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Synthesis, characterization and biological evaluation of 1-(1*H*-1,2,3- triazol-4-yl)methyl)-1-pyrazolo[3,4-*b*]quinoline derivatives

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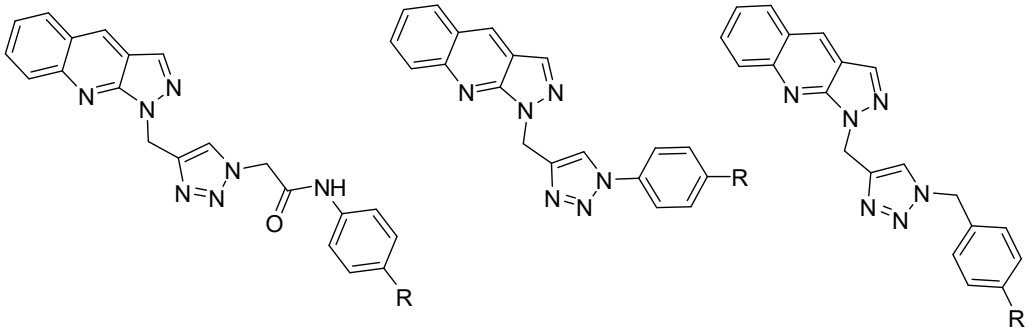
Abstract

Twenty novel 1-(1*H*-1,2,3- triazol-4-yl)methyl)-1-pyrazolo[3,4-*b*]quinoline compounds were synthesized via the copper(I) catalyzed [3+2] dipolar cycloaddition (CuAAC) of different organic azides and 1-(prop-2-yn-1-yl)-1*H*-pyrazolo[3,4-*b*]quinoline. Their structures were confirmed by NMR spectroscopy and HRMS. Antibacterial and antitubercular assays showed activity between 299 and 383 µM. The *α*-glucosidae assay showed promising results for the unsubstituted derivatives of all three series of compounds (59 µM, 73 µM and 70 µM). The compounds were not effective as anticancer agents with IC_{50} values >814 µM against Caco2, HepG2 and HeLa cell lines.



Keywords: Pyrazoles, quinolines, anticancer, antibacterial, antidiabetic, antitubercular

Introduction

Drug resistance has become a major threat to public health with third world countries having the highest risks.[1,2] There is thus a need to synthesise and identify additional antibiotics, that can be used to combat the pathogens when currently used drugs are no longer effective. One of the ways to increase activity and efficacy of small molecule drugs is through molecular hybridization, creating conjugate molecules of two or more bioactive pharmacophores with the aim of forming more active but less toxic drugs. Conjugate molecules have the ability to act on multiple sites or by multiple modes, and therefore may have different mechanisms of action to current antibiotics, making them good alternatives if safe and active compounds could be identified.[3]

Quinoline and pyrazole moieties are two popular heterocyclic scaffolds in small molecule drug design and development. They are known to have broad biological activity such as antibacterial, anticancer, antimalarial, antitubercular, anti-inflammatory and antiviral activity.[4,5] Pyrazoloquinoline derivatives are planar heterocyclic compounds formed by the fusion of quinoline and pyrazole moieties. These compounds were discovered in the early 1900s and exhibit a range of bioactivities such as antimicrobial,[6] anticancer,[7] antimalarial,[8] antitubercular[9] and anti-inflammatory.[10] Pyrazolo[3,4-*b*]quinolinyl acetamide derivatives were synthesised by chlorinating quinoline-2(1*H*)ones using $POCl_3$ and forming the fused derivative using hydrazine hydrate with promising antimicrobial and anticancer activity.[11] Pyrazolo[3,4-*b*]quinolines were also synthesised by a water-mediated one pot cyclocondensation reaction of 2-chloro-quinoline-3-carbaldehyde and hydrazine hydrate.[12] Lewis acid catalysts such as $InCl_3$ improved yields in the synthesis of pyrazoloquinolines.[13]

Triazoles are found in many bioactive molecules having antibacterial,[14] anticancer,[15] antitubercular,[16] anti-inflammatory,[17] antidiabetic,[18] antimalarial,[19] antiparasitic,[20] antioxidant,[21] antiviral,[22] anti-Alzheimer's,[23] in neuroprotective agents,[24] and in carbonic anhydrase inhibition agents.[25] Examples of some clinically approved and commercialized 1,2,3-triazoles are tazobactam (a β-lactam antibiotic), rufinamide (anticonvulsant agent), TSAO (an antiviral agent - HIV reverse transcriptase inhibitor), and carboxyamidotriazole (CAI, an anticancer agent). The presence of the three nitrogen atoms (one pyrrole type and two pyridine type) makes the triazole ring electron rich resulting in increased hydrogen bonding ability and resistance to biodegradation, favourable for binding to biomolecular targets.[26] Their ability to act as both a hydrogen bond donor and acceptor has made this moiety one of the more popular moieties in drug design and discovery.[26] It is also a popular linker, connecting two or more pharmacophores, and replacing an amide group with the 1,2,3-triazole moiety has shown enhanced activity.[22,27,28] The 1,2,3-triazole unit has also been used to mimic the amide linker in peptide synthesis, since it is stable and able to resist biodegradation by enzymes.[29-31]

The most commonly used method of synthesising 1,2,3-triazoles is using a Copper (I) catalyzed azide-alkyne cycloaddition reaction, also known as click chemistry.[32,33] Different methods of synthesis were also explored such as the ruthenium catalyzed azide-alkyne cycloaddition (RuAAC) that affords the 1,5-disubstituted 1,2,3-triazole moiety;[34] the one-pot three component reaction of aldehydes with nitroalkanes and sodium azide;[35] the reaction of enamines with tosyl azide;[36] metal free synthesis such as the Knoevenagel/azide-alkyne cycloaddition reaction;[37] solvent-free synthesis using a supported catalyst[38] and a metal free catalytic reaction of aldehydes and arylazides.[39] Triazole-containing cystatin A derivatives were synthesised through a peptidomimetic alkyne-azide ligation reaction replacing the amides in order to synthesize peptides that can withstand enzyme degradation under normal physiological conditions. These cystatin A derivatives were shown to be active against breast cancer cells.[40]

More recently, quinoline-1,2,3-triazole hybrids were synthesised using different aromatic azides and quinolines, and evaluated for their antibacterial, antifungal and anticancer activity, where compounds with broad-spectrum antimicrobial and selective anticancer potency were identified with significantly low

cytotoxicity against normal cell lines.[41,42] This prompted us to investigate the synthesis of pyrazoloquinoline-triazole hybrid compounds and their bioactivity.

