nitrogen-containing heterocycle. The possibility of exploiting the binding affinity of a nitrogen atom (via the electron lone pair) to the Fe^{2+} ion of the haem in the aromatase active site was realised with the discovery of the first NSAI, aminoglutethimide (Figure 1). Although compounds devoid of a prominent haem-ligating moiety such as flavones and isoflavones[1–3] have been report-

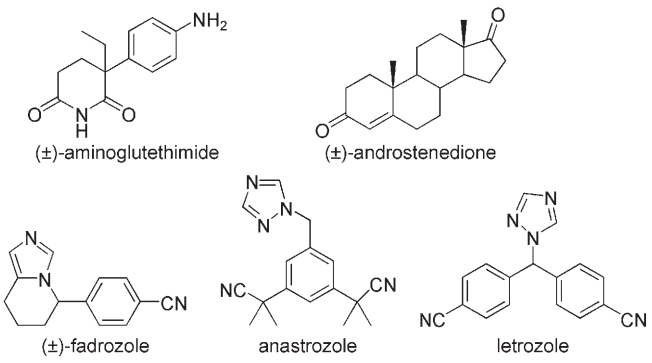

Figure 1. Non-steroidal aromatase inhibitors and the natural substrate for aromatase, androstenedione.

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ed to act as NSAIs, the incorporation of an aza-heterocycle has become the key structural feature in many highly potent NSAIs. Examples include the benzylimidazole fragment in fadrozole and the benzyltriazole motif in leading AIs such as anastrozole and letrozole (Figure 1). Whereas coordination to the haem is considered to be a crucial factor for the binding of this type of inhibitor to the aromatase active site, the incorporation of hydrogen bond acceptor(s) at an appropriate distance from the heterocycle is believed to provide important auxiliary interactions that further improve the binding affinity of the inhibitor and hence render its potent inhibition of aromatase.[6–9] For anastrozole and letrozole, the respective isobutyronitrile and benzonitrile groups are thought to act as hydrogen bond acceptors. Modelling studies of fadrozole have suggested that its cyano group effectively mimics the carbonyl group on the D ring of the natural substrate of aromatase, androstenedione (Figure 1), which potentially undergoes energetically favourable hydrogen bonding interactions with amino acid residue(s) in the aromatase active site.[6] Simons and co-workers have demonstrated the importance of small hydrogen bond accepting groups located *para* to the haem-ligating moiety in 1-[(benzofuran-2-yl)phenylmethyl]imidazole and -triazole compounds.[10] The development of AIs, both steroidal and non-steroidal, has been comprehensively reviewed by Recanatini,[1] and more recently by Brueggemeier,[2] highlighting the great structural diversity of NSAIs. Many research groups, including our own, are still active in pursuing new entities that possess aromatase inhibitory properties. The latest publications in this field report flavone derivatives,[11] imidazolylmethylbenzophenones,[12] and (±)-abyssinone II derivatives[13] as AIs; additionally, YM511-, letrozole-, and anastrozole-based derivatives have been reported as dual aromatase and steroid sulfatase inhibitors.[14–16] However, to the best of our knowledge, the exploitation of the biphenyl system, a putative steroidal A/C ring mimic, as a scaffold in the design of NSAIs has yet to be realised, although Hartmann et al. have previously reported several imidazole- and triazole-substituted biphenyls as highly potent 17α-hydroxylase-C17,20-lyase (Cyp17) inhibitors for the potential treatment of prostate cancer.[17,18] Given that Cyp17 is a member of the cytochrome P450 family of enzymes that includes aromatase, it is reasonable to explore the possibility of adopting the biphenyl scaffold as a template for designing a new structural class of AIs. Herein we report a series of novel AIs by incorporating the triazolylmethyl moiety into a biphenyl framework. In addition, the synthetic accessibility of the biphenyl motif and its structural versatility are exploited to incorporate additional functional group(s) on both phenyl rings. One particular objective for varying the structural features is to investigate the effects of a hydrogen bond acceptor introduced at varied distances from the heterocycle and the different aromatic substitution patterns that result in aromatase inhibition. The palladium-catalysed Suzuki cross-coupling reaction[19–21] was employed for the preparation of this library of biphenyl compounds, and its versatility was further maximised by the application of microwave technology.[22] Biological evaluation of the ability of these compounds to inhibit aromatase in vitro was performed with a human choriocarcinoma cell line (JEG-3) assay. To rationalise the SAR obtained for the inhibitors, several representative compounds were docked into the homology model of human aromatase recently published by Favia et al.,[23] and any potential interactions that these biphenyl-based inhibitors may have with the active site of aromatase were explored.

Results and Discussion

1. Chemistry

The focal transformation in the synthesis of this series of biphenyl-based AIs is the Suzuki cross-coupling reaction. This reaction typically takes place between an aryl boronic acid and an aryl bromide in the presence of base and a source of Pd^0. The functional groups inherent in these precursors are retained in the biphenyl motif. As illustrated in Figure 2, the haem-ligating triazolylmethyl group resides on the "A" phenyl ring with complementary substitution at R^1 (typically a hydrogen bond acceptor), and these substituents are retained from a similarly substituted aryl bromide (bromobenzyltriazoles). The "B" phenyl ring exhibits the substitution at R^2 gained from an aryl boronic acid precursor. With commercial aryl boronic acids being readily available, the synthetic work focused on the preparation of the bromobenzyltriazole precursors, which are summarised in Scheme 1. Initially, conversion of the commercially available benzoic acids **1** and **2**, via benzamides **3** and **4**, into benzonitriles **5** and **6** was achieved in good yield. Compounds **5** and **6** and the commercially available benzonitriles **7**–**10** were then radically brominated with *N*-bromosuccinimide (NBS) to furnish the benzyl bromide derivatives **12**–**15**, **17**, and **18** (**11** and **16** were obtained commercially). Subsequent substitution with 1*H*-1,2,4-triazole in the presence of base completed the set of triazole functionalised aryl bromide intermediates **19**–**26**. The synthesis of precursor **27**, 2-{3-[(1*H*-1,2,4-triazol-1-yl)methyl]-5-bromophenyl}-2-methylpropionitrile, was recently reported elsewhere.[16] Biphenyl compounds **28**–**68** (except **60** and **66**, see below) were prepared, and can be separated into distinct structural groups related to the bromobenzyltriazole precursors **19**–**27** (see Scheme 2). Suzuki reactions using commercially available boronic acids were carried out either by simultaneous batch convection reactions or by rapid microwave heating in a sequential manner. Initial efforts to prepare compounds **60** and **66** from the appropriate bromobenzyltriazole precursor via cross-coupling with 2-cyanophe-

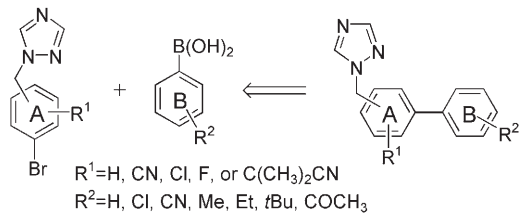
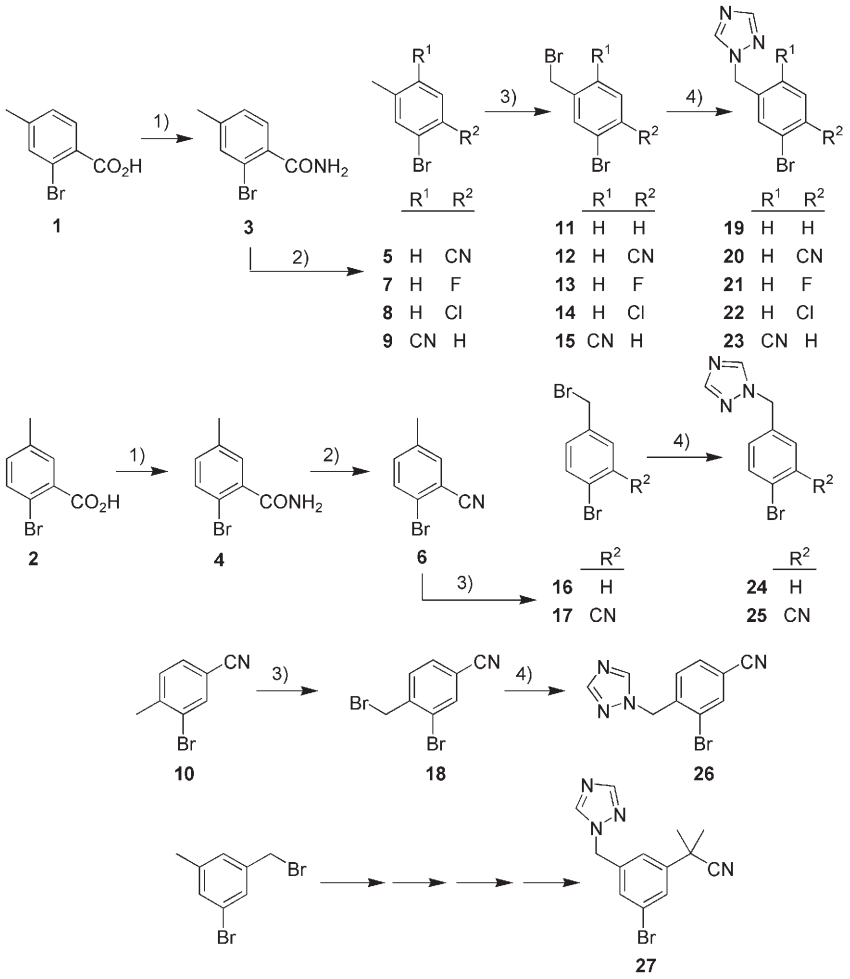


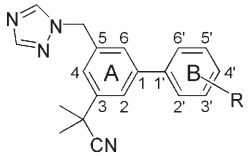
Figure 2. General retrosynthesis of the biphenyl AIs.



Scheme 1. Synthesis of bromobenzyltriazole precursors **19**–**26**. Reagents and conditions: 1) a) $SOCl_2$, b) NH_4OH, THF, 84–94%; 2) $POCl_3$, NaCl, 71–93%; 3) NBS, Bz_2O_2, CCl_4, 80–95%; 4) 1*H*-1,2,4-triazole, K_2CO_3, KI, acetone, Δ, 64–74%. The synthesis of precursor **27** was published elsewhere.[16]

nylboronic acid failed (see Scheme 2). From these reactions only the aryl bromide starting material and benzamide were isolated. The failure of these reactions can likely be attributed to the lack of thermal stability of 2-cyanophenylboronic acid. Urawa et al. have previously observed the thermal instability of 2-cyanophenylboronic acid and postulate that at elevated temperatures the *ortho*-positioned cyano group in this boronic acid undergoes hydrolysis to the amide, a process initiated by proto-deborylation.[24] Given these difficulties, an alternative strategy for the preparation of these compounds was adopted (Scheme 3). Compound **60** was obtained by a Suzuki reaction between commercially available 2-bromobenzonitrile (**69**) and 3-tolylboronic acid to afford the required biphenyl template **70**, which then underwent bromination to the benzyl bromide **71**, and was completed by substitution with 1*H*-1,2,4-triazole. The commercial availability of 4′-(bromomethyl)biphenyl-2-carbonitrile (**72**) allowed the convenient synthesis of **66** in one step by treatment with 1*H*-1,2,4-triazole.

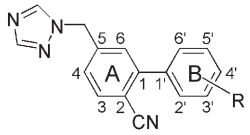
Table 1. Inhibition of aromatase activity in JEG-3 cells by anastrozole and compounds **28**–**30**.



Compd	R	Inhibition [%][a]	IC_{50} [nM]
anastrozole			1.5 ± 0.5
28	H	99.6 ± 0.1	0.5 ± 0.1
29	3′-Cl	99.8 ± 0.1	2.2 ± 0.2
30	3′-CN[b]	99.6 ± 0.2	1.5 ± 0.5

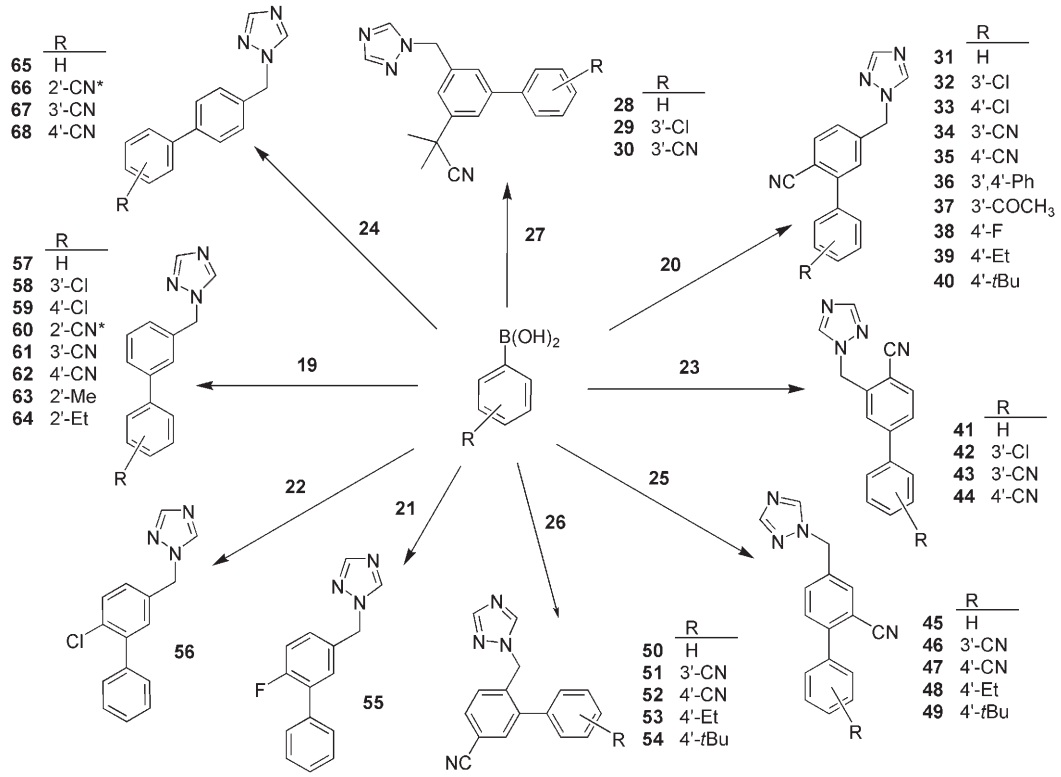
[a] Determined at a compound concentration of 1 μM. [b] Substituents are numbered as shown for presentational uniformity; see Experimental Section for correct numbering of substituents.