Results and Discussion

Chemistry

The synthesis of the twenty hybrid compounds began with the formation of the alkyne precursor via a four-step reaction (Scheme 1). Aniline was reacted with acetic acid and acetic anhydride to afford the intermediate acetanilide (**1**). The 2-chloroquinoline-3-carbaldehyde (**2**) was then formed through a Vilsmeier Haack reaction using phosphoryl chloride and dimethyl formamide.[43] This formed the basis for synthesising the pyrazoloquinoline (**3**) with hydrazine in a short 2-hour reaction with conventional heating.[12] The pyrazoloquinoline (**3**) was then propargylated to yield the propargylated pyrazoloquinoline intermediate (**4**).[41]

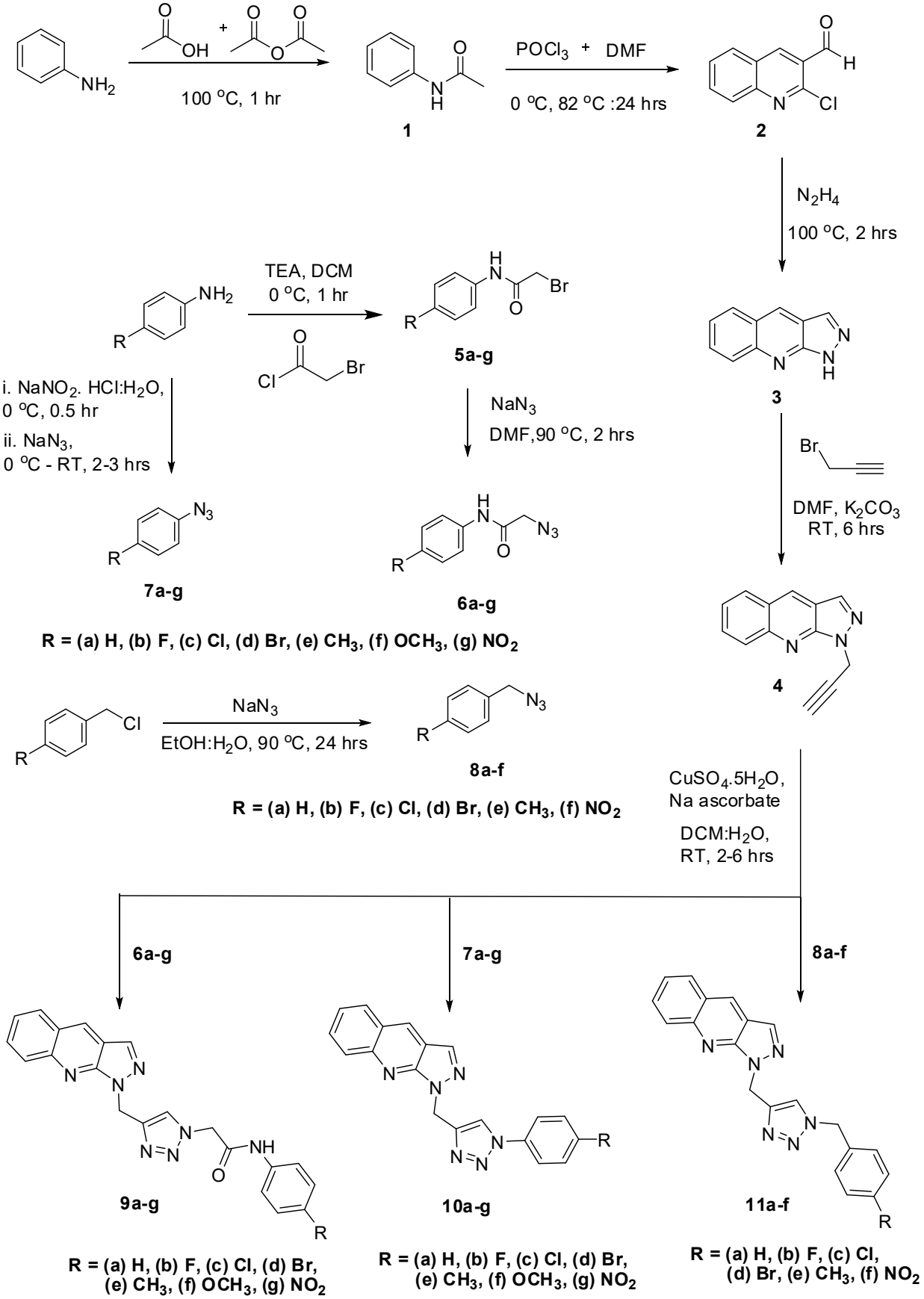
The azide precursors were synthesized separately either from anilines or benzyl chlorides (Scheme 1). In the case of anilines, substituted anilines were either treated with bromo acetyl chlorides resulting in 2-bromo-*N*-phenylacetamides (**5a-g**), which were refluxed with sodium azide in DMF producing azidophenylacetamides (**6a-g**) or the anilines themselves treated with sodium nitrite in a diazotisation reaction forming the diazonium salt and then sodium azide to form azidobenzenes (**7a-g**). The benzyl chloride precursors were treated with sodium azide to form azidomethylbenzenes (**8a-f**). The methoxy derivative did not form with the benzyl chloride precursor, despite several attempts.

The target molecules (**9a-g, 10a-g** and **11a-f**) were synthesised by coupling the propargylated pyrazoloquinoline (**4**) with the azides (**6a-g**, **7a-g** and **8a-f**) via the CuAAC reaction, an azide-alkyne Huisgen cycloaddition reaction, a 1,3-dipolar cycloaddition reaction between an azide and a terminal alkyne.[41,44,45] Structural elucidation of the synthesized hybrid molecules was carried out with NMR (^{1}H,^{13}C, 2D), and their structures confirmed by HRMS.

Structural elucidation

The synthesized compounds were characterized using NMR and their exact masses confirmed by HRMS. The numbering of the compounds is shown in Figure 1. Using compound **9a** as an example, the amide proton NH-18 was seen as a singlet at δ 10.42. Two other singlets in the aromatic region were that of H-4 at δ 9.00 and H-3 at δ 8.51. They were distinguished by an HMBC correlation between H-4 and C-5 at δ 128.3. H-4 also showed HMBC correlations to C-3a, C-3, C-8a and C-9a at δ 116.9, δ 134.2, δ 148.1 and δ 150.0, and H-3 showed correlations to C-3a and C-9a only. On the quinoline ring, H-5 and H-8 appeared as doublets at δ 8.09 (J = 8.6 Hz) and δ 8.18 (J = 8.4 Hz), with H-7 appearing as a multiplet at δ 7.81-7.85 and H-6 overlapping with the H-2'/6' resonance at δ 7.50-7.56. The H-7 resonance showed a HMBC correlation to C-8a at δ 148.1, distinguishing H-7 from H-6.

The two methylene proton resonances, H-10 and H-16 appeared as two-proton singlet resonances at δ 5.88 and δ 5.28, while the triazole proton H-15 can be seen at δ 8.07 as a singlet. Being three bonds apart, both the methylene protons showed HMBC correlations to C-15 at δ 125.7. H-10 also showed HMBC correlations to C-9a and C-11 at δ 149.9 and 143.3 respectively, and H-16, a HMBC correlation to the carbonyl resonance, C-17 at δ 164.6. The aromatic proton resonances of H-2'/6', H-3'/5' and H-4' were present as multiplets at δ 7.50-7.56, δ 7.29-7.33 and δ 7.05-7.09.