Table 2. Inhibition of aromatase activity in JEG-3 cells by compounds **31**–**40**.

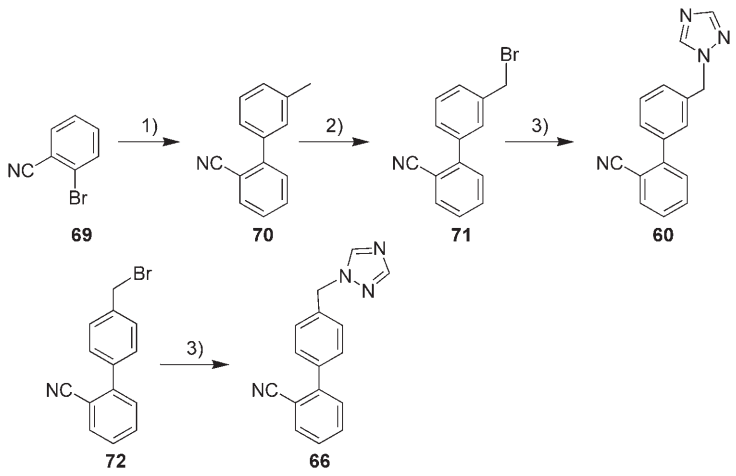


Compd	R	Inhibition [%][a]	IC_{50} [nM]
31	H	100	0.2 ± 0.02
32	3′-Cl	–	0.22 ± 0.02
33	4′-Cl	–	0.45 ± 0.03
34	3′-CN	99.5 ± 0.1	0.2 ± 0.02
35	4′-CN	–	0.33 ± 0.08
36	3′,4′-Ph[b]	–	2.2 ± 0.4
37	3′-$COCH_3$	–	0.12 ± 0.02
38	4′-F	99.5 ± 0.1	0.2 ± 0.04
39	4′-CH_2CH_3	99.7 ± 0.1	0.3 ± 0.03
40	4′-$C(CH_3)_3$	98.3 ± 0.2	4.0 ± 2.0

[a] Determined at a compound concentration of 1 μM (–: not determined). [b] Substituents are numbered as shown for presentational uniformity; see Experimental Section for correct numbering of substituents.



Scheme 2. Suzuki cross-coupling reactions between arylboronic acids and bromobenzyltriazoles (**19**–**27**) to complete a series of biphenyl AIs (**28**–**68**). Reagents and conditions: $Pd(OAc)_2$, K_2CO_3, tetra-*N*-butylammonium bromide (TBAB), H_2O/EtOH, Δ, 36–94%. * The synthesis of compounds **60** and **66** failed by this method; see Scheme 3 for the successful routes to these derivatives.



Scheme 3. Alternative synthesis for compounds **60** and **66**. Reagents and conditions: 1) $Pd(OAc)_2$, K_2CO_3, TBAB, tolylboronic acid, EtOH/H_2O, 96%; 2) NBS, Bz_2O_2, CCl_4, 93%; 3) 1*H*-1,2,4-triazole, K_2CO_3, KI, acetone, 60–63%.

2. Inhibition of aromatase in vitro

The in vitro inhibitory activities of compounds **28**–**68** against the aromatase enzyme in a preparation of JEG-3 cells are shown in Tables 1–7. Anastrozole,[16] an established and potent AI, is included in Table 1 as reference.

2.A. The [5-triazolylmethyl-3-(2-methylpropionitrile)]-biphenyl motif

This group of compounds containing the [5-triazolylmethyl-3-(2-methylpropionitrile)]biphenyl motif is structurally related to anastrozole (see Figure 1), with one of the isobutyronitrile groups of anastrozole replaced in each case by a substituted or unsubstituted aryl ring (the "B" phenyl ring). From the results listed in Table 1, it is apparent that this replacement, and indeed the resulting loss of molecular symmetry, are not detrimental to the in vitro inhibition of aromatase by these compounds relative to anastrozole. Interestingly, whereas substitution on the "B" ring in compounds **29** (R = 3′-Cl) and **30** (R = 3′-CN) conserves activity, it is the unsubstituted compound **28** (R = H) that displays a threefold increase in potency over anastrozole.

2.B. The (5-triazolylmethyl-2-cyano)biphenyl motif

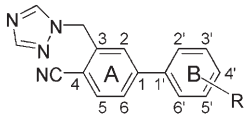
The (5-triazolylmethyl-2-cyano)biphenyl motif is present in compounds **31**–**40** (Table 2). This class of compound has the triazolylmethyl moiety and the cyano group positioned *meta* and *ortho* to the biphenyl bridge, respectively. Like the arrangement found in letrozole (Figure 1), the cyano group and the triazolylmethyl moiety on the "A" ring of the compounds are *para* to each other. As listed in Table 2, compound **37**

($IC_{50} = 0.12$ nM) is the most potent AI discovered in this work, although its congeners (**31**–**35** and **37**–**39**) are also highly potent ($IC_{50} \leq 0.5$ nM). These AIs are an order of magnitude more potent than anastrozole. Unexpectedly, however, they show only a small variation in activity amongst them (IC_{50} range: 0.12–0.45 nM). This finding suggests that the relatively smaller substituents (hydrogen, cyano, chloro, acetyl, and ethyl) placed at either the 3′- or 4′-position on the "B" ring in this series of inhibitors are better tolerated by the enzyme, although their impact on the inhibitory activities of the resulting inhibitors is small. In contrast, compounds **36** and **40** have activities similar to anastrozole. Their relatively weaker potencies observed are presumably derived from the bulk of their respective naphthyl and *tert*-butyl groups on the "B" ring.

2.C. The (3-triazolylmethyl-4-cyano)biphenyl motif

With compounds bearing the (5-triazolylmethyl-2-cyano)biphenyl motif showing highly potent inhibition against aromatase, an investigation on the importance of the positioning of the cyano group relative to the triazolylmethyl moiety is warranted. The first variation is to keep the triazolylmethyl moiety at the 3-position *meta* to the biphenyl bridge, but to relocate the cyano group from the 2- to the 4-position on the "A" ring, where it is positioned *ortho* to the heterocycle. The resulting scaffold possesses a (3-triazolylmethyl-4-cyano)biphenyl motif. As listed in Table 3, this group of compounds shows a substantial decrease in inhibitory activity against aromatase relative to those compounds in Table 2. At an inhibitor concentration of 1 μM, compounds **41**–**44** inhibit aromatase by only 37.6–79.4%. The best inhibitor of the series is compound **44;** even so, its efficacy as an AI compares unfavourably against **40** (98.3% at 1 μM), the weakest inhibitor listed in Table 2. Despite the presence of a cyano group on the "A" ring, the substitution pattern as displayed by the (3-triazolylmethyl-4-cyano)biphenyl motif is clearly not beneficial to aromatase inhibition. It is possible that, among other things, when the cyano group is placed at the 4-position in this series of compounds and *ortho* to the heterocycle, it is no longer accessible to neighbouring amino acid residue(s) in the enzyme active site for hydrogen bonding. Such interactions are clearly more productively exploited by the (5-triazolylmethyl-2-cyano)biphenyl motif of those compounds in Table 2.

Table 3. Inhibition of aromatase activity in JEG-3 cells by compounds **41**–**44**.



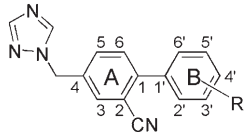
Compd	R	Inhibition [%][a]
41	H	68.8 ± 1.4
42	3′-Cl	75.1 ± 0.7
43	3′-CN	37.6 ± 3.4
44	4′-CN	79.4 ± 0.1

[a] Determined at a compound concentration of 1 μM (IC_{50} values not determined).

2.D. The (4-triazolylmethyl-2-cyano)biphenyl motif

To further expand the SAR derived for those compounds in Table 3, the next combination of cyano group and triazolylmethyl moiety investigated was to keep the former group at the 2-position on the "A" ring, like the compounds in Table 2, but to move the heterocycle from the 5- to the 4-position. The resulting compounds bear a (4-triazolylmethyl-2-cyano)biphenyl motif, the triazolylmethyl and cyano groups of which are arranged *meta* to each other on the "A" ring and are positioned *para* and *ortho* to the biphenyl bridge, respectively. According to the biological activities listed in Table 4, it is clear that this *meta* relationship between the triazolylmethyl moiety and the cyano group on the "A" ring results in an increase in potency of the compounds relative to the *ortho* relationship of those examples in Table 3. The greater separation between the cyano group and the heterocycle on the "A" ring clearly imparts improved aromatase inhibitory activity to the compounds. However, the inhibitors listed in Table 4 are three orders of magnitude less active than those bearing the (5-triazolylmethyl-2-cyano)biphenyl motif in Table 2. This finding further demonstrates the superiority of a *para* arrangement between the cyano group and the triazolylmethyl moiety on the "A" ring of the biphenyl scaffold for aromatase inhibition.

Table 4. Inhibition of aromatase activity in JEG-3 cells by compounds **45**–**49**.



Compd	R	Inhibition [%][a]	IC_{50} [nM]
45	H	98.6 ± 0.1	4.6 ± 1.2
46	3′-CN	89.6 ± 0.5	120 ± 10
47	4′-CN	91.7 ± 0.1	103 ± 40
48	4′-CH_2CH_3	85.3 ± 2.0	160 ± 36
49	4′-$C(CH_3)_3$	55.9 ± 3.4	650 ± 140

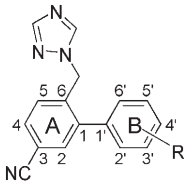
[a] Determined at a compound concentration of 1 μM.

When the substituents on the "B" ring are assessed in this series of compounds, there is an apparent relationship between the size of the R substituent on the "B" ring and the inhibitory activity of the resulting compounds: an increase in R group size results in decreased potency. However, given the fact that the most active compound here is **45**, it can be argued that any substitution on the "B" ring in this series of compounds bearing the (4-triazolylmethyl-2-cyano)biphenyl motif is indeed detrimental to aromatase inhibitory activity.

2.E. The (6-triazolylmethyl-3-cyano)biphenyl motif

The SAR derived from Tables 2–4 so far highlights one important criterion for substituted biphenyl compounds to exhibit potent aromatase inhibition: an "A" ring bearing a triazolylmethyl moiety and a cyano group positioned *para* to each other. However, the (5-triazolyl-2-cyano)biphenyl motif is not the only *para* orientation that is conceivable on the "A" ring. A series of compounds bearing a (6-triazolylmethyl-3-cyano)biphenyl motif was also prepared. This arrangement effectively maintains the *para* orientation between the two groups but reverses the substitution pattern on the "A" ring relative to the biphenyl bridge so that the triazolylmethyl moiety and the cyano group are now positioned *ortho* and *meta* to this junction, respectively. As listed in Table 5, although the inhibitory activities of this group of compounds were found to be an order of magnitude less potent than those observed for their (5-triazolylmethyl-2-cyano)biphenyl counterparts in Table 2, they are nonetheless still highly potent AIs, with these compounds **50** (IC_{50} = 1.7 nM) showing a similar potency to anastrozole (IC_{50} = 1.5 nM, Table 1). This finding further demonstrates that the *para* relationship between these two substituents on the "A" ring is far superior to an *ortho* (Table 3) or *meta* (Table 4) relationship. As previously observed, a steric factor is in operation for the substituents on the "B" ring. For example, the *tert*-butyl substituent in compound **54** (IC_{50} = 14.0 nM) renders an eightfold reduction in potency relative to **50**.

Table 5. Inhibition of aromatase activity in JEG-3 cells by compounds **50**–**54**.



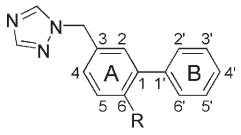
Compd	R	Inhibition [%][a]	IC_{50} [nM]
50	H	99.0 ± 0.1	1.7 ± 0.8
51	3′-CN	98.7 ± 0.1	4.0 ± 0.7
52	4′-CN	99.5 ± 0.1	3.0 ± 0.5
53	4′-CH_2CH_3	99.1 ± 0.1	2.5 ± 0.1
54	4′-$C(CH_3)_3$	97.4 ± 0.3	14.0 ± 3.0

[a] Determined at a compound concentration of 1 μM.

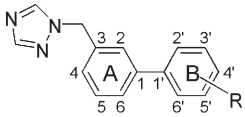
2.F. Replacement or removal of the cyano group on the "A" ring

To confirm that a cyano group is indeed an essential feature for supporting the heterocycle and the biphenyl scaffold as the basic pharmacophore for this structural class of AIs, the cyano group of the (5-triazolylmethyl-2-cyano)biphenyl motif was replaced with halogens to give compounds **55** (fluoro) and **56** (chloro) (Table 6). In addition, the effects of removing the cyano group altogether from the (5-triazolylmethyl-2-cyano)biphenyl (**57**–**64**, Table 6) and (4-triazolylmethyl-2-cyano)biphenyl (**65**–**68**, Table 7) motifs were also studied.

Table 6. Inhibition of aromatase activity in JEG-3 cells by compounds **55**, **56**, and compounds **57**–**64**.



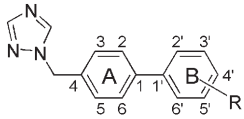
Compd	R[a]	Inhibition [%][b]	IC_{50} [nM]
55	F	96.0 ± 0.3	16.0 ± 8.0
56	Cl	97.3 ± 0.5	12.0 ± 1.0



Compd	R[a]	Inhibition [%][b]	IC_{50} [nM][c]
57	H	70.0 ± 4.1	210 ± 30
58	3′-Cl	88.4 ± 0.5	–
59	4′-Cl	92.6 ± 0.3	–
60	2′-CN	96.8 ± 0.1	21.5 ± 1.7
61	3′-CN	66.0 ± 4.3	–
62	4′-CN	83.5 ± 1.3	–
63	2′-CH_3	89.1 ± 0.5	54.8 ± 24.3
64	2′-CH_2CH_3	90.4 ± 0.5	70 ± 17

[a] Substituents are numbered as shown for presentational uniformity; see Experimental Section for correct numbering of substituents. [b] Determined at a compound concentration of 1 μM. [c] –: not determined.

Table 7. Inhibition of aromatase activity in JEG-3 cells by compounds **65**–**68**.