Scheme 1. Synthesis of pyrazoloquinoline-1,2,3-triazole hybrids.

In the ^{13}C NMR spectrum, all the singlet aromatic C-N resonances, C-1', C-11, C-8a and C-9a appeared more downfield at δ 138.4, 143.3, 148.1 and 150.0, while the other two singlet resonances, C-4a and C-3a appeared more upfield from these at δ 124.6 and δ 116.8. These resonances were assigned by the HMBC correlations mentioned above, either to H-4, H-3 or H-10. C-1' also showed HMBC correlations to H-3'/5' and H-2'/6'. The other ^{13}C NMR resonances were assigned using their corresponding ^{1}H NMR resonances in the HSQC spectrum.

The structural elucidation of the other two sets of compounds were carried out in a similar manner. The resonances remained largely similar, with slight shifts for H-10 being noted (Figure 1). When the phenyl ring is directly attached to the triazole ring, this affects the chemical shift of H-15 (Figure 1). The H-15 resonance is now notably more downfield, possibly through the conjugation between the triazole and aromatic rings. Thus, in **10a**, H-15 now appears at δ 8.77 as opposed to δ 8.06 in **9a**. Notably, H-16 is more shielded in **9a** at δ 5.28 than in **11a**, where it appears at δ 5.56. This is due to the electron donation from the amide group in **9a**, shielding the resonance.

Most of the carbon resonances were also similar among the three sets of compounds appearing in the same region with the C-15 resonance moving upfield as you remove the amide group and methylene groups from the molecule respectively (δ 125.6 to δ 124.2 to δ 122.3) (Figure 2). The chemical shift of C-1' is also deshielded by the presence of the amide group in **9a** resonating at δ 138.4. An overlay of the ^{1}H and ^{13}C NMR spectra for compounds **9a**, **10a** and **11a** are shown in Figures 1 and 2.

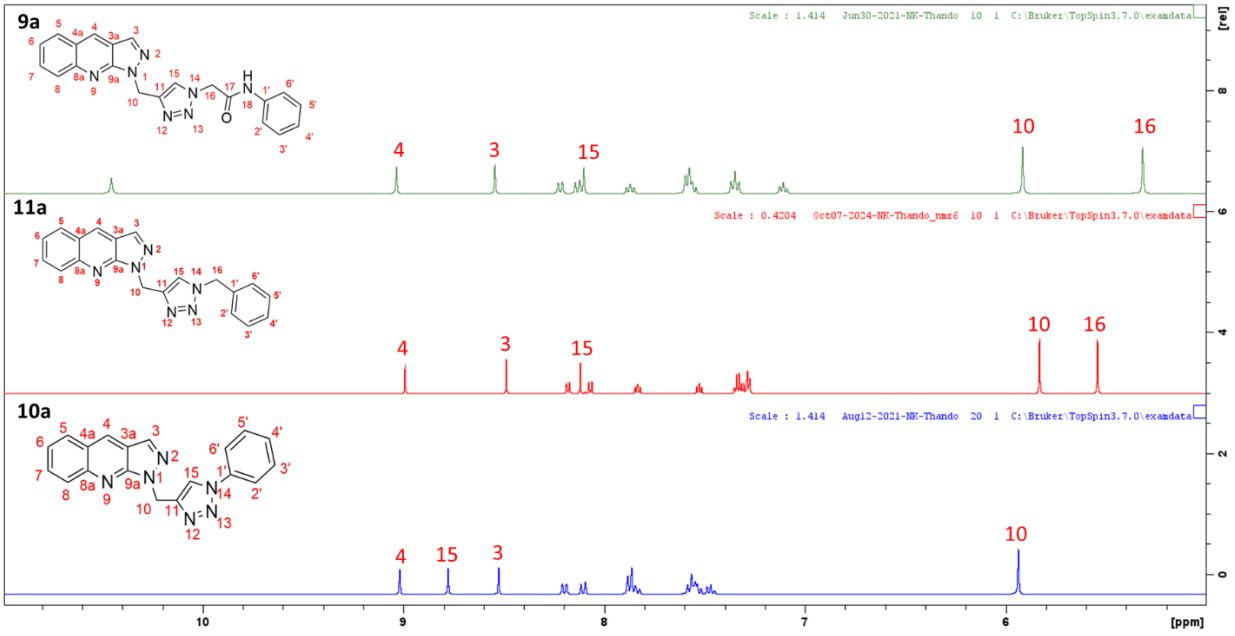


Figure 1. Overlay of the ^{1}H NMR spectra for compounds **9a**,**10a** and **11a** (unsubstituted derivatives).

Antibacterial activity

The antibacterial activity of the synthesized compounds (**9a-g**,**10a-g** and **11a-f**) was determined for five Gram-positive bacteria (MRSA - ATCC 10069, *Streptococcus pyogenes* ATCC 49247, *Bacillus subtilis* ATCC 12344, *Enterococcus faecium* ATCC 19434 and *Staphylococcus aureus* ATCC 25923), and three Gram-negative bacteria (*Enterococcus hormaechei* ATCC 700232, *Pseudomonas aeruginosa* ATCC 27853 and *Escherichia coli* ATCC 35218). Compounds **9a-c**, **9e**, **10a-d**, **10f**, **11a** and **11e** showed potential activity by exhibiting a significant zone of inhibition, showing activity for 3 or more bacterial strains and met the criteria for having potential broad-spectrum activity against both Gram-positive and Gram-negative bacteria. These compounds were further tested for their minimum inhibition concentration (MIC) values by means of a serial dilution assay comparing them to the currently commercialised drug standard ciprofloxacin. Unfortunately, all the tested compounds showed weak antibacterial activity of >200 µM (Table 1).