Compd	R[a]	Inhibition [%][b]	IC_{50} [nM][c]
65	H	24.0 ± 3.6	–
66	2′-CN	59.7 ± 3.7	612 ± 135
67	3′-CN	40.9 ± 1.2	–
68	4′-CN	43.7 ± 3.4	–

[a] Substituents are numbered as shown for presentational uniformity; see Experimental Section for correct numbering of substituents. [b] Determined at a compound concentration of 1 μM. [c] –: not determined.

Although significant inhibitory activities were observed for compounds **55** and **56**, as shown in Table 6, the replacement of the cyano group with a halogen atom renders a >60-fold decrease in the IC_{50} values observed for the two halogenated derivatives (16 nM for **55** and 12 nM for **56**) with respect to **31** (0.2 nM, Table 2). Similarly, but to a greater extent, the removal of the cyano group from the (5-triazolylmethyl-2-cyano)bi-

phenyl motif seriously limits the ability of the resulting compounds (**57**–**64**) to inhibit aromatase. Compound **57** (IC_{50} = 210 nM), which has no substituent on the "B" ring, is some 1000-fold less active as an AI than its counterpart **31**. The only structural difference between these two compounds is the presence of a cyano group at the 2-position on the "A" ring of compound **31**. These findings clearly demonstrate the importance of having a cyano group at the 2-position on the "A" ring for producing the potent aromatase inhibitory activities observed in those compounds that contain the (5-triazolylmethyl-2-cyano)biphenyl motif (Table 2). The most likely explanation for this impact that a cyano group has on biological activity is its ability, as part of the benzonitrile motif, to function effectively as a hydrogen bond acceptor for interacting with hydrogen bond donating amino acid residue(s) within the aromatase active site. As discussed above, compounds bearing the (4-triazolylmethyl-2-cyano)biphenyl motif are only comparatively moderate-to-weak AIs (Table 4). From the results listed in Table 7, it is clear that the removal of the cyano group from this motif further weakens the resulting derivatives as AIs. Hence, while having the (4-triazolylmethyl-2-cyano)biphenyl motif is not optimal for aromatase inhibition, the SAR obtained here shows that the cyano group at the 2-position nonetheless contributes positively to the biological activity exhibited by those compounds in Table 4. However, this contribution is evidently not as prominent as that produced by the cyano group in those compounds bearing the (5-triazolylmethyl-2-cyano)biphenyl motif.

3. Molecular modelling studies

The SAR generated so far clearly indicates that the ability of various biphenyl templates to inhibit aromatase depends on the substituents on the "A" ring and how they are positioned with respect to one another. At the molecular level, this means that some biphenyl templates and their substituents interact better than others with the aromatase active site. To explore any potential interactions and to rationalise the SAR observed, compounds **28**, **31**, **41**, **45**, **50**, **57**, and **65**, alongside anastrozole (as reference), were docked into the homology model of human aromatase reported by Favia et al.[23] Recently, another 3D model of aromatase was reported by Karkola et al.,[25] but is not adopted herein because the model is derived from a crystallised rabbit cytochrome enzyme. Furthermore, all previous docking studies we conducted for AIs have been carried out using the model reported by Favia et al. The compounds selected for docking studies were chosen to represent each structural variation studied in this work. None of them bears substituents on the "B" ring; the focus was on understanding the interactions of "A" ring substituents with the enzyme active site. Like the protocol that we recently applied,[14] the distance between the coordinating N atom (N4) of the triazolyl group and the Fe atom of the haem group was constrained to between 2.0 and 2.3 Å by using the constraint distance functionality within GOLD. To facilitate comparison of results between docked compounds, the docking modes obtained are grouped together according to structural similarity of the templates and compared with those of compound **31** and anastrozole. Hence, the following figures are presented below: anastrozole-like, **28** versus anastrozole versus **31** (Figure 3); containing a 3-triazolylmethyl moiety, **41** versus **57** versus **31** (Figure 4); containing a 6-triazolylmethyl moiety, **50** versus **31** (Figure 5); and containing a 4-triazolylmethyl moiety, **45** versus **65** versus **31** (Figure 6).

3.A. 28 vs. anastrozole vs. 31

Anastrozole docks into the active site of aromatase so that its two isobutyronitrile side groups are close to Ser478, which is a putative hydrogen bond donating amino acid residue postulated to be involved pivotally in the interaction with some non-steroidal AIs.[23] However, the side group distances from this residue are different, with one docked closer at 2.99 Å, and the other docked further away at 5.08 Å. From this observation, it is possible that at least one of the isobutyronitrile side groups forms a hydrogen bond with Ser478 through its cyano group. In its docking mode as shown, a phenyl ring of compound **31** overlays the central phenyl ring of anastrozole tightly. As a result, this places its "B" ring close to the isobutyronitrile group of anastrozole, which is furthest from Ser478, and toward a small hydrophobic pocket created by Pro429, Pro368, Val370, and Val369. The cyano group of **31** at the 2-position of the "A" ring is situated in the space between the two side groups of anastrozole, about 4.40 Å away from Ser478. Although this distance between the cyano group and Ser478 is not within the usual range expected for hydrogen bonding, it may be effectively situated much closer upon possible induced fit of the inhibitor to the enzyme, given the potent aromatase inhibitory activity observed for compound **31**. Compound **28**, which is structurally most similar to anastrozole in this work, shows an interesting docking mode. Its isobutyronitrile group overlays nicely with the anastrozole side group that is most distal from Ser478. This leaves its "B" ring docked in the same region as that of the other side group of anastrozole that is proximal (2.99 Å) to Ser478. Clearly, such a docking mode of **28** is very different from that observed for **31**. Given their structural similarity, it could have been envisaged that both compounds would dock in a similar fashion. On examination of the various docking modes generated for compound **28** by GOLD, there is one that overlaps the docking mode of **31** reasonably well, placing its "B" ring toward the same hydrophobic pocket of the enzyme and overlaying its isobutyronitrile side group with that of anastrozole nearest to Ser478. However, such a docking mode is ranked 22 places below that shown for **28** in Figure 3. There is a difference of >5 kJ mol^{-1} between their GOLD fitness scores (GOLDscore: 57.56 versus 62.76). Hence, according to the docking parameters of GOLD, the docking mode of **28** presented in Figure 3 is considered to give an overall better interaction with the enzyme active site residues, making this compound one of the most potent AIs reported herein.

3.B. 41 vs. 57 vs. 31

Compound **41** differs from **31** by having the cyano group placed at the 4-position of the "A" ring. Compound **57**, is effectively **31** without the cyano group at the 2-position. Both **41** and **57** dock in a similar mode to **31** with their "B" rings oriented toward the same hydrophobic pocket exploited by that of **31** (see above). However, whereas the "A" ring of **41** closely overlays that of **31**, the same is not observed for compound **57**. Because the cyano group of **41** is at the 4-position of the "A" ring, it points toward Asp 309 and away from Ser 478, which is about 5.8 Å away. From these docking results, the poor aromatase inhibitory activities observed for **57** and **41** can be attributed respectively to the lack of a cyano group, or one that is accessible for participating in a hydrogen bond with Ser 478 (Figure 4). While the haem-ligating property of the triazolyl group is an important contributing factor in aromatase inhibition, any auxiliary functional group which assists in the binding of the inhibitor to the enzyme active site is clearly synergistic to the overall potency of the inhibitor.

3.C. 50 vs. 31 vs. anastrozole

Because of its (6-triazolylmethyl-3-cyano)biphenyl motif, compound **50** docks in a very different mode from that of **31**. Their "A" rings no longer overlap each other in the same position in the enzyme active site. However, the "B" ring of **50** points toward the same hydrophobic pocket as does the "B" ring of **31**, although it is situated significantly further away from this pocket. The cyano group of **50** docks in the same region as that of the anastrozole side group nearest to Ser 478 and at a distance of 3.58 Å from this residue. Given that compound **50** is a potent AI, albeit an order of magnitude less than **31**, some of the putative interactions as suggested by the docking mode of **51** as shown in Figure 5 are indeed productive.

3.D. 45 vs. 65 vs. 31

The docking modes of compounds **45** and **65** are virtually the same according to Figure 6, with their "A" and "B" rings tightly overlaying each other. Although their "A" rings reside close to that of compound **31**, their "B" rings occupy an entirely different location within the active site because their triazolylmethyl moieties are *para* to the biphenyl junction. The amino acid residues nearest to the "B" ring of **45** and **65** are Gln 367 and Pro 368. In the docking mode of **45** as shown, which has the highest GOLD fitness score, its cyano group is clearly pointing away from Ser 478, precluding any potential hydrogen bond in-

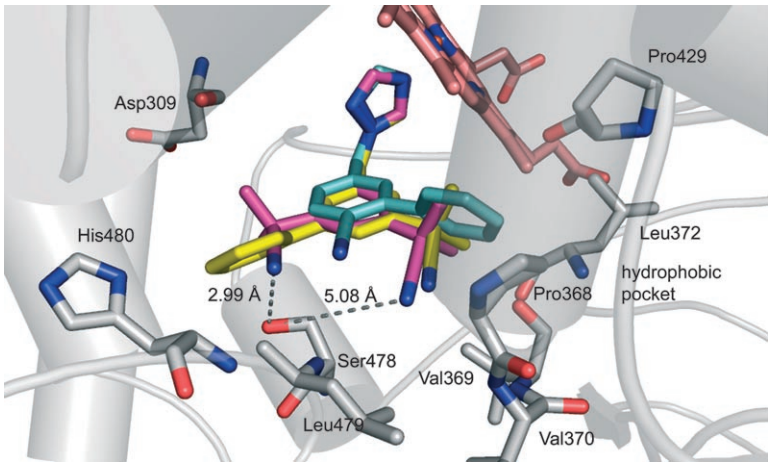


Figure 3. Docking of anastrozole (purple), **31** (cyan), and **28** (yellow) into the human aromatase homology model[23] using the GOLD docking program version 3.1.1;[26] the haem group is shown in bronze.

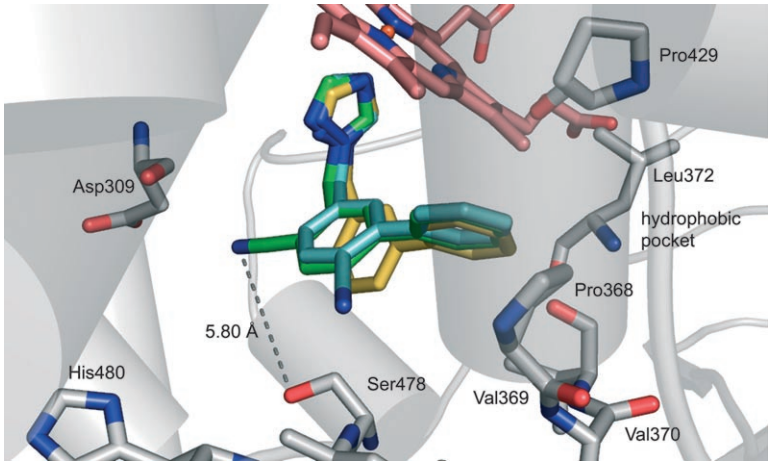


Figure 4. Docking of **41** (green), **57** (gold), and **31** (cyan) into the human aromatase homology model[23] using the GOLD docking program version 3.1.1;[26] the haem group is shown in bronze, and the haem iron centre is presented as a brown ball.

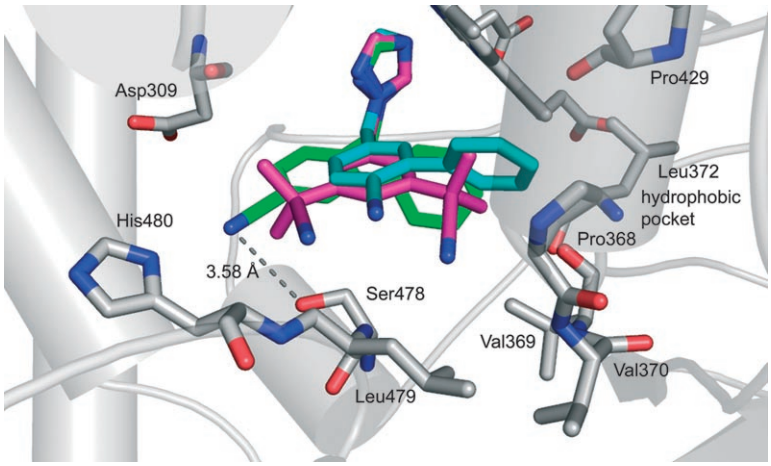


Figure 5. Docking of **50** (green), **31** (cyan), and anastrozole (purple) into the human aromatase homology model[23] using the GOLD docking program version 3.1.1;[26] the haem group is shown in bronze, and the haem iron centre is presented as a brown ball.

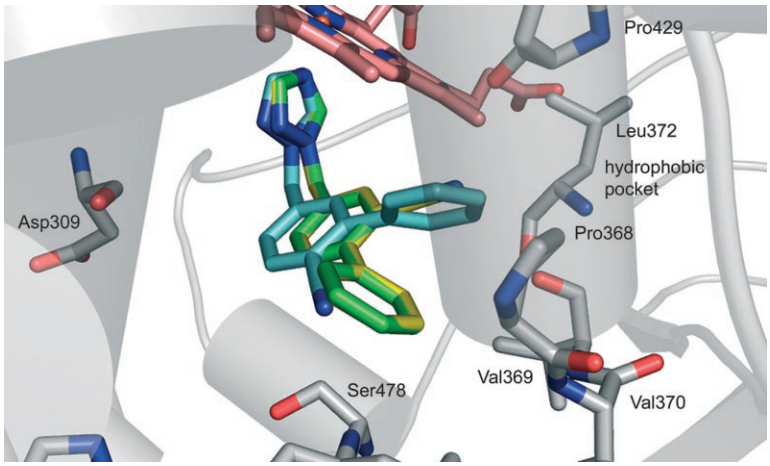


Figure 6. Docking of **45** (gold), **65** (green), and **31** (cyan) into the human aromatase homology model[23] using the GOLD docking program version 3.1.1;[26] the haem group is shown in bronze.

teractions with this amino acid residue. However, given the reasonably strong aromatase inhibitory activity observed for **45** ($IC_{50}=4.6$ nM), it can be reasoned that its docking mode as shown nonetheless provides some fruitful interactions with the enzyme active site. In summary, for compounds studied in this work that show highly potent aromatase inhibitory activity, the selective docking studies presented herein support the importance of a cyano group on the "A" ring of the biphenyl template that is accessible to hydrogen bonding with Ser478. Other interactions by the "B" ring, such as those with a hydrophobic pocket in the active site, may also contribute toward the high potency observed in some of these compounds.

Conclusions

A new structural class of aromatase inhibitor has been discovered. The biphenyl system was explored as a template for designing AIs by incorporating a triazolylmethyl moiety with or without additional substituents. In assays of these biphenyl compounds in JEG-3 cells, those with the following substituents on the "A" ring were observed to inhibit aromatase (listed in order of descending potency): 5-triazolylmethyl-2-cyano (Table 2), 5-triazolylmethyl-3-(2-methylpropionitrile) (Table 1) $>>$ 6-triazolylmethyl-3-cyano (Table 5) $>$ 3-triazolylmethyl-6-halo (Table 6) $>$ 4-triazolylmethyl-2-cyano (Table 4), 3-triazolylmethyl (Table 6) $>$ 3-triazolylmethyl-4-cyano (Table 3), 4-triazolylmethyl (Table 7). The most potent compound discovered in this work is **37** ($IC_{50}=0.12$ nM), although its congeners **31**–**35**, **38**, and **39** in Table 2 are also highly potent AIs ($IC_{50}\leq 0.5$ nM). These results indicate that the substitution pattern on the "A" ring of these biphenyl-based inhibitors is a key determinant for potency in aromatase inhibition. The most effective combination of substituents is a triazolylmethyl moiety *para* to a cyano group (substituents at the 5- and 2-positions of the biphenyl template, respectively). The results of docking representative compounds from various structural classes into a homology model of human aromatase with their triazolylmethyl moiety ligating the haem iron support, among other things, the crucial role of a cyano group accessible to hydrogen bond interactions with Ser478. Further development of these compounds as potential therapeutic agents for the treatment of hormone-dependent breast cancer is warranted given the high potency observed for this class of AIs in vitro.

Experimental Section

Chemistry

HPLC-grade solvents were used, and commercial reagents and starting materials were used without further purification, unless otherwise stated. NMR spectra were recorded on either a Jeol Delta 270 MHz or a Varian Mercury VX 400 MHz spectrometer. ^{1}H NMR spectra were recorded at 270 or 400 MHz with shifts reported in ppm (δ) relative to residual $CHCl_3$ ($\delta_H=7.26$ ppm) or residual DMSO ($\delta_H=2.50$ ppm). Coupling constants (J) are reported in Hz. ^{13}C NMR spectra were recorded at either 67.9 or 100.6 MHz with the central peak of $CHCl_3$ ($\delta_C=77.16$ ppm) or DMSO ($\delta_C=39.52$ ppm) as internal standard. LC–MS (APCI or ES) was performed on a micromass ZQ4000 coupled with a Waters Alliance HT 2790 separations module and a 996 PDA detector. A Symmetry C_{18} column (4.6×150 mm) eluting with MeCN/H_2O at 1.0 mL min^{-1} was used for LC analyses, and all biologically tested compounds attained a purity level of $>95\%$ by this method. FAB HRMS data were determined at the EPSRC mass spectrometry centre (Swansea, UK). Electrospray (ES) HRMS data were obtained with a Bruker micrOTOF-Focus instrument. Elemental analyses were performed by the Microanalysis Service, University of Bath. Melting points were determined using a Stanford Research Systems Optimelt MPA100 automated melting point system and are uncorrected. TLC was carried out with Kieselgel 60 F_{254} plates (Merck). Flash column chromatography was performed on silica gel (Sorbsil/Matrex C60) or by using Argonaut pre-packed columns with FlashMaster II. Microwave reactions were carried out using a CEM Discover microwave.

Biology

The extent of in vitro inhibition of aromatase was assessed using intact monolayers of JEG-3 cells. Cells were seeded into 24-well culture plates and maintained in MEM (Flow Laboratories, Irvine, UK) containing supplements and used when 80% confluent. To determine aromatase activity, 1β-[^{3}H]androstenedione (5 pmol, 30 Ci mmol^{-1}, PerkinElmer, MA, USA) was incubated with JEG-3 cells for 1 h in the presence or absence of inhibitor. The product, ^3H_2O, was separated from the substrates using dextran-coated charcoal at 4 °C for 2 h, and remaining radioactivity was measured by scintillation spectrometry. Each IC_{50} value represents the mean ± SE of triplicate measurements.

Molecular modelling

The models of anastrozole, **28**, **31**, **41**, **45**, **50**, **57**, and **65** were built in the SYBYL 7.1[27] molecular modelling program. To obtain low-energy conformations of the model, energy minimization was performed to convergence using the MMFF94s force field with MMFF94 charges.[28]

A homology model of the human aromatase enzyme (PDB code: 1TQA), which is based on the crystal structure of the human

CYP2C9 metabolic enzyme[29] as described by Favia et al.[23] was read into SYBYL 7.1. Hydrogen atoms were built onto the model, and all atoms except hydrogens were fixed in aggregates. Hydrogen atom positions were then optimized to convergence using the Tripos force field with Gasteiger–Hückel charges.

The GOLD docking program version 3.1.1[26] was used to dock the compound model to the aromatase model. The aromatase active site was defined as a sphere of $r = 12$ Å around the haem group iron centre. As in our previous report,[14] a distance constraint (minimum = 2.00 Å, maximum = 2.30 Å) was applied between the ligating triazole nitrogen atom of the ligand (N4) to the haem iron. The coordination number of the iron ion was defined as 6. The ligand was then docked to the enzyme a total of 25 times using the GOLDscore fitness function. Structure representations were generated using PyMOL.[30]

Syntheses

1-(3-Bromobenzyl)-1*H*-1,2,4-triazole 19. 1*H*-1,2,4-Triazole (10.8 g, 120 mmol), K_2CO_3 (11.0 g, 80.0 mmol), and KI (0.790 g, 4.72 mmol) were added to a solution of **11** (20.0 g, 80.0 mmol) in acetone (300 mL). The resulting white suspension was heated at 55 °C with vigorous stirring for 16 h. The yellow reaction mixture was cooled, and EtOAc (100 mL) added. This was then washed with distilled H_2O (2×100 mL), 1 M $NaOH_{(aq)}$ (2×100 mL) and brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and solvent removed in vacuo to leave a yellow oil. Column chromatography (EtOAc) eluted **19** as a yellow crystalline solid (12.4 g, 65%); mp: 45–48 °C; $C_9H_8BrN_3$ requires C 45.4, H 3.4, N 17.7%, found: C 45.6, H 3.6, N 17.5%; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 5.27$ (2H, s, $ArCH_2N$), 7.15–7.42 (4H, m, ArH), 7.95 (1H, s, $C_2H_2N_3$) and 8.07 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 52.7$, 123.1, 126.5, 130.6, 130.9, 131.8, 136.9, 143.2 and 152.4 ppm; MS (FAB) *m/z* 240 ($[^{81}BrM+H]^+$, 100%), 238 ($[^{79}BrM+H]^+$, 100).

4-[(1*H*-1,2,4-Triazol-1-yl)methyl]-2-bromobenzonitrile 20. Compound **20** was prepared from compound **12** (12.4 g, 45 mmol) using similar conditions to those described for the synthesis of compound **19**. Column chromatography (EtOAc) eluted a pale yellow solid. Recrystallisation (EtOAc/hexanes) gave **20** as a light yellow crystalline solid (8.76 g, 74%); mp: 94–97 °C; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 5.38$ (2H, s, $ArCH_2N$), 7.24–7.27 (1H, dd, $J =$ 1.5 & 8.2 Hz, ArH), 7.53–7.54 (1H, d, $J = 1.5$ Hz, ArH), 7.63–7.68 (1H, d, $J = 8.2$ Hz, ArH), 8.01 (1H, s, $C_2H_2N_3$) and 8.17 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 52.1$ (CH_2), 115.9 (C), 116.8 (C), 126.1 (C), 126.9 (CH), 132.2 (CH), 134.8 (CH), 141.5 (C), 143.7 (CH) and 153.0 ppm (CH); LC–MS (APCI) *m/z* 263 ($[^{81}BrM-H]^-$, 90%), 261 ($[^{79}BrM-H]^-$, 100).

1-(3-Bromo-4-fluorobenzyl)-1*H*-1,2,4-triazole 21. Compound **21** was prepared from compound **13** (3.54 g, 13.2 mmol) using similar conditions to those described for the synthesis of compound **19**. Column chromatography (EtOAc) eluted **21** as a white solid (1.76 g, 52%); mp: 85–87 °C; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 5.28$ (2H, s, $ArCH_2N$), 7.06–7.21 (2H, m, ArH), 7.44–7.47 (1H, dd, $J = 1.9$ & 6.3 Hz, ArH), 7.96 (1H, s, $C_2H_2N_3$) and 8.09 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 52.2$ (CH_2), 109.6–110.0 (C, $J_{C-F} =$ 30.5 Hz), 117.0–117.3 (CH, $J_{C-F} = 23.0$ Hz), 128.7–128.8 (CH, $J_{C-F} =$ 7.5 Hz), 132.1 (C), 133.2 (CH), 143.2 (CH), 152.6 (CH) and 157.4–161.0 ppm (C, $J_{C-F} = 249.6$ Hz); LC–MS (APCI) *m/z* 257 ($[^{81}BrM+H]$, 90%), 255 ($[^{79}BrM+H]^+$, 100).

1-(3-Bromo-4-chlorobenzyl)-1*H*-1,2,4-triazole 22. Compound **22** was prepared from compound **14** (2.27 g, 8 mmol) using similar conditions to those described for the synthesis of compound **19**. Column chromatography (EtOAc) eluted **22** as a yellow viscous oil (2.00 g, 92%); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 5.33$ (2H, s, $ArCH_2N$), 7.10–7.14 (1H, dd, $J = 2.2$ & 8.3 Hz, ArH), 7.41–7.44 (1H, d, $J =$ 8.3 Hz, ArH), 7.50–7.51 (1H, d, $J = 1.9$ Hz, ArH), 7.97 (1H, s, $C_2H_2N_3$) and 8.10 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 52.1$ (CH_2), 123.1 (C), 127.8 (CH), 130.9 (CH), 133.0 (CH), 134.8 (C), 135.0 (C), 143.2 (CH) and 152.6 ppm (CH); LC–MS (APCI) *m/z* 273 ($[M+H]^+$, 100%).

2-[(1*H*-1,2,4-Triazol-1-yl)methyl]-4-bromobenzonitrile 23. Compound **23** was prepared from compound **15** (2.50 g, 9.1 mmol) using similar conditions to those described for the synthesis of compound **19**. Column chromatography (EtOAc) eluted **23** as a yellow solid. Recrystallisation (EtOAc/hexanes) gave a yellow crystalline solid (1.58 g, 66%); mp: 107–108 °C; $C_{10}H_7BrN_4$ requires C 45.7, H 2.7, N 21.3%, found: C 45.6, H 2.7, N 20.9%; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 5.51$ (2H, s, $ArCH_2N$), 7.50 (1H, s, ArH), 7.53–7.56 (1H, d, $J = 8.8$ Hz, ArH), 7.59–7.62 (1H, dd, $J = 1.7$ & 8.5 Hz, ArH), 7.99 (1H, s, $C_2H_2N_3$) and 8.27 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 50.7$, 110.6, 116.3, 128.8, 132.8, 132.9, 134.2, 139.8, 143.9 and 153.0 ppm; MS (EI) *m/z* 264 ($[^{81}BrM]^+$, 100%), 262 ($[^{79}BrM]^+$, 99).

1-(4-Bromobenzyl)-1*H*-1,2,4-triazole 24. Compound **24** was prepared from **16** (5.0 g, 20 mmol) using similar conditions to those described for the synthesis of compound **19**. Column chromatography (EtOAc) eluted **24** as a white solid (3.24 g, 68%); mp: 68–71 °C; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 5.29$ (2H, s, $ArCH_2N$), 7.10–7.13 (2H, d, $J = 8.7$, ArH), 7.47–7.50 (2H, d, $J = 8.7$, ArH), 7.96 (1H, s, $C_2H_2N_3$) and 8.06 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 52.9$ (CH_2), 122.9 (C), 129.7 (CH), 132.3 (CH), 133.7 (C), 143.2 (CH) and 152.5 ppm (CH); LC–MS (APCI) *m/z* 240 ($[^{81}BrM+H]$, 95%), 238 ($[^{79}BrM+H]^+$, 100).

5-[(1*H*-1,2,4-Triazol-1-yl)methyl]-2-bromobenzonitrile 25. Compound **25** was prepared from compound **17** (2.48 g, 9 mmol) using similar conditions to those described for the synthesis of compound **19**. Column chromatography (EtOAc) eluted the **25** as a white solid (1.52 g, 64%); mp: 135–138 °C; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 5.33$ (2H, s, $ArCH_2N$), 7.31–7.34 (1H, dd, $J = 2.2$ & 8.4 Hz, ArH), 7.53–7.54 (1H, d, $J = 2.2$ Hz, ArH), 7.66–7.70 (1H, d, $J = 8.4$ Hz, ArH), 7.99 (1H, s, $C_2H_2N_3$) and 8.15 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 51.9$ (CH_2), 116.6 (C), 116.7 (C), 125.7 (C), 133.2 (CH), 133.4 (CH), 134.0 (CH), 135.2 (C), 143.5 (CH) and 153.0 ppm (CH); LC–MS (APCI) *m/z* 265 ($[^{81}BrM+H]$, 100%), 263 ($[^{79}BrM+H]^+$, 95); HRMS (ES) calcd for $C_{10}H_8BrN_4$ $[M^+ + H]$ 262.9927, found 262.9925.

4-[(1*H*-1,2,4-Triazol-1-yl)methyl]-3-bromobenzonitrile 26. Compound **26** was prepared from compound **18** (2.87 g, 10.5 mmol) using similar conditions to those described for the synthesis of compound **19**. Column chromatography (EtOAc) eluted **26** as a white solid (2.09 g, 76%); mp: 151–153 °C; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 5.49$ (2H, s, $ArCH_2N$), 7.09–7.12 (1H, d, $J = 7.9$ Hz, ArH), 7.56–7.60 (1H, dd, $J = 1.5$ & 7.9 Hz, ArH), 7.88–7.89 (1H, d, $J =$ 1.5 Hz, ArH), 8.00 (1H, s, $C_2H_2N_3$) and 8.22 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 53.0$ (CH_2), 114.2 (C), 116.8 (C), 123.5 (C), 130.2 (CH), 131.7 (CH), 136.3 (CH), 139.7 (C), 144.2 (CH) and 152.9 ppm (CH); LC–MS (APCI) *m/z* 263 ($[^{81}BrM-H]^-$, 100%), 261 ($[^{79}BrM-H]^-$, 95).