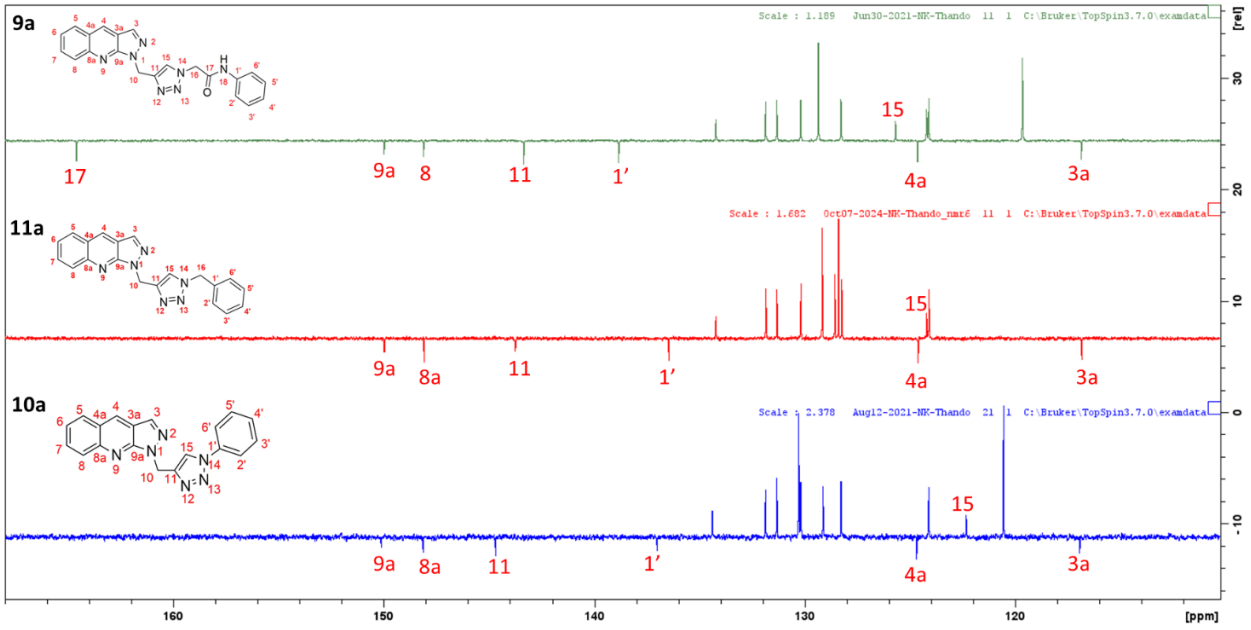


Figure 2. Overlay of the ^{13}C NMR spectra for compounds **9a**,**10a** and **11a** (unsubstituted derivatives).

Table 1. Antibacterial activity of selected compounds against 8 bacterial strains (MIC in μM**)**

Entry	MRSA	SA	SP	BS	EC	EH	EF	PA
9a	326	-	326	-	-	-	-	326
9b	311	-	311	-	>500	-	311	311
9c	299	-	-	-	-	-	-	299
9e	315	-	-	-	-	315	-	315
9f	302	-	-	-	-	-	-	302
10a	383	-	383	-	-	383	383	383
10b	363	-	-	-	-	-	-	363
10c	>500	-	347	347	-	-	-	347
10f	>500	-	351	-	351	-	-	351
10g	-	-	337	-	-	-	-	-
11a	-	-	367	-	-	-	-	367
11b	>500	-	349	-	-	-	-	349
11c	>500	-	-	-	-	-	-	334
11e	>500	-	-	353	353	-	-	353
DMSO	>500	>500	>500	>500	>500	>500	>500	>500
CIP	12	2	2	2	2	2	2	2

MRSA = methicillin resistant *Staphylococcus aureus* ATCC 10069; SA = *Staphylococcus aureus* ATCC 25923; SP = *Streptococcus pyogenes* ATCC 49247; BS = *Bacillus subtilis* ATCC 12344; EC = *Escherichia coli* ATCC 35218; EH = *Enterobacter hormaechei* ATCC 700232; EF = *Enterococcus faecalis* ATCC 19434; PA = *Pseudomonas aeruginosa* ATCC 27853.

Antitubercular activity

All 20 compounds were tested for their antitubercular activity against the *Mycobacterium tuberculosis* H37Rv strain using a microbroth dilution assay with erythromycin as the positive standard. Table 2 shows the IC_{90} values (the concentration needed to inhibit 90% of growth) of the tested compounds and the standard. Although nine compounds showed some activity, five were active at concentrations > 500 μM. The other four showed activity with IC_{90} values 5-8 times higher than erythromycin, a known antitubercular drug. Compounds **9b**, **9c** and **9f** had activity in the region of 300 μM, while compound **10a** had the best activity with an IC_{90} of 192 μM, five times higher than erythromycin.

Table 2. Antitubercular activity of the synthesised compounds (IC_{90} in μM)

Entry	IC_{90}
9a	>500
9b	311
9c	299
9f	302
10a	192
10b	>500
10f	>500
11a	>500
11e	>500
Erythromycin	40

Antidiabetic Activity

The synthesized compounds were evaluated for their α-glucosidase inhibitory activity according to Ademiluyi and Oboh[46] and α-amylase inhibitory activity according to Ibitoye *et al*[47] with slight modifications and using acarbose as the standard. The percentage inhibition and IC_{50} values of the tested compounds are shown in table 3.

With the exception of compounds **9d**, **10b-10d** and **11e**, all other compounds had a % inhibition greater than or equal to 75% against α-glucosidase at 125 μg mL^{-1}. Compounds **9a**, **10a** and **11a** had a % inhibition between 88-90% at 125 μg mL^{-1}, comparable to acarbose, with a % inhibition of 89% at the same concentration. Compound **9a** was the most active with a % inhibition of 90% and IC_{50} value of 59 μM, followed by **9f** (% inhibition of 87% and IC_{50} of 61 μM) and **9g** (% inhibition of 81% and IC_{50} of 68 μM). The IC_{50} of these three compounds were 2-fold higher than that of acarbose with an IC_{50} of 32 μM.

The only compound that showed any appreciable activity against α-amylase was **9a** with a % inhibition of 60% at 125 μg mL^{-1} and IC_{50} value of 253 μM, comparable to acarbose in the same assay which had a % inhibition of 57% at the same concentration, and an IC_{50} value of 182 μM. Although compounds **9f**, **10a**, and **11a-b** had a % inhibition between 49-55% at 125 μg mL^{-1}, they all had IC_{50} values of greater than 400 μM against α-amylase.

Thus, compound **9a**, being active in both the α-glucosidase and α-amylase assays, could be considered a hit compound for further development as a potential antidiabetic drug. This compound had an unsubstituted phenylamide methylene moiety attached to the triazole linker.

Table 3. α-Glucosidase and α-amylase activity of the synthesised compounds (Percentage inhibition determined at a concentration of 125 µg mL^{-1}; IC_{50} in µM)

	α-Glucosidase		α-Amylase	
Entry	% Inhibition	IC_{50}	% Inhibition	IC_{50}
9a	90	59	60	253
9b	78	73	16	-
9c	77	74	8	-
9d	68	92	5	-
9e	78	73	14	-
9f	87	61	49	724
9g	81	68	33	-
10a	88	73	55	476
10b	55	-	4	-
10c	49	-	3	-
10d	74	90	3	-
10e	82	86	32	-
10f	78	86	47	-
10g	79	76	19	-
11a	88	70	54	418
11b	85	71	54	730
11c	75	85	4	-
11d	80	75	14	-
11e	60	-	4	-
11f	78	75	9	-
Acarbose	89	32	57	182

The dash denotes greater than 100 µM for α-Glucosidase and 1000 µM for α-Amylase

Anticancer activity

The anti-proliferative activity of the synthesized compounds was investigated *in vitro* against three cancer cell lines, HepG2 (liver cancer), HeLa (cervical cancer) and Caco2 (colon cancer) using the MTT assay, and comparing the activity with the anticancer drug 5-fluorouracil (5-FU). However, none of the compounds were active. All had IC_{50} values >814 µM, two orders of magnitude greater than the standard 5-FU with IC_{50} values of 17.45 µM against HepG2, 13.76 µM against Caco2, and 2.40 µM against HeLa.

Conclusions

A library of novel pyrazoloquinoline-1,2,3-triazole hybrids was successfully synthesized using click chemistry (CuAAC mediated) with good yields, successfully combining phenyl amide, benzyl and phenyl moieties to a pyrazoloquinoline backbone through a triazole linker. The synthesised compounds showed moderate

antibacterial, antidiabetic and antitubercular activity, and was inactive against the HepG2 (liver) and Caco2 (colon) cancer cell lines.

Experimental Section

General. Chemicals and reagents were purchased from Sigma Aldrich and Merck, and used without any further purification while organic solvents were distilled according to standard procedures. TLC analysis was carried out using silica gel aluminium 60 F_{254} plates purchased from Merck South Africa. Purifications were carried out by column chromatography with silica gel (60- 120 mesh) as the stationary phase and ethyl acetate and hexane mixtures with varying polarity as the mobile phase. ^{1}H, ^{13}C and 2D nuclear magnetic resonance (NMR) analysis was carried out on a BRUKER AVANCE 400 and 600 MHz spectrometer. Chemical shifts (δ) were reported in parts per million (ppm) and coupling constants (J) in Hertz. Deuterated chloroform ($CDCl_3$) and dimethyl sulfoxide-d_6 (DMSO-d_6) were used for NMR analysis referenced to 7.24 ppm (^{1}H) and 77.23 ppm (^{13}C) for $CDCl_3$ and 2.50 ppm (^{1}H) and 39.51 ppm (^{13}C) for DMSO-d_6. TopSpin 4.0.7 software (Bruker) was used to process the NMR data. Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer with universal ATR sampling accessory. High resolution mass spectra were obtained using a Waters LCT Premier instrument operated at ambient temperatures. Calibration and lock standards were prepared according to Waters procedural document (#715001062, rev. A). Calibration standard: sodium formate at concentration of 5 mM. The lockmass was sample-dependant, and selected based on closest mass. Melting points of compounds were determined in an electrothermal melting point apparatus (Cole-Palmer Stuart, 75 W, 230 V).

Synthesis of 2-chloroquinolin-3-carbaldehyde (2). Dry *N*,*N*-dimethylformamide (1.5 mL, 19 mmol) was added under inert conditions using nitrogen gas to a 2-neck round bottom flask placed in an ice bath at 0 °C. Phosphoryl chloride (5.2 mL, 56 mmol) was then added dropwise while stirring, followed by acetanilide (1.0 g, 7.4 mmol), and the reaction was refluxed at 100 °C for 24 h with the condenser fitted with a $CaCl_2$ drying tube. Upon completion, the reaction mixture was cooled, poured onto crushed ice, and stirred at 0-10 °C for 1 h. The precipitate that formed was filtered, washed with water, and dried to produce 1.17 g (83%). ^{1}H-NMR (400 MHz, $CDCl_3$-*d*): δ 10.54 (1H, s, H-9), 8.74 (1H, s, H-4), 8.06 (1H, d, *J* = 8.5 Hz, H-8), 7.97 (1H, d, *J* = 8.2 Hz, H-5), 7.87 (1H, dd, *J* = 7.6, 8.5 Hz, H-7), 7.64 (1H, dd, *J* = 7.3, 8.2 Hz, H-6). ^{13}C NMR (100 MHz, $CDCl_3$-d): 189.2 (C-9), 140.3 (C-4), 133.6 (C-7), 129.7 (C-5), 128.6 (C-6), 128.1 (C-8), 126.5 (C-2). The quaternary carbons C-3, 4a and 8a could not be detected. The ^{1}H NMR resonances are consistent with that reported in Toth et al.[48]

Synthesis of pyrazolo[3,4-*b*]quinoline (3). The 2-chloroquinoline-3-carbaldehyde (1.0 g, 5.2 mmol) and hydrazine hydrate (6.0 mL, 123 mmol) were dissolved in water and refluxed at 100 °C for 2 h. The reaction was monitored by TLC. Upon completion, the reaction was cooled, and the precipitate that formed was filtered, washed with water and dried to produce 677 mg (77%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 13.58 (1H, s, NH), 8.97 (1H, s, H-4), 8.47 (1H, s, H-3), 8.17 (1H, d, *J* = 8.4 Hz, H-8), 8.03 (1H, d, *J* = 8.7 Hz, H-5), 7.81 (1H, dd, *J* = 8.4, 7.0 Hz, H-7), 7.52 (1H, dd, *J* = 8.7, 7.3 Hz, H-6). ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.1 (C-9a), 148.2 (C-8a), 134.6 (C-3), 130.9 (C-4), 130.8 (C-7), 130.1 (C-8), 128.2 (C-5), 124.4 (C-4a), 123.8 (C-6), 116.3 (C-3a). The ^{1}H NMR data is consistent with that in Afghan et al.[49]

Synthesis of 1-(prop-2-yn-1-yl)-1H-pyrazolo[3,4-b]quinoline (4). Pyrazolo[3,4-*b*]quinoline (500 mg, 3.0 mmol) was dissolved in DMF. K_2CO_3 (553 mg, 4.00 mmol) and propargyl bromide (0.5 mL, 6.6 mmol) were then added, and the reaction mixture stirred for 24 h at room temperature. Upon completion, the reaction mixture

was poured onto crushed ice, and the precipitate that formed was filtered, washed with water, and dried. The solid precipitate was then purified by column chromatography (80:20, ethyl acetate:hexane) to produce **4** (392 mg, 64%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.01 (1H, s, H-4), 8.53 (1H, s, H-3), 8.19 (1H, d, *J* = 8.5 Hz, H-8), 8.07 (1H, d, *J* = 8.3 Hz, H-5), 7.84 (1H, dd, *J* = 8.5, 7.2 Hz, H-7), 7.54 (1H, dd, *J* = 8.3, 7.2 Hz, H-6), 5.41 (2H, s, H-10), 3.33 (1H, s, H-12). ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.7 (C-9a), 148.1 (C-8a), 134.7 (C-3), 132.1 (C-4), 131.5 (C-7), 130.2 (C-8), 128.2 (C-5), 124.7 (C-4a), 124.3 (C-6), 116.9 (C-3a), 79.4 (C-11), 75.5 (C-12), 36.5 (C-10).