2-{5-[(1*H*-1,2,4-Triazol-1-yl)methyl]biphenyl-3-yl}-2-methylpropionitrile 28. Compound **27** (0.100 g 0.328 mmol), phenylboronic acid (0.060 g, 0.492 mmol), K_2CO_3 (0.113 g, 0.820 mmol), tetra-*N*-butylammonium bromide (0.109 g, 0.328 mmol), distilled H_2O (3.5 mL)

and EtOH (1.5 mL) were combined and degassed with N_2 for 30 min. $Pd(OAc)_2$ (3 mol%) was added, and the reaction mixture was heated with vigorous stirring at 70 °C for 1 h. Upon cooling, EtOAc (50 mL) was added and washed with distilled H_2O (2× 50 mL) and brine (50 mL). The organic portion was separated and dried ($MgSO_4$), filtered and solvent removed in vacuo to leave a yellow/brown residue. Column chromatography (EtOAc) eluted **28** as a yellow viscous oil (0.065 g, 66%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.67 (6H, s, ArC$(CH_3)_2$CN), 5.35 (2H, s, ArCH_2N), 7.23–7.47 (7H, m, ArH), 7.56–7.57 (1H, t, J = 1.8 Hz, ArH), 7.92 (1H, s, $C_2H_2N_3$) and 8.08 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 29.2, 37.3, 53.4, 123.4, 124.2, 124.4, 126.6, 127.3, 128.1, 129.0, 136.1, 139.8, 143.0, 143.2, 143.3 and 152.5 ppm; LC–MS (APCI) m/z 303 ([M+H]$^+$, 100%); HRMS (ES) calcd for $C_{19}H_{19}N_4$ [M+H]$^+$ 303.1604, found 303.1598.

2-{5-[(1*H*-1,2,4-Triazol-1-yl)methyl]-3′-chlorobiphenyl-3-yl}-2-methylpropionitrile 29. Compound **29** was prepared from compound **27** (0.100 g, 0.33 mmol) and 3-chlorophenylboronic acid (0.077 g, 0.5 mmol) using similar conditions to those described for the synthesis of compound **28**. Column chromatography (EtOAc) eluted **29** as a colourless viscous oil (0.077 g, 70%). $C_{19}H_{17}ClN_4$ requires C 67.7, H 5.1, N 16.6%, found: C 67.4, H 5.1, N 16.8%; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.73 (6H, s, ArC$(CH_3)_2$CN), 5.40 (2H, s, ArCH_2N), 7.29–7.38 (5H, m, ArH), 7.46–7.48 (1H, d, J = 1.7 Hz, ArH), 7.57–7.58 (1H, t, J = 1.7 Hz, ArH), 7.98 (1H, s, $C_2H_2N_3$) and 8.14 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 29.4 (CH_3), 37.5 (C), 53.5 (CH_2), 124.2 (CH), 124.2 (C), 124.6 (CH), 125.7 (CH), 126.5 (CH), 127.6 (CH), 128.4 (CH), 130.5 (CH), 135.1 (C), 136.6 (C), 141.9 (C), 142.0 (C), 143.6 (C), 143.5 (CH) and 152.5 ppm (CH); LC–MS (APCI) m/z 339 ([^{37}ClM+H]$^+$, 42%), 337 ([^{35}ClM+H]$^+$, 100); HRMS (ES) calcd for $C_{19}H_{18}ClN_4$ [M+H]$^+$ 337.1215, found 337.1207.

3′-[(1*H*-1,2,4-Triazol-1-yl)methyl]-5′-(2-cyanopropan-2-yl)biphenyl-3-carbonitrile 30. Compound **30** was prepared from compound **27** (0.098 g, 0.32 mmol) and 3-cyanophenylboronic acid (0.071 g, 0.48 mmol) using similar conditions to those described for the synthesis of compound **28**. Column chromatography (EtOAc) eluted **30** as a yellow viscous oil (0.038 g, 36%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.70 (6H, s, ArC$(CH_3)_2$CN), 5.38 (2H, s, ArCH_2N), 7.30–7.74 (7H, m, ArH), 7.93 (1H, s, $C_2H_2N_3$) and 8.12 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 29.1, 37.3, 53.1, 113.3, 118.5, 123.9, 124.4, 124.5, 126.2, 129.9, 130.8, 131.5, 131.7, 136.8, 140.9, 141.1, 143.4, 143.6 and 152.5 ppm; LC–MS (APCI) m/z 328 ([M+H]$^+$, 100%); HRMS (ES) calcd for $C_{20}H_{18}N_5$ [M+H]$^+$ 328.1557, found 328.1562.

5-[(1*H*-1,2,4-Triazol-1-yl)methyl]biphenyl-2-carbonitrile 31. A 10-mL microwave vial was loaded with **20** (0.150 g, 0.570 mmol), phenylboronic acid (0.139 g, 1.14 mmol), K_2CO_3 (0.198 g, 1.43 mmol), tetra-*N*-butylammonium bromide (0.189 g, 0.570 mmol), $Pd(OAc)_2$ (3 mol%), EtOH (1.5 mL), and distilled H_2O (3.5 mL). The vial was sealed and loaded (with no prior degassing) into a CEM Discover microwave. After a run time of 5 min at 120 °C (150 W) the reaction mixture was allowed to cool, and EtOAc (50 mL) was added. This was then washed with distilled H_2O (3×25 mL) and brine (25 mL). The organic layer was dried ($MgSO_4$), filtered and solvent removed in vacuo to leave a yellow/brown residue. Column chromatography (EtOAc) eluted **31** as a white solid (0.118 g, 80%); mp: 128–130 °C; $C_{16}H_{12}N_4$ requires C 73.8, H 4.7, N 21.5%, found: C 73.3, H 4.7, N 21.4%; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.40 (2H, s, ArCH_2N), 7.24–7.34 (2H, m, ArH), 7.45–7.48 (5H, m, ArH), 7.74–7.77 (1H, d, J = 7.9 Hz, ArH), 8.00 (1H, s, $C_2H_2N_3$) and 8.17 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 52.8 (CH_2), 111.6 (C), 118.2 (C), 126.7 (CH), 128.8 (CH), 128.9 (CH), 129.2 (CH), 129.3 (CH), 134.5 (CH), 137.4 (C), 140.0 (C), 143.6 (CH), 146.7 (C) and 152.8 ppm (CH); LC–MS (APCI) m/z 261 ([M+H]$^+$, 100%); HRMS (ES) calcd for $C_{16}H_{13}N_4$ [M+H]$^+$ 261.1135, found 261.1134.

5-[(1*H*-1,2,4-Triazol-1-yl)methyl]-3′-chlorobiphenyl-2-carbonitrile 32. Compound **32** was prepared from compound **20** (0.150 g, 0.57 mmol) and 3-chlorophenylboronic acid (0.178 g, 1.14 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **32** as a white solid (0.131 g, 78%); mp: 105–108 °C; $C_{16}H_{11}ClN_4$ requires C 65.2, H 3.8, N 19.0%, found: C 65.1, H 3.7, N 18.9%; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.44 (2H, s, ArCH_2N), 7.28–7.33 (2H, m, ArH), 7.38–7.46 (4H, m, ArH), 7.75–7.78 (1H, d, J = 7.9 Hz, ArH), 8.00 (1H, s, $C_2H_2N_3$) and 8.18 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 52.7 (CH_2), 111.6 (C), 117.8 (C), 127.0 (CH), 127.2 (CH), 128.8 (CH), 129.2 (CH), 129.3 (CH), 130.2 (CH), 134.6 (CH), 139.1 (C), 140.2 (C), 143.6 (CH), 144.8 (C) and 152.9 ppm (CH); LC–MS (APCI) m/z 295 ([^{37}ClM−H]$^-$, 35%), 293 ([^{35}ClM−H]$^-$, 100); HRMS (ES) calcd for $C_{16}H_{12}ClN_4$ [M]$^+$ 295.0745, found 295.0746.

5-[(1*H*-1,2,4-Triazol-1-yl)methyl]-4′-chlorobiphenyl-2-carbonitrile 33. Compound **33** was prepared from compound **20** (0.149 g, 0.57 mmol) and 4-chlorophenylboronic acid (0.178 g, 1.14 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **33** as a white solid (0.085 g, 51%); mp: 144–147 °C; $C_{16}H_{11}ClN_4$ requires C 65.2, H 3.8, N 19.0%, found: C 65.3, H 3.9, N 18.4.); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.44 (2H, s, ArCH_2N), 7.27–7.31 (2H, m, ArH), 7.41–7.48 (3H, m, ArH), 7.74–7.77 (2H, d, J = 7.9 Hz, ArH), 8.00 (1H, s, $C_2H_2N_3$) and 8.17 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 52.7 (CH_2), 111.5 (C), 117.9 (C), 127.0 (CH), 129.1 (CH), 129.2 (CH), 130.1 (CH), 134.6 (CH), 135.6 (C), 135.8 (C), 140.2 (C), 143.6 (CH), 145.2 (C) and 152.9 ppm (CH); LC–MS (APCI) m/z 295 ([^{37}ClM−H]$^-$, 40%), 293 ([^{35}ClM−H]$^-$, 100); HRMS (ES) calcd for $C_{16}H_{12}ClN_4$ [M+H]$^+$ 295.0745, found 295.0743.

5-[(1*H*-1,2,4-Triazol-1-yl)methyl]biphenyl-2,3′-dicarbonitrile 34. Compound **34** was prepared from compound **20** (0.151 g, 0.57 mmol) and 3-cyanophenylboronic acid (0.168 g, 1.14 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **34** as a white solid (0.077 g, 47%); mp: 190–193 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.47 (2H, s, ArCH_2N), 7.34–7.38 (2H, m, ArH), 7.59–7.64 (1H, m, ArH), 7.74–7.82 (4H, m, ArH), 8.02 (1H, s, $C_2H_2N_3$) and 8.20 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 52.6 (CH_2), 111.6 (C), 113.4 (C), 117.5 (C), 118.2 (C), 127.8 (CH), 129.1 (CH), 129.9 (CH), 132.2 (CH), 132.7 (CH), 133.2 (CH), 134.7 (CH), 138.7 (C), 140.6 (C), 143.7 (CH), 143.8 (C) and 153.0 ppm (CH); LC–MS (APCI) m/z 284 ([M−H]$^-$, 100%); HRMS (ES) calcd for $C_{17}H_{12}N_5$ [M+H]$^+$ 286.1087, found 286.1085.

5-[(1*H*-1,2,4-Triazol-1-yl)methyl]biphenyl-2,4′-dicarbonitrile 35. Compound **35** was prepared from compound **20** (0.149 g, 0.56 mmol) and 4-cyanophenylboronic acid (0.165 g, 1.12 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **35** as a white solid (0.087 g, 54%); mp: 186–188 °C; $C_{17}H_{11}N_5$ requires C 71.6, H 3.9, N 24.2%, found: C 71.1, H 3.8, N 24.2%; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.46 (2H, s, ArCH_2N), 7.32–7.38 (2H, m, ArH), 7.59–7.62 (2H, d, J = 8.4 Hz, ArH), 7.76–7.82 (3H, m, ArH), 8.01 (1H, s, $C_2H_2N_3$) and 8.19 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 52.6 (CH_2), 111.5 (C), 113.1 (C), 117.5 (C), 118.3 (C), 127.9 (CH), 129.1 (CH), 129.6 (CH), 132.7 (CH), 134.7 (CH), 140.6 (C), 141.8 (C), 143.7 (CH), 144.2 (C) and 153.0 ppm (CH); LC–MS (APCI) m/z 284 ([M−H]$^-$, 100%); HRMS (ES) calcd for $C_{17}H_{12}N_5$ [M+H]$^+$ 286.1087, found 286.1080.

4-[(1*H*-1,2,4-Triazol-1-yl)methyl]-2-(naphthalen-2-yl)benzonitrile 36. Compound **36** was prepared from compound **20** (0.151 g, 0.57 mmol) and 2-naphthaleneboronic acid (0.196 g, 1.14 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **36** as a light yellow solid (0.151 g, 85%); mp: 138–139 °C; $C_{20}H_{14}N_4$ requires C 77.4, H 4.5, N 18.1%, found: C 77.0, H 4.5, N 18.1%; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 5.47$ (2H, s, $ArCH_2N$), 7.28–7.32 (1H, dd, $J =$ 1.5 & 7.9 Hz, ArH), 7.46–7.47 (1H, d, $J = 1.5$ Hz, ArH), 7.52–7.57 (2H, m, ArH), 7.58–7.62 (1H, dd, $J = 2.0$ & 8.6 Hz, ArH), 7.78–7.81 (1H, d, $J = 7.9$ Hz, ArH), 7.87–7.98 (4H, m, ArH), 8.01 (1H, s, $C_2H_2N_3$) and 8.19 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 52.9$ (CH_2), 111.8 (C), 118.3 (C), 126.1 (CH), 126.7 (C), 126.8 (CH), 127.1 (CH), 127.9 (CH), 128.4 (CH), 128.5 (CH), 128.8 (CH), 129.5 (CH), 133.2 (C), 133.3 (C), 134.6 (CH), 134.8 (C), 140.0 (C), 143.6 (CH), 146.4 (C) and 152.9 ppm (CH); LC–MS (APCI) *m/z* 309 ([*M*−H]$^-$, 100%); HRMS (ES) calcd for $C_{20}H_{15}N_4$ [*M*+H]$^+$ 311.1291, found 311.1287.