Synthesis of 2-(4-((1*H*-pyrazolo[3,4-*b*]quinolin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamides (9a-g). Substituted anilines (10.6 mmol) were dissolved in dichloromethane and cooled to 0 °C. Triethylamine (1.2 g, 11.9 mmol) was then added with stirring, followed by bromoacetyl chloride (1.5 mL, 18.1 mmol), added dropwise at 0 °C while continually stirring for 1 h. Upon completion, the reaction mixture was diluted with dichloromethane, washed with 2 M HCl, water, saturated $NaHCO_3$, brine, and then dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to obtain the amide, which was used immediately for the next step. The substituted 2-bromo-*N*-phenylacetamides (1.20 mmol) were dissolved in DMF, and sodium azide (114 mg, 1.75 mmol) was added. The contents were refluxed at 80-90 °C for 1-2 h, then poured onto crushed ice where most of the azide products precipitated out. The few azide products that did not precipitate were extracted with DCM, dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo*. Yields of 73 to 98% were achieved for the azides **6a-g**.

The propargylated pyrazolo quinoline intermediate **4** (100 mg, 0.483 mmol) was dissolved in DCM:H_2O (1:1) (10 mL). A mixture of $CuSO_4.5H_2O$ (25 mg, 0.100 mmol) and sodium ascorbate (42 mg, 0.212 mmol) was mixed in 2.5 mL H_2O, forming a yellow solution, and added to the solution. The 2-azido-*N*-phenylacetamides (0.5 mmol) (**6a-g**) were dissolved in 2.5 mL dichloromethane and added to the mixture (in separate reactions). The reaction was stirred at room temperature for 2 h. Upon completion, the contents were extracted with DCM (20 mL) and dried over anhydrous $MgSO_4$, and the solvent was removed *in vacuo*. The product was purified by column chromatography with a 40% EtOAc:60% hexane mobile phase to yield the products **9a-g** in yields of 56 to 92%.

2-(4-((1*H*-Pyrazolo[3,4-*b*]quinolin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide (**9a**) off white powder. mp 211-212 °C. yield 65%. IR (solid, KBr, ν_{max}, cm^{-1}): 3199, 3091, 2921, 1678, 1596, 1555. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.42 (1H, s, H-18), 9.00 (1H, s, H-4), 8.51 (1H, s, H-3), 8.18 (1H, d, *J* = 8.5 Hz, H-8), 8.09 (1H, d, *J* = 8.7 Hz, H-5), 8.06 (1H, s, H-15), 7.83 (1H, dd, *J* = 8.5, 7.6 Hz, H-7), 7.50-7.56 (3H, m, H-2'/6',6), 7.31 (2H, dd, *J* = 7.8, 7.5 Hz, H-3'/5'), 7.01 (1H, dd, *J* = 7.3, 7.3 Hz, H-4'), 5.88 (2H, s, CH_2-10), 5.28 (2H, s, CH_2-16). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.6 (C-17), 150.0 (C-9a), 148.1 (C-8a), 143.4 (C-11), 138.8 (C-1'), 134.2 (C-3), 131.8 (C-4), 131.3 (C-7), 130.2 (C-8), 129.4 (C-3'/5'), 128.3 (C-5), 125.6 (C-15), 124.6 (C-4a), 124.2 (C-6), 124.1 (C-4'), 119.6 (C-2'/6'), 116.8 (C-3a), 52.6 (C-16), 42.3 (C-10). HRMS: (ESI$^+$-MS, *m/z*) calcd for $C_{21}H_{17}N_7ONa$ (M + Na)$^+$: 406.1392 found 406.1382.

2-(4-((1*H*-Pyrazolo[3,4-*b*]quinolin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-fluorophenyl)acetamide (**9b**) yellow powder. mp 222-224 °C. yield 92%. IR (solid, KBr, ν_{max}, cm^{-1}): 3207, 3056, 2922, 2161, 2019, 1670, 1617, 1556. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.46 (1H, s, H-18), 9.03 (1H, s, H-4), 8.53 (1H, s, H-3), 8.21 (1H, d, *J* = 8.4 Hz, H-8), 8.12 (1H, d, *J* = 8.7 Hz, H-5), 8.08 (1H, s, H-15), 7.87 (1H, dd, *J* = 7.8, 7.4 Hz, H-7), 7.54-7.61 (3H, m, H-6,3'/5'), 7.19 (1H, dd, *J* = 8.7, 8.6 Hz, H-2'/6'), 5.91 (2H, s, CH_2-10), 5.29 (2H, s, CH_2-16). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.5 (C-17), 158.6 (d, *J* = 238.8 Hz, C-4'), 150.0 (C-9a), 148.1 (C-8a), 143.4 (C-11), 135.2 (C-1'), 134.2 (C-3), 131.9 (C-4), 131.3 (C-7), 130.2 (C-8), 128.3 (C-5), 125.6 (C-15), 124.6 (C-4a), 124.1 (C-6), 121.5 (d, *J* = 7.8 Hz, C-2'/6'), 116.9 (3a), 115.9 (d, *J* = 22.2 Hz, C-3'/5'), 52.6 (C-16), 42.3 (C-10). HRMS: (ESI$^+$-MS, *m/z*) calcd for $C_{21}H_{16}N_7OFNa$ (M + Na)$^+$: 424.1298 found 424.1296.

2-(4-((1*H*-Pyrazolo[3,4-*b*]quinolin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-chlorophenyl)acetamide (**9c**) brown powder. mp 251-252 °C. yield 58%. IR (solid, KBr, ν_{max}, cm^{-1}): 3322, 3073, 2934, 2160, 2007, 1680, 1599. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.62 (1H, s, H-18), 9.04 (1H, s, H-4), 8.54 (1H, s, H-3), 8.22 (1H, d, *J* = 8.3 Hz, H-8), 8.12 (1H, d, *J* = 8.7 Hz, H-5), 8.09 (1H, s, H-15), 7.87 (1H, dd, *J* = 7.8, 7.5 Hz, H-7), 7.59 (2H, d, *J* = 8.6 Hz, H-3'/5'), 7.56 (1H, dd, *J* = 7.8, 7.4 Hz, H-6), 7.40 (2H, d, *J* = 8.5 Hz, H-2'/6'), 5.91 (2H, s, H-10), 5.32 (2H, s H-16). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.8 (C-17), 149.9 (C-9a), 148.1 (C-8a), 143.4 (C-11), 137.8 (C-1'), 134.2 (C-3), 131.9 (C-4), 131.6 (C-7), 130.2 (C-8), 129.3 (C-2'/6'), 128.3 (C-5), 127.8 (C-4'), 125.6 (C-15), 124.6 (C-4a), 124.1 (C-6), 121.1 (C-3'/5'), 116.8 (C-3a), 52.6 (C-16), 42.3 (C-10). HRMS: (ESI$^+$-MS, *m/z*) calcd for $C_{21}H_{16}N_7OClNa$ (M + Na)$^+$: 440.1003 found 441.0991.