5-[(1*H*-1,2,4-Triazol-1-yl)methyl]-3′-acetylbiphenyl-2-carbonitrile 37. Compound **37** was prepared from compound **20** (0.150 g, 0.57 mmol) and 3-acetylphenylboronic acid (0.187 g, 1.14 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **37** as a white solid (0.125 g, 73%); mp: 135–136 °C; $C_{18}H_{14}N_4O$ requires C 71.2, H 4.7, N 18.5%, found: C 71.3, H 4.6, N 18.3%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.65$ (3H, s, $ArCOCH_3$), 5.46 (2H, s, $ArCH_2N$), 7.30–7.33 (1H, dd, $J =$ 1.6 & 7.6 Hz, ArH), 7.39–7.40 (1H, d, $J =$ 1.6 Hz, ArH), 7.58–7.62 (1H, t, $J = 7.6$ Hz, ArH), 7.71–7.74 (1H, dt, $J =$ 1.6 & 7.6 Hz, ArH), 7.77–7.79 (1H, d, $J = 8.4$ Hz, ArH), 8.00 (1H, s, $C_2H_2N_3$), 8.02–8.05 (1H, d, $J = 7.6$ Hz, ArH), 8.08–8.09 (1H, t, $J =$ 1.6 Hz, ArH) and 8.19 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 26.9$ (CH_3), 52.8 (CH_2), 111.6 (C), 117.9 (C), 127.2 (CH), 128.6 (CH), 129.0 (CH), 129.3 (CH), 129.4 (CH), 133.3 (CH), 134.6 (CH), 137.7 (C), 137.9 (C), 140.3 (C), 143.6 (CH), 145.3 (C) and 152.9 ppm (CH); LC–MS (APCI) *m/z* 301 ([*M*−H]$^-$, 100%); HRMS (ES) calcd for $C_{18}H_{15}N_4O$ [*M*]$^+$ 303.1240, found 303.1233.

5-[(1*H*-1,2,4-Triazol-1-yl)methyl]-4′-fluorobiphenyl-2-carbonitrile 38. Compound **38** was prepared from compound **20** (0.30 g, 1.14 mmol) and 4-fluorophenylboronic acid (0.319 g, 2.28 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **38** as a white solid (0.298 g, 94%); mp: 128–132 °C; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 5.44$ (2H, s, $ArCH_2N$), 7.13–7.20 (2H, m, ArH), 7.26–7.31 (2H, m, ArH), 7.45–7.53 (2H, m, ArH), 7.74–7.77 (1H, d, $J = 4.9$ Hz, ArH), 8.00 (1H, s, $C_2H_2N_3$) and 8.17 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 52.8$ (CH_2), 111.5 (C), 115.9–116.2 (CH, $J_{C-F} =$ 21.8 Hz), 118.1 (C), 126.8 (CH), 129.2 (CH), 130.6–130.7 (CH, $J_{C-F} =$ 8.1 Hz), 133.4–133.5 (C, $J_{C-F} = 3.1$ Hz), 134.5 (CH), 140.1 (C), 143.6 (CH), 145.4 (C), 152.9 (CH) and 161.5–165.2 ppm (C, $J_{C-F} = 249$ Hz); LC–MS (APCI) *m/z* 278 ([*M*+H]$^+$, 100%); HRMS (ES) calcd for $C_{16}H_{12}FN_4$ [*M*+H]$^+$ 279.1041, found 279.1042.

5-[(1*H*-1,2,4-Triazol-1-yl)methyl]-4′-ethylbiphenyl-2-carbonitrile 39. Compound **39** was prepared from compound **20** (0.10 g, 0.38 mmol) and 4-ethylphenylboronic acid (0.114 g, 0.76 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **39** as a white crystalline solid (0.058 g, 53%); mp: 122–124 °C; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 1.25$–1.29 (3H, t, $J = 7.7$ Hz, $ArCH_2CH_3$), 2.66–2.74 (2H, q, $J = 7.7$ Hz, $ArCH_2CH_3$), 5.43 (2H, s, $ArCH_2N$), 7.23–7.33 (4H, m, ArH), 7.41–7.44 (2H, d, $J = 8.2$ Hz, ArH), 7.72–7.75 (1H, d, $J = 8.0$ Hz, ArH), 8.00 (1H, s, $C_2H_2N_3$) and 8.16 ppm (1H, m, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 15.5$ (CH_3), 28.7 (CH_2), 52.9 (CH_2), 111.4 (C), 118.4 (C), 126.4 (CH), 128.5 (CH), 128.7 (CH), 129.2 (CH), 134.5 (C), 134.7 (CH), 139.9 (C), 143.5 (CH), 145.5 (C), 146.5 (C) and 152.8 ppm (CH); LC–MS (ES) *m/z* 287 ([*M*−H]$^-$, 100%); HRMS (ES) calcd for $C_{18}H_{17}N_4$ [*M*+H]$^+$ 289.1448, found 289.1438.

5-[(1*H*-1,2,4-Triazol-1-yl)methyl]-4′-*tert*-butylbiphenyl-2-carbonitrile 40. Compound **40** was prepared from compound **20** (0.151 g, 0.57 mmol) and 4-*tert*-butylphenylboronic acid (0.203 g, 1.14 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **40** as a yellow viscous oil (0.134 g, 74%); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta =$ 1.34 (9H, s, $ArC(CH_3)_3$), 5.43 (2H, s, $ArCH_2N$), 7.23–7.26 (1H, dd, $J =$ 1.9 & 8.0 Hz, ArH), 7.32 (1H, s, ArH), 7.42–7.51 (4H, dd, $J = 8.8$ & 13.7 Hz, ArH), 7.73–7.76 (1H, d, $J = 8.0$ Hz, ArH), 8.00 (1H, s, $C_2H_2N_3$) and 8.16 ppm (1H, m, $C_2H_2N_3$);^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 31.4$ (CH_3), 34.7 (C), 52.9 (CH_2), 111.3 (C), 118.5 (C), 125.9 (CH), 126.4 (CH), 128.4 (CH), 129.2 (CH), 134.4 (C), 134.6 (CH), 139.9 (C), 143.5 (CH), 146.3 (C), 152.4 (C) and 152.8 ppm (CH); LC–MS (ES), *m/z* 317.14 ([*M*+H]$^+$, 100%); HRMS (ES) calcd for $C_{20}H_{21}N_4$ [*M*+H]$^+$ 317.1761, found 317.1754.

3-[(1*H*-1,2,4-Triazol-1-yl)methyl]biphenyl-4-carbonitrile 41. Compound **41** was prepared from compound **23** (0.985 g, 3.74 mmol) and phenylboronic acid (0.912 g, 7.48 mmol) using similar conditions to those described for the synthesis of compound **28**. Column chromatography (EtOAc) eluted **41** as a white solid (0.760 g, 78%); mp: 107–108 °C; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 5.59$ (2H, s, $ArCH_2N$), 7.42–7.56 (6H, m, ArH), 7.63–7.67 (1H, dd, $J =$ 1.8 & 8.2 Hz, ArH), 7.74–7.77 (1H, d, $J = 8.2$ Hz, ArH), 7.98 (1H, s, $C_2H_2N_3$) and 8.30 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 51.4$, 110.3, 117.1, 127.3, 127.8, 128.2, 129.1, 129.2, 133.6, 138.4, 138.6, 143.9, 146.7 and 152.8 ppm; LC–MS (APCI) *m/z* 261 ([*M*+H]$^+$, 100%); HRMS (ES) calcd for $C_{16}H_{13}N_4$ [*M*+H]$^+$ 261.1135, found 261.1134.

3-[(1*H*-1,2,4-Triazol-1-yl)methyl]-3′-chlorobiphenyl-4-carbonitrile 42. Compound **42** was prepared from compound **23** (0.100 g, 0.38 mmol) and 3-chlorophenylboronic acid (0.089 g, 0.57 mmol) using similar conditions to those described for the synthesis of compound **28**. Column chromatography (EtOAc) eluted **42** as a yellow waxy solid (0.076 g, 68%); mp: 107–108 °C; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 5.59$ (2H, s, $ArCH_2N$), 7.38 (3H, d, $J = 1.5$ Hz, ArH), 7.49–7.64 (3H, m, ArH), 7.75–7.77 (1H, d, $J = 7.9$ Hz, ArH), 7.98 (1H, s, $C_2H_2N_3$) and 8.31 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 51.3$, 111.0, 116.9, 125.5, 127.4, 127.9, 128.3, 129.1, 130.5, 133.7, 135.2, 138.8, 140.2, 143.9, 145.2 and 152.8 ppm; LC–MS (APCI) *m/z* 297 ([^{37}Cl*M*+H]$^+$, 30%), 295 ([^{35}Cl*M*+H]$^+$, 100); HRMS (ES) calcd for $C_{16}H_{12}ClN_4$ [*M*+H]$^+$ 295.0745, found 295.0743.

3′-[(1*H*-1,2,4-Triazol-1-yl)methyl]biphenyl-3,4′-dicarbonitrile 43. Compound **43** was prepared from compound **23** (0.10 g, 0.38 mmol) and 3-cyanophenylboronic acid (0.084 g, 0.57 mmol) using similar conditions to those described for the synthesis of compound **28**. Column chromatography (EtOAc) eluted **43** as a white solid (0.066 g, 61%); mp: 160–161 °C; $C_{17}H_{11}N_5$ requires C 71.6, H 3.9, N 24.2%, found: C 71.3, H 3.8, N 24.1%; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 5.60$ (2H, s, $ArCH_2N$), 7.36–7.81 (7H, m, ArH), 7.97 (1H, s, $C_2H_2N_3$) and 8.32 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 51.2$, 111.6, 113.6, 116.7, 118.2, 127.9, 128.4, 130.2, 130.8, 131.6, 132.4, 133.9, 139.1, 139.8, 143.9, 144.2 and 152.9 ppm; LC–MS (APCI) *m/z* 286 ([*M*+H]$^+$, 100%); HRMS (ES) calcd for $C_{17}H_{12}N_5$ [*M*+H]$^+$ 286.1087, found 286.1090.

3-[(1*H*-1,2,4-Triazol-1-yl)methyl]biphenyl-4,4′-dicarbonitrile 44. Compound **44** was prepared from compound **23** (0.10 g, 0.38 mmol) and 4-cyanophenylboronic acid (0.084 g, 0.57 mmol) using similar conditions to those described for the synthesis of

compound **28**. Column chromatography (EtOAc) eluted **44** as a white solid (0.082 g, 76%); mp: 222–223 °C; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 5.56$ (2H, s, $ArCH_2N$), 7.52–7.77 (7H, m, ArH), 7.94 (1H, s, $C_2H_2N_3$) and 8.27 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 53.1$, 111.8, 112.8, 116.6, 118.3, 128.0, 128.0, 128.4, 133.0, 133.9, 139.1, 142.8, 144.0, 144.6 and 152.9 ppm; LC–MS (APCI) *m/z* 286 ($[M+H]^+$, 100%); HRMS (ES) calcd for $C_{17}H_{12}N_5$ $[M+H]^+$ 286.1086, found 286.1086.

4-[(1*H*-1,2,4-Triazol-1-yl)methyl]biphenyl-2-carbonitrile 45. Compound **45** was prepared from compound **25** (0.152 g, 0.58 mmol) and phenylboronic acid (0.071 g, 1.16 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **45** as a white solid (0.102 g, 68%); mp: 102–104 °C; $C_{16}H_{12}N_4$ requires C 73.8, H 4.6, N 21.5%, found: C 73.5, H 4.6, N 21.5%; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 5.41$ (2H, s, $ArCH_2N$), 7.44–7.58 (7H, m, ArH), 7.65 (1H, s, ArH), 8.01 (1H, s, $C_2H_2N_3$) and 8.18 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 52.3$ (CH_2), 112.1 (C), 118.2 (C), 128.8 (CH), 128.9 (CH), 129.2 (CH), 131.0 (CH), 132.2 (CH), 132.9 (CH), 134.7 (C), 137.4 (C), 143.4 (CH), 145.8 (C) and 152.9 ppm (CH); LC–MS (APCI) *m/z* 259 ($[M-H]^-$, 100%); HRMS (ES) calcd for $C_{16}H_{13}N_4$ $[M+H]^+$ 261.1135, found 261.1128.

4-[(1*H*-1,2,4-Triazol-1-yl)methyl]biphenyl-2,3′-dicarbonitrile 46. Compound **46** was prepared from compound **25** (0.160 g, 0.61 mmol) and 3-cyanophenylboronic acid (0.179 g, 1.22 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **46** as a white solid (0.066 g, 38%); mp: 143–144 °C; $C_{17}H_{11}N_5$ requires C 71.6, H 3.9, N 24.2%, found: C 71.2, H 3.9, N 24.2.); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 5.44$ (2H, s, $ArCH_2N$), 7.48–7.68 (4H, m, ArH), 7.73–7.80 (3H, m, ArH), 8.03 (1H, s, $C_2H_2N_3$) and 8.20 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 52.2$ (CH_2), 112.2 (C), 113.4 (C), 117.5 (C), 118.3 (C), 129.9 (CH), 130.8 (CH), 132.3 (CH), 132.6 (CH), 132.7 (CH), 133.1 (CH), 133.2 (CH), 136.1 (C), 138.6 (C), 143.2 (C), 143.6 (CH) and 153.0 ppm (CH); LC–MS (APCI) *m/z* 284 ($[M-H]^-$, 100%); HRMS (ES) calcd for $C_{17}H_{12}N_5$ $[M+H]^+$ 286.1087, found 286.1081.

4-[(1*H*-1,2,4-Triazol-1-yl)methyl]biphenyl-2,4′-dicarbonitrile 47. Compound **47** was prepared from compound **25** (0.148 g, 0.56 mmol) and 4-cyanophenylboronic acid (0.165 g, 1.12 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **47** as a white solid (0.061 g, 38%); mp: 172–173 °C; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 5.44$ (2H, s, $ArCH_2N$), 7.49–7.53 (1H, d, $J = 8.2$ Hz, ArH), 7.55–7.58 (1H, dd, $J = 1.7$ & 8.2 Hz, ArH), 7.62–7.65 (2H, d, $J = 7.9$ Hz, ArH), 7.68 (1H, m, ArH), 7.77–7.80 (2H, d, $J = 7.9$ Hz, ArH), 8.02 (1H, s, $C_2H_2N_3$) and 8.20 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 52.2$ (CH_2), 112.1 (C), 113.1 (C), 117.5 (C), 118.4 (C), 129.6 (CH), 130.8 (CH), 132.5 (CH), 132.8 (CH), 133.1 (CH), 136.1 (C), 141.7 (C), 143.6 (CH), 143.8 (C) and 153.0 ppm (CH); LC–MS (APCI) *m/z* 284 ($[M-H]^-$, 100%); HRMS (ES) calcd for $C_{17}H_{12}N_5$ $[M+H]^+$ 286.1087, found 286.1084.