2-(4-((1*H*-Pyrazolo[3,4-*b*]quinolin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-bromophenyl)acetamide (**9d**) light brown powder. mp 246-250 °C. yield 60%. IR (solid, KBr, ν_{max}, cm^{-1}): 3258, 2918, 2851, 2160, 2022, 1674, 1616, 1589. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.68 (1H, s, H-18), 9.04 (1H, s, H-4), 8.54 (1H, s, H-3), 8.22 (1H, d, *J* = 8.3 Hz, H-8), 8.12 (1H, d, *J* =8.7 Hz, H-5), 8.08 (1H, s, H-15), 7.87 (1H, dd, *J* = 7.7, 7.6 Hz, H-7), 7.51-7.57 (5H, m, H-6,2'/6',3'/5'), 5.90 (2H, s, H-10), 5.35 (2H, s, H-16). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.8 (C-17), 149.9 (C-9a), 148.1 (C-8a), 143.4 (C-11), 138.2 (C-1'), 134.2 (C-3), 132.2 (C-2'/6'), 131.9 (C-4), 131.3 (C-7), 130.2 (C-8), 128.3 (C-5), 125.7 (C-15), 124.6 (C-4a), 124.1 (C-6), 121.6 (C-3'/5'), 116.9 (C-3a), 115.8 (C-4'), 52.6 (C-16), 42.3 (C-10). HRMS: (ESI$^+$-MS, *m/z*) calcd for $C_{21}H_{16}N_7OBrNa$ (M + Na)$^+$: 484.0497 found 484.0494.

2-(4-((1*H*-Pyrazolo[3,4-*b*]quinolin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-methylphenyl)acetamide (**9e**) white powder. mp 216-220 °C. yield 61%. IR (solid, KBr, ν_{max}, cm^{-1}): 3266, 3092, 2920, 2160, 2013, 1676, 1608, 1553. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.39 (1H, s, H-18), 9.05(1H, s, H-4), 8.54 (1H, s, H-3), 8.22 (1H, d, *J* = 8.3 Hz, H-8), 8.13 (1H, d, *J* = 7.2 Hz, H-5), 8.09 (1H, s, H-15), 7.87 (1H, dd, *J* = 7.6, 7.5 Hz, H-7), 7.56 (1H, dd, *J* = 7.5, 7.4 Hz, H-6), 7.46 (2H, d, *J* = 8.2 Hz, H-2'/4'), 7.14 (2H, d, *J* = 8.2 Hz, H-3'/5'), 5.91 (2H, s, CH_2-10), 5.29 (2H, s, CH_2-16), 2.27 (3H, s, H-19). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.3 (C-17), 149.9 (C-9a), 148.1 (C-8a), 143.3 (C-11), 136.3 (C-1'), 134.2 (C-3), 133.1 (C-4'), 131.8 (C-4), 131.3 (C-7), 130.2 (C-8), 129.7 (C-3'/5'), 128.3 (C-5), 125.6 (C-15), 124.6 (C-4a), 124.1 (C-6), 119.6 (C-2'/6'), 116.8 (C-3a), 52.5 (C-16), 42.2 (C-10), 20.29 (C-19). HRMS: (ESI$^+$-MS, *m/z*) calcd for $C_{22}H_{19}N_6ONa$ (M + Na)$^+$: 420.1549 found 420.1553.

2-(4-((1*H*-Pyrazolo[3,4-*b*]quinolin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-methoxyphenyl)acetamide (**9f**) light brown powder. mp 219-221 °C. yield 59%. IR (solid, KBr, ν_{max}, cm^{-1}): 3266, 2947, 2920, 2160, 2013, 1676, 1608, 1552. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.30 (1H, s, H-18), 9.03 (1H, s, H-4), 8.53 (1H, s, H-3), 8.22 (1H, d, *J* = 8.3 Hz, H-8), 8.12 (1H, d, *J* = 8.7 Hz, H-5), 8.07 (1H, s, H-15), 7.87 (1H, dd, *J* = 7.8, 7.3 Hz, H-7), 7.56 (1H, dd, *J* = 7.5, 7.4 Hz, H-6), 7.48 (2H, d, *J* = 8.7 Hz , H-3'/5'), 6.91 (2H, d, *J* = 8.8 Hz, H-2'/6'), 5.90 (2H, s, CH_2-10), 5.26 (2H, s, CH_2-16), 3.74 (3H, s, H-19). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.8 (C-17), 155.9 (C-4'), 149.9 (C-9a), 148.1 (C-8a), 143.4 (C-11), 134.2 (C-3), 131.9 (C-1'), 131.8 (C-4), 131.3 (C-7), 130.2 (C-8), 128.2 (C-5), 125.6 (C-15), 124.6 (C-4a), 124.1 (C-6), 121.2 (C-2'/6'), 116.8 (C-3a), 114.4 (C-3'/5'), 55.6 (C-19), 52.5 (C-16), 42.3 (C-10). HRMS: (ESI$^+$-MS, *m/z*) calcd for $C_{22}H_{19}N_7O_2Na$ (M + Na)$^+$: 436.1498 found 436.1496.

2-(4-((1*H*-Pyrazolo[3,4-*b*]quinolin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-nitrophenyl)acetamide (**9g**) brown powder. mp 251-253 °C. yield = 56%. IR (solid, KBr, ν_{max}, cm^{-1}): 3323, 2919, 2161, 2021, 1696, 1617, 1554. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.2 (1H, s, H-18), 9.03 (1H, s, H-4), 8.53 (1H, s, H-3), 8.22 (2H, d, *J* = 9.1 Hz, H-3'/5'), 8.20 (1H, d, *J* = 8.8 Hz, H-8), 8.12 (1H, d, *J* = 8.9 Hz, H-5), 8.10 (1H, s, H-15), 7.83-7.88 (3H, m, H-2'/6',7), 7.55 (1H, dd, *J* = 7.4, 7.4 Hz, H-6), 5.91 (2H, s, CH_2-16), 5.41 (2H, s, CH_2-10). ^{13}C NMR (100 MHz, DMSO-*d*): 165.7 (C-17), 149.9 (C-9a), 148.1 (C-8a), 145.0 (C-4'), 143.4 (C-11), 143.0 (C-1'), 134.2 (C-3), 131.9 (C-4), 131.3 (C-7), 130.2 (C-8), 128.2 (C-5), 125.7 (C-15), 125.5 (C-3'/5'), 124.6 (C-4a), 124.1 (C-6), 119.4 (C-2'/6'), 116.8 (C-3a), 52.7 (C-16), 42.3 (C-10). HRMS: (ESI$^+$-MS, *m/z*) calcd for $C_{21}H_{16}N_8O_3Na$ (M + Na)$^+$: 451.1243 found 451.1243.

Synthesis of substituted 1-((1-(4-Phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrazolo[3,4-*b*]quinolines (10a-g). *Para substituted* anilines (10.0 mmol) were dissolved in 6M aqueous HCl (10 mL) at 0 °C. Sodium nitrite (0.5 mL, 15.7 mmol) was dissolved in water (25 mL) and added to the aniline. The reaction was stirred at 0 °C for 30 min. Sodium azide (1.0 g, 15.4 mmol) was then dissolved in water (50 mL), added to the reaction mixture, and stirred at 0-10 °C for 2 h. Upon completion, the reaction mixture was extracted with dichloromethane (30 mL), dried over anhydrous $MgSO_4$, and the solvent removed in vacuo to obtain the azidobenzenes (**7a-g**) in yields of 61-96%.