4-[(1*H*-1,2,4-Triazol-1-yl)methyl]-4′-ethylbiphenyl-2-carbonitrile 48. Compound **48** was prepared from compound **25** (0.10 g, 0.38 mmol) and 4-ethylphenylboronic acid (0.114 g, 0.76 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **48** as a white solid (0.044 g, 40%); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 1.23$–1.29 (3H, t, $J = 7.7$ Hz, $ArCH_2CH_3$), 2.65–2.74 (2H, q, $J = 7.7$ Hz, $ArCH_2CH_3$), 5.40 (2H, s, $ArCH_2N$), 7.29–7.32 (2H, d, $J = 8.3$ Hz, ArH), 7.42–7.46 (2H, d, $J = 8.3$ Hz, ArH), 7.49–7.53 (2H, m, ArH), 7.63 (1H, s, ArH), 8.00 (1H, s, $C_2H_2N_3$) and 8.17 ppm (1H, m, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 15.5$ (CH_3), 28.7 (CH_2), 52.3 (CH_2), 111.9 (C), 118.3 (C), 128.5 (CH), 128.7 (CH), 130.9 (CH), 132.2 (CH), 133.6 (CH), 134.4 (C), 134.7 (C), 143.4 (CH), 145.5 (C), 145.9 (C) and 152.8 ppm (CH); LC–MS (APCI) *m/z* 287 ($[M-H]^-$, 45%); HRMS (ES) calcd for $C_{18}H_{17}N_4$ $[M+H]^+$ 289.1448, found 289.1461.

4-[(1*H*-1,2,4-Triazol-1-yl)methyl]-4′-*tert*-butylbiphenyl-2-carbonitrile 49. Compound **49** was prepared from compound **25** (0.10 g, 0.38 mmol) and 4-*tert*-butylphenylboronic acid (0.135 g, 0.76 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **49** as a colourless viscous oil (0.074 g, 61%); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 1.35$ (9H, s, $ArC(CH_3)_3$), 5.40 (2H, s, $ArCH_2N$), 7.46–7.54 (6H, m, ArH), 7.63 (1H, s, ArH), 8.01 (1H, s, $C_2H_2N_3$) and 8.17 ppm (1H, m, $C_2H_2N_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 31.2$ (CH_3), 34.7 (C), 52.2 (CH_2), 111.8 (C), 118.2 (C), 125.9 (CH), 128.3 (CH), 130.8 (CH), 132.1 (CH), 132.9 (CH), 134.2 (C), 134.6 (C), 143.3 (CH), 145.7 (C), 152.2 (C) and 152.7 ppm (CH); LC–MS (ES) *m/z* 339 ($[M+Na]^+$, 35%), 317 ($[M+H]^+$, 100%); HRMS (ES) calcd for $C_{20}H_{21}N_4$ $[M+H]^+$ 317.1761, found 317.1749.

6-[(1*H*-1,2,4-Triazol-1-yl)methyl]biphenyl-3-carbonitrile 50. Compound **50** was prepared from compound **26** (0.150 g, 0.57 mmol) and phenylboronic acid (0.140 g, 1.14 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **50** as a colourless viscous oil (0.111 g, 75%); $C_{16}H_{12}N_4$ requires C 73.8, H 4.7, N 21.5%, found: C 73.5, H 4.7, N 21.4%; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 5.31$ (2H, s, $ArCH_2N$), 7.16–7.27 (2H, m, ArH), 7.29–7.32 (1H, d, $J = 7.9$ Hz, ArH), 7.42–7.49 (3H, m, ArH), 7.58–7.59 (1H, d, $J = 1.7$ Hz, ArH), 7.62–7.66 (1H, dd, $J = 1.7$ & 6.4 Hz, ArH), 7.68 (1H, s, $C_2H_2N_3$) and 7.91 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 50.9$ (CH_2), 112.7 (C), 118.2 (C), 128.8 (CH), 128.8 (CH), 129.1 (CH), 129.8 (CH), 131.6 (CH), 133.9 (CH), 137.5 (C), 137.7 (C), 143.0 (C), 143.5 (CH) and 152.6 ppm (CH); LC–MS (APCI) *m/z* 259 ($[M-H]^-$, 100%); HRMS (ES) calcd for $C_{16}H_{13}N_4$ $[M+H]^+$ 261.1135, found 261.1134.

6-[(1*H*-1,2,4-Triazol-1-yl)methyl]biphenyl-3,3′-dicarbonitrile 51. Compound **51** was prepared from compound **26** (0.137 g, 0.52 mmol) and 3-cyanophenylboronic acid (0.153 g, 1.04 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **51** as a colourless viscous oil that crystallised to a white crystalline solid (0.086 g, 58%); mp: 96–97 °C; $C_{17}H_{11}N_5$ requires C 71.6, H 3.9, N 24.2%, found: C 71.4, H 4.0, N 24.3%; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 5.26$ (2H, s, $ArCH_2N$), 7.29–7.32 (1H, d, $J = 8.2$ Hz, ArH), 7.49–7.53 (1H, d, $J = 7.9$ Hz, ArH), 7.56–7.57 (1H, d, $J = 2.0$ Hz, ArH), 7.60–7.63 (2H, m, ArH), 7.68–7.72 (1H, dd, $J = 1.7$ & 7.9 Hz, ArH), 7.74–7.78 (1H, d, $J = 7.7$ Hz, ArH), 7.86 (1H, s, $C_2H_2N_3$) and 7.93 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): $\delta = 50.7$ (CH_2), 113.2 (C), 113.5 (C), 117.7 (C), 118.0 (C), 130.0 (CH), 130.1 (CH), 132.2 (CH), 132.4 (CH), 132.6 (CH), 133.2 (CH), 133.8 (CH), 137.4 (C), 139.0 (C), 140.5 (C), 143.6 (CH) and 152.8 ppm (CH); LC–MS (APCI) *m/z* 284 ($[M-H]^-$, 65%), 215 ($[M-H)-C_2H_2N_3]^+$, 100); HRMS (ES) calcd for $C_{17}H_{12}N_5$ $[M+H]^+$ 286.1087, found 286.1092.

6-[(1*H*-1,2,4-Triazol-1-yl)methyl]biphenyl-3,4′-dicarbonitrile 52. Compound **52** was prepared from compound **26** (0.149 g, 0.57 mmol) and 4-cyanophenylboronic acid (0.168 g, 1.14 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **52** as a white solid (0.089 g, 55%); mp: 125–127 °C; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 5.26$ (2H, s, $ArCH_2N$), 7.29–7.32 (1H, d, $J = 8.2$ Hz, ArH), 7.40–7.43 (2H, d, $J = 8.2$ Hz, ArH), 7.55–7.56 (1H, d, $J = 1.7$ Hz, ArH),

7.67–7.71 (1H, dd, J=1.7 & 8.2 Hz, ArH), 7.75–7.78 (2H, d, J=8.2 Hz, ArH), 7.85 (1H, s, $C_2H_2N_3$) and 7.91 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ=50.6 (CH_2), 113.0 (C), 113.1 (C), 117.7 (C), 118.2 (C), 129.8 (CH), 130.1 (CH), 132.5 (CH), 132.8 (CH), 133.6 (CH), 137.2 (C), 141.0 (C), 142.3 (C), 143.6 (CH) and 152.8 ppm (CH); LC–MS (APCI) m/z 284 ([M−H]$^-$, 100%); HRMS (ES) calcd for $C_{17}H_{12}N_5$ [M+H]$^+$ 286.1087, found 286.1091.

6-[(1*H*-1,2,4-Triazol-1-yl)methyl]-4′-ethylbiphenyl-3-carbonitrile 53. Compound **53** was prepared from compound **26** (0.149 g, 0.57 mmol) and 4-ethylphenylboronic acid (0.171 g, 1.14 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **53** as a colourless viscous oil that crystallised on standing to give a white crystalline solid (0.075 g, 46%); mp: 108–110 °C; $C_{18}H_{16}N_4$ requires C 75.0, H 5.6, N 19.4%, found: C 74.7, H 5.3, N 19.3.); ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.24–1.31 (3H, t, J=7.7 Hz, $ArCH_2CH_3$), 2.67–2.76 (2H, m, $ArCH_2CH_3$), 5.31 (2H, s, $ArCH_2N$), 7.12–7.15 (2H, d, J=8.0 Hz, ArH), 7.27–7.31 (3H, m, ArH), 7.57–7.58 (1H, d, J=1.7 Hz, ArH), 7.60–7.63 (1H, dd, J=1.7 & 8.0 Hz, ArH), 7.70 (1H, s, $C_2H_2N_3$), and 7.90 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ=15.6 (CH_3), 28.7 (CH_2), 50.9 (CH_2), 112.6 (C), 118.2 (C), 128.6 (CH), 128.8 (CH), 129.7 (CH), 131.4 (CH), 134.0 (CH), 134.8 (C), 137.5 (C), 143.0 (C), 143.5 (CH), 145.1 (C) and 152.5 ppm (CH); LC–MS (ES) m/z 289 ([M+H]$^+$, 100%); HRMS (ES) calcd for $C_{18}H_{17}N_4$ [M+H]$^+$ 289.1448, found 289.1451.

6-[(1*H*-1,2,4-Triazol-1-yl)methyl]-4′-*tert*-butylbiphenyl-3-carbonitrile 54. Compound **54** was prepared from compound **26** (0.150 g, 0.57 mmol) and 4-*tert*-butylphenylboronic acid (0.203 g, 1.14 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **54** as a colourless viscous oil (0.105 g, 58%); ^{1}H NMR (270 MHz, $CDCl_3$): δ=1.36 (9H, s, $ArC(CH_3)_3$), 5.33 (2H, s, $ArCH_2N$), 7.15–7.19 (2H, d, J=8.5 Hz, ArH), 7.25–7.31 (1H, d, J=7.7 Hz, ArH), 7.46–7.50 (2H, d, J=6.6 Hz, ArH), 7.58–7.63 (2H, m, ArH), 7.70 (1H, s, $C_2H_2N_3$), and 7.92 ppm (1H, m, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ=31.4 (CH_3), 34.8 (C), 50.9 (CH_2), 112.6 (C), 118.3 (C), 126.0 (CH), 128.5 (CH), 129.6 (CH), 131.4 (CH), 134.0 (CH), 134.6 (C), 137.6 (C), 142.9 (C), 143.5 (CH), 151.9 (C) and 152.5 ppm (CH); LC–MS (ES) m/z 317 ([M+H]$^+$, 100%); HRMS (ES) calcd for $C_{20}H_{21}N_4$ [M+H]$^+$ 317.1761, found 317.1748.

1-[(6-Fluorobiphenyl-3-yl)methyl]-1*H*-1,2,4-triazole 55. Compound **55** was prepared from compound **21** (0.149 g, 0.58 mmol) and phenylboronic acid (0.141 g, 1.16 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **55** as a colourless viscous oil (0.115 g, 78%); ^{1}H NMR (270 MHz, $CDCl_3$): δ=5.35 (2H, s, $ArCH_2N$), 7.01–7.26 (2H, m, ArH), 7.31–7.52 (5H, m, ArH), 7.98 (1H, s, $C_2H_2N_3$) and 8.10 ppm (1H, m, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ=53.0 (CH_2), 116.8–117.2 (CH, J_{C-F}=23.7 Hz), 128.2 (CH), 128.7 (CH), 128.8 (CH), 129.0–129.1 (CH, J_{C-F}=2.5 Hz), 130.6–130.7 (CH, J_{C-F}=4.4 Hz), 130.8–130.9 (C, J_{C-F}=5.0 Hz), 135.0 (C), 142.6 (C), 143.1 (CH), 152.4 (CH) and 157.9–161.6 ppm (C, J_{C-F}=249.6 Hz); LC–MS (ES) m/z 254 ([M+H]$^+$, 100%); HRMS (ES) calcd for $C_{15}H_{13}FN_3$ [M+H]$^+$ 254.1088, found 254.1101.

1-[(6-Chlorobiphenyl-3-yl)methyl]-1*H*-1,2,4-triazole 56. Compound **56** was prepared from compound **22** (0.149 g, 0.55 mmol) and phenylboronic acid (0.134 g, 1.10 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **56** as a colourless viscous oil (0.053 g, 36%); ^{1}H NMR (270 MHz, $CDCl_3$): δ=5.34 (2H, s, $ArCH_2N$), 7.14–7.18 (1H, dd, J=2.2 & 8.5 Hz, ArH), 7.22–7.23 (1H, d, J=2.2 Hz, ArH), 7.34–7.48 (5H, m, ArH), 7.97 (1H, s, $C_2H_2N_3$) and 8.10 ppm (1H, m, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ=52.9 (CH_2), 128.0 (CH), 128.1 (CH), 128.3 (CH), 129.4 (CH), 130.7 (CH), 130.9 (CH), 133.0 (C), 133.5 (C), 138.6 (C), 141.3 (C), 143.2 (CH) and 152.5 ppm (CH); LC–MS (ES) m/z 272 ([^{37}ClM+H]$^+$, 40%), 270 ([^{35}ClM+H]$^+$, 100); HRMS (ES) calcd for $C_{15}H_{13}ClN_3$ [M+H]$^+$ 270.0793, found 270.0785.

1-(Biphenyl-3-ylmethyl)-1*H*-1,2,4-triazole 57. Compound **57** was prepared from compound **19** (0.151 g, 0.63 mmol) and phenylboronic acid (0.154 g, 1.26 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **57** as a white solid (0.067 g, 45%); mp: 79–80 °C; $C_{15}H_{12}N_3$ requires C 76.6, H 5.6, N 17.9%, found: C 76.4, H 5.6, N 17.8%; ^{1}H NMR (270 MHz, $CDCl_3$): δ=5.40 (2H, s, $ArCH_2N$), 7.24–7.55 (9H, m, ArH), 7.98 (1H, s, $C_2H_2N_3$) and 8.09 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=53.7 (CH_2), 126.8 (CH), 126.8 (CH), 127.2 (CH), 127.5 (CH), 127.7 (CH), 128.9 (CH), 129.6 (CH), 135.1 (C), 140.4 (C), 142.2 (C), 143.2 (CH) and 152.3 ppm (CH); LC–MS (APCI) m/z 236 ([M+H]$^+$, 100). HRMS (ES) calcd for $C_{15}H_{14}N_3$ [M+H]$^+$ 236.1182, found 236.1190.

1-[(3′-Chlorobiphenyl-3-yl)methyl]-1*H*-1,2,4-triazole 58. Compound **58** was prepared from compound **19** (0.239 g, 1.0 mmol) and 3-chlorophenylboronic acid (0.235 g, 1.5 mmol) using similar conditions to those described for the synthesis of compound **28**. Column chromatography (EtOAc) eluted **58** as a white solid (0.219 g, 81%); mp: 71–72 °C; $C_{15}H_{12}ClN_3$ requires C 66.8, H 4.5, N 15.6%, found: C 66.5, H 4.4, N 15.6%; ^{1}H NMR (270 MHz, $CDCl_3$): δ=5.39 (2H, s, $ArCH_2N$), 7.24–7.51 (8H, m, ArH), 7.97 (1H, s, $C_2H_2N_3$) and 8.09 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=53.5, 125.4, 126.8, 127.3, 127.4, 127.5, 127.7, 129.7, 130.1, 134.8, 135.4, 140.8, 142.2, 143.1 and 152.3 ppm; LC–MS (APCI) m/z 271 ([^{37}ClM+H]$^+$, 35%), 269 ([^{35}ClM+H]$^+$, 100); HRMS (FAB) calcd for $C_{15}H_{13}ClN_3$ [M+H]$^+$ 269.0720, found 269.0725.

1-[(4′-Chlorobiphenyl-3-yl)methyl]-1*H*-1,2,4-triazole 59. Compound **59** was prepared from compound **19** (0.236 g, 1.0 mmol) and 4-chlorophenylboronic acid (0.235 g, 1.5 mmol) using similar conditions to those described for the synthesis of compound **28**. Column chromatography (EtOAc) eluted **59** as a white solid (0.123 g, 46%); mp: 57–59 °C; $C_{15}H_{12}ClN_3$ requires C 66.8, H 4.5, N 15.6%, found: C 66.7, H 4.4, N 15.5%; ^{1}H NMR (270 MHz, $CDCl_3$): δ=5.39 (2H, s, $ArCH_2N$), 7.37–7.50 (8H, m, ArH), 7.97 (1H, s, $C_2H_2N_3$) and 8.09 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=53.6 (CH_2), 126.7 (CH), 127.2 (CH), 127.4 (CH), 128.5 (CH), 129.1 (CH), 129.8 (CH), 133.9 (C), 135.4 (C), 138.8 (C), 141.0 (C), 143.2 (CH) and 152.3 ppm (CH); LC–MS (APCI) m/z 272 ([^{37}ClM+H]$^+$, 35%), 270 ([^{35}ClM+H]$^+$, 100); HRMS (FAB) calcd for $C_{15}H_{13}ClN_3$ [M+H]$^+$ 269.0720, found 269.0733.

3′-[(1*H*-1,2,4-Triazol-1-yl)methyl]biphenyl-2-carbonitrile 60. Compound **60** was prepared from compound **71** (0.380 g, 1.40 mmol) using similar conditions to those described for the synthesis of compound **19**. Column chromatography (EtOAc) eluted **60** as a white solid (0.218 g, 60%); mp: 68–69 °C; $C_{16}H_{12}N_4$ requires C 73.8, H 4.7, N 21.5%, found: C 73.8, H 4.6, N 21.6.); ^{1}H NMR (270 MHz, $CDCl_3$): δ=5.43 (2H, s, $ArCH_2N$), 7.32–7.35 (1H, d, J=6.9 Hz, ArH), 7.42–7.52 (5H, m, ArH), 7.61–7.67 (1H, m, ArH), 7.74–7.77 (1H, d, J=8.2 Hz, ArH), 7.98 (1H, s, $C_2H_2N_3$) and 8.14 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ=53.4 (CH_2), 111.4 (C), 118.6 (C), 128.1 (CH), 128.3 (CH), 128.4 (CH), 129.2 (CH), 129.6 (CH), 130.1 (CH), 133.0 (CH), 133.9 (CH), 135.4 (C), 139.1 (C), 143.4 (CH), 144.6 (C) and 152.4 ppm (CH); LC–MS (APCI) m/z 260 ([M+H]$^+$, 10%), 191

([(*M*+H)−$C_2H_2N_3$]$^+$, 100); HRMS (ES) calcd for $C_{16}H_{13}N_4$ [*M*+H]$^+$ 261.1135, found 261.1125.

3′-[(1*H*-1,2,4-Triazol-1-yl)methyl]biphenyl-3-carbonitrile 61. Compound **61** was prepared from compound **19** (0.238 g, 1.0 mmol) and 3-cyanophenylboronic acid (0.181 g, 1.5 mmol) using similar conditions to those described for the synthesis of compound **28**. Column chromatography (EtOAc) eluted **61** as a viscous colourless oil (0.190 g, 73%). $C_{16}H_{12}N_4$ requires C 73.8, H 4.6, N 21.5%, found: C 73.5, H 4.6, N 21.3%; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.36 (2H, s, $ArCH_2N$), 7.22–7.26 (1H, d, *J* = 9.0 Hz, ArH), 7.38–7.51 (4H, m, ArH), 7.56–7.60 (1H, d, *J* = 7.5 Hz, ArH), 7.67–7.71 (1H, d, *J* = 7.5 Hz, ArH), 7.75–7.76 (1H, m, ArH), 7.93 (1H, s, $C_2H_2N_3$) and 8.07 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 53.4, 113.1, 118.7, 126.7, 127.5, 127.9, 129.8, 130.0, 130.8, 131.2, 131.6, 135.7, 139.9, 141.6, 143.2 and 152.4 ppm; LC–MS (APCI) *m/z* 261 ([*M*+H]$^+$, 82%), 192 ([(*M*+H)−$C_2H_2N_3$]$^+$, 100); HRMS (ES) calcd for $C_{16}H_{13}N_4$ [*M*+H]$^+$ 261.1135, found 261.1137.

3′-[(1*H*-1,2,4-Triazol-1-yl)methyl]biphenyl-4-carbonitrile 62. Compound **62** was prepared from compound **19** (0.238 g, 1.0 mmol) and 4-cyanophenylboronic acid (0.181 g, 1.5 mmol) using similar conditions to those described for the synthesis of compound **28**. Column chromatography (EtOAc) eluted **62** as a white crystalline solid (0.190 g, 73%); mp: 117–118 °C; $C_{16}H_{12}N_4$ requires C 73.8, H 4.6, N 21.5%, found: C 73.3, H 4.6, N 21.4%; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.38 (2H, s, $ArCH_2N$), 7.28–7.31 (1H, m, ArH), 7.44–7.57 (3H, m, ArH), 7.62–7.74 (4H, dd, *J* = 2.0 & 8.5 Hz, ArH), 7.97 (1H, s, $C_2H_2N_3$) and 8.07 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 53.4, 111.4, 118.8, 126.8, 127.6, 127.8, 128.1, 129.9. 132.7, 135.8, 140.2, 143.2, 144.8 and 152.4 ppm; LC–MS (APCI) *m/z* 261 ([*M*+H]$^+$, 100%); HRMS (ES) calcd for $C_{16}H_{13}N_4$ [*M*+H]$^+$ 261.1135, found 261.1135.

1-[(2′-Methylbiphenyl-3-yl)methyl]-1*H*-1,2,4-triazole 63. Compound **63** was prepared from compound **19** (0.150 g, 0.63 mmol) and *o*-tolylboronic acid (0.171 g, 1.26 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **63** as a colourless viscous oil (0.107 g, 68%). $C_{16}H_{15}N_3$ requires C 77.1, H 6.1, N 16.9%, found: C 76.6, H 6.0, N 16.9%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.21 (3H, s, $ArCH_3$), 5.39 (2H, s, $ArCH_2N$), 7.16–7.26 (6H, m, ArH), 7.29–7.31 (1H, d, *J* = 7.4 Hz, ArH), 7.39–7.43 (1H, t, *J* = 7.4 Hz, ArH), 7.97 (1H, s, $C_2H_2N_3$) and 8.08 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.4, 53.5, 125.8, 126.3, 127.6, 128.7, 128.8, 129.5, 129.6, 130.4, 134.4, 135.2, 140.9, 142.8, 143.1 and 152.2 ppm; LC–MS (APCI) *m/z* 250 ([*M*+H]$^+$, 100%); HRMS (ES) calcd for $C_{16}H_{16}N_3$ [*M*+H]$^+$ 250.1339, found 250.1333.

1-[(2′-Ethylbiphenyl-3-yl)methyl]-1*H*-1,2,4-triazole 64. Compound **64** was prepared from compound **19** (0.150 g, 0.63 mmol) and 2-ethylphenylboronic acid (0.189 g, 1.26 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **64** as a light yellow viscous oil (0.142 g, 86%); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.03–1.11 (3H, t, *J* = 7.7 Hz, $ArCH_2CH_3$), 2.48–2.56 (2H, q, *J* = 7.7 Hz, $ArCH_2CH_3$), 5.38 (2H, s, $ArCH_2N$), 7.12–7.43 (8H, m, ArH), 7.97 (1H, s, $C_2H_2N_3$), and 8.07 ppm (1H, m, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 15.8 (CH_3), 26.2 (CH_2), 53.7 (CH_2), 125.7 (CH), 126.4 (CH), 127.9 (CH), 128.8 (CH), 128.9 (CH), 129.6 (CH), 129.9 (CH), 134.5 (C), 140.7 (C), 141.6 (C), 143.0 (C), 143.2 (CH) and 152.3 ppm (CH) (one overlapping resonance); LC–MS (ES) *m/z* 264 ([*M*+H]$^+$, 100%); HRMS (ES) calcd for $C_{17}H_{18}N_3$ [*M*+H]$^+$ 264.1495, found 264.1489.

1-(Biphenyl-4-ylmethyl)-1*H*-1,2,4-triazole 65. Compound **65** was prepared from compound **24** (0.149 g, 0.63 mmol) and phenylboronic acid (0.154 g, 1.26 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **65** as a white solid (0.130 g, 88%); mp: 162–164 °C; $C_{15}H_{13}N_3$ requires C 76.6, H 5.6, N 17.9%, found: C 76.3, H 5.5, N 17.7%; ^{1}H NMR (270 MHz, $CDCl_3$) 5.37 (2H, s, $ArCH_2N$), 7.31–7.47 (5H, m, ArH), 7.54–7.61 (4H, m, ArH), 7.99 (1H, s, $C_2H_2N_3$) and 8.10 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 53.4 (CH_2), 127.2 (CH), 127.8 (CH), 127.9 (CH), 128.6 (CH), 129.0 (CH), 133.5 (C), 140.4 (C), 141.8 (C), 143.2 (CH) and 152.4 ppm (CH); LC–MS (APCI) *m/z* 236 ([*M*+H]$^+$, 100%); HRMS (ES) calcd for $C_{15}H_{14}N_3$ [*M*+H]$^+$ 236.1182, found 236.1177.

4′-[(1*H*-1,2,4-Triazol-1-yl)methyl]biphenyl-2-carbonitrile 66. Compound **66** was prepared from **72** (2.51 g, 9.2 mmol) using similar conditions to those described for the synthesis of compound **19**. Column chromatography (EtOAc) eluted **66** as a white solid (1.51 g, 63%); mp: 111–112 °C; $C_{16}H_{12}N_4$ requires C 73.8, H 4.7, N 21.5%, found: C 73.9, H 4.6, N 21.5%; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.41 (2H, s, $ArCH_2N$), 7.35–7.38 (2H, d, *J* = 7.9 Hz, ArH), 7.42–7.49 (2H, m, ArH), 7.54–7.58 (2H, d, *J* = 7.9 Hz, ArH), 7.61–7.67 (1H, m, ArH), 7.74–7.78 (1H, m, ArH), 8.00 (1H, s, $C_2H_2N_3$), and 8.14 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 53.2 (CH_2), 111.3 (C), 118.6 (C), 128.0 (CH), 128.3 (CH), 129.6 (CH), 130.9 (CH), 133.1 (CH), 133.9 (CH), 135.4 (C), 138.6 (C), 143.4 (CH), 144.6 (C) and 152.5 ppm (CH); LC–MS (APCI) *m/z* 261 ([*M*+H]$^+$, 25%), 191 ([(*M*+H)−$C_2H_2N_3$]$^+$, 100); HRMS (ES) calcd for $C_{16}H_{13}N_4$ [*M*+H]$^+$ 261.1135, found 261.1127.

4′-[(1*H*-1,2,4-Triazol-1-yl)methyl]biphenyl-3-carbonitrile 67. Compound **67** was prepared from compound **24** (0.149 g, 0.62 mmol) and 3-cyanophenylboronic acid (0.150 g, 1.24 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **67** as a light yellow solid (0.065 g, 40%); mp: 159–161 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.39 (2H, s, $ArCH_2N$), 7.34–7.40 (2H, d, *J* = 8.4 Hz, ArH), 7.51–7.58 (3H, m, ArH), 7.62–7.65 (1H, d, *J* = 7.9 Hz, ArH), 7.76–7.79 (1H, t, *J* = 1.5 Hz, ArH), 7.99 (1H, s, $C_2H_2N_3$) and 8.12 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 53.2 (CH_2), 112.3 (C), 118.9 (C), 127.9 (CH), 128.8 (CH), 129.8 (CH), 130.7 (CH), 131.2 (CH), 131.5 (CH), 134.9 (C), 139.4 (C), 141.5 (C), 143.3 (CH) and 152.5 ppm (CH); LC–MS (APCI) *m/z* 259 ([*M*−H]$^-$, 100%); HRMS (ES) calcd for $C_{16}H_{13}N_4$ [*M*+H]$^+$ 261.1135, found 261.1129.

4′-[(1*H*-1,2,4-Triazol-1-yl)methyl]biphenyl-4-carbonitrile 68. Compound **68** was prepared from compound **24** (0.150 g, 0.63 mmol) and 4-cyanophenylboronic acid (0.152 g, 1.26 mmol) using similar conditions to those described for the synthesis of compound **31**. Column chromatography (EtOAc) eluted **68** as a white solid (0.092 g, 56%); mp: 110–112 °C; $C_{16}H_{12}N_4$ requires C 73.8, H 4.6, N 21.5%, found: C 73.5, H 4.5, N 21.2%; ^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.40 (2H, s, $ArCH_2N$), 7.35–7.60 (4H, dd, *J* = 8.2 & 59.6 Hz, ArH), 7.63–7.74 (4H, dd, *J* = 8.2 & 20.8 Hz, ArH), 7.99 (1H, s, $C_2H_2N_3$) and 8.12 ppm (1H, s, $C_2H_2N_3$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 53.2 (CH_2), 111.4 (C), 118.9 (C), 127.8 (CH), 128.0 (CH), 128.8 (CH), 132.8 (CH), 135.2 (C), 139.7 (C), 143.3 (CH), 144.8 (C) and 152.5 ppm (CH); LC–MS (APCI) *m/z* 259 ([*M*−H]$^-$, 100%); HRMS (ES) calcd for $C_{16}H_{13}N_4$ [*M*+H]$^+$ 261.1135, found 261.1127.

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