The propargylated pyrazole quinoline (**4**) (80 mg, 0.386 mmol) was dissolved in DCM:H_2O (1:1) (10 mL), mixed with $CuSO_4.5H_2O$ (25 mg, 0.100 mmol) and sodium ascorbate (42 mg, 0.212 mmol) in 2.5 mL water, forming a yellow solution. The azidobenzenes (0.400 mmol) (**7a-g**) were each dissolved in 2.5 mL dichloromethane, added to the mixture and stirred at room temperature for 2 h. Upon completion, the product was extracted with dichloromethane (20 mL), dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo*. The product was purified with column chromatography using a mobile phase of EtOAc:MeOH (99:1) in good yields of 54 – 61 %.

1-((1-Phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrazolo[3,4-*b*]quinoline (**10a**) yellow powder. mp 146-148 °C; yield 54%. IR (solid, KBr, ν_{max}, cm^{-1}): 3135, 2926, 2179, 1735, 1614, 1498. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.01 (1H, s, H-4), 8.77 (1H, s, H-15), 8.52 (1H, s, H-3), 8.19 (1H, d, *J* = 8.3 Hz, H-8), 8.10 (1H, d, *J* = 8.7 Hz, H-5), 7.85 (2H, d, *J* = 8.2 Hz, H-2'/6'), 7.83 (1H, dd, *J* = 8.2, 8.2 Hz, H-7), 7.51-7.58 (3H, m, H-6, 3'/5'), 7.46 (1H, dd, *J* = 7.3, 7.4 Hz, H-4'), 5.93 (2H, s, H-10). ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.1 (C-9a), 148.1 (C-8a), 144.7 (C-11), 137.0 (C-1'), 134.4 (C-3), 131.9 (C-4), 131.3 (C-7), 130.3 (C-3'/5'), 130.1 (C-8), 129.1 (C-4'), 128.3 (C-5), 124.6 (C-4a), 124.1 (C-6), 122.3 (C-15), 120.5 (C-2'/6'),116.9 (C-3a), 42.2 (C-10). HRMS: (ESI$^+$-MS, *m/z*) calcd for $C_{19}H_{14}N_6Na$ $(M + Na)^+$: 349.1178 found 349.1187.

1-((1-(4-Fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrazolo[3,4-*b*]quinoline (**10b**) light brown powder. mp 159-161 °C. yield 66 %. IR (solid, KBr, ν_{max}, cm^{-1}): 3129, 2927, 2166, 1704, 1617, 1508. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.03 (1H, s, H-4), 8.78 (1H, s, H-15), 8.55 (1H, s, H-3), 8.23 (1H, d, *J* = 8.4 Hz, H-8), 8.12 (1H, d, *J* = 8.7 Hz, H-5), 7.94 (2H, dd, *J* = 8.7, 4.6 Hz, H-3'/5'), 7.86 (1H, dd, *J* = 7.7, 7.7 Hz, H-7), 7.58 (1H, dd, *J* = 7.8, 7.2 Hz, H-6), 7.43 (2H, dd, *J* = 8.8, 8.6 Hz, H-2'/6'), 5.96 (2H, s, H-10). ^{13}C NMR: δ 162.0 (d, *J* = 244.2 Hz, C-4'), 150.1 (C-9a), 148.1 (C-8a), 144.7 (C-11), 134.4 (C-3), 133.6 (C-1'), 131.9 (C-4), 131.3 (C-7), 130.1 (C-8), 128.2 (C-5), 124.6 (C-4a), 124.1 (C-6), 122.8 (d, *J* = 8.7 Hz, C-2'/6'), 122.5 (C-15), 117.1 (d, *J* = 23.2 Hz, C-3'/5'), 116.9 (C-3a), 42.1 (C-10). HRMS: (ESI$^+$-MS, *m/z*) calcd for $C_{19}H_{13}N_6FNa$ $(M + Na)^+$: 367.1083 found 367.1080.

1-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrazolo[3,4-*b*]quinoline (**10c**) brown powder. mp 145-147 °C. yield 60%. IR (solid, KBr, ν_{max}, cm^{-1}): 3147, 2924, 2182, 1733, 1618, 1498. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.02 (1H, s, H-4), 8.82 (1H, s, H-15), 8.54 (1H, s, H-3), 8.21 (1H, d, *J* = 8.3 Hz, H-8), 8.12 (1H, d, *J* = 8.7 Hz, H-5), 7.94 (2H, d, *J* = 8.7 Hz, H-3'/5'), 7.86 (1H, dd, *J* = 8.2, 7.2 Hz, H-7), 7.64 (2H, d, *J* = 8.9 Hz, H-2'/6'), 7.55 (1H, dd, *J* = 7.7, 7.3 Hz, H-6), 5.96 (2H, s, H-10). ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.0 (C-9a), 148.1 (C-8a), 144.9 (C-11), 135.8 (C-4'), 134.4 (C-3), 133.4 (C-1'), 131.9 (C-4), 131.3 (C-7), 130.2 (C-2'/6'), 130.1 (C-8), 128.2 (C-5), 124.7 (C-4a), 124.0 (C-6), 122.4 (C-15), 122.2 (C-3'/5'), 116.9 (C-3a), 42.1 (C-10). HRMS: (ESI$^+$-MS, *m/z*) calcd for $C_{19}H_{13}N_6ClNa$ $(M + Na)^+$: 383.0788 found 383.0776.

1-((1-(4-Bromophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrazolo[3,4-*b*]quinoline (**10d**) brown powder. mp 178-180 °C. yield 53%. IR (solid, KBr, ν_{max}, cm^{-1}): 3101, 2925, 2171, 1731, 1617, 1491. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.01 (1H, s, H-4), 8.79 (1H, s, H-15), 8.52 (1H, s, H-3), 8.19 (1H, d, *J* = 8.2 Hz, H-8), 8.09 (1H, d, *J* = 8.7 Hz, H-5), 7.85 (2H, d, *J* = 8.9 Hz, H-2'/6'), 7.82-7.84 (1H, m, H-7), 7.75 (2H, d, *J* = 8.8 Hz, H-3'/5'), 7.53 (1H, dd, *J* = 7.6, 7.3 Hz, H-6), 5.93 (2H, s, H-10). ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.0 (C-9a), 148.1 (C-8a), 144.9 (C-11), 136.1 (C-1'), 134.4 (C-3), 133.1 (3'/5'), 131.9 (C-4), 131.3 (C-7), 130.1 (C-8), 128.2 (C-5), 124.7 (C-4a),

124.1 (C-6), 122.4 (C-2'/6'), 122.3 (C-15), 121.7 (C-4'), 116.9 (C-3a), 42.1 (C-10). HRMS: (ESI$^+$-MS, *m/z*) calcd for $C_{19}H_{13}N_6BrNa$ (M + Na)$^+$: 427.0283 found 427.0292.

1-((1-(*p*-Tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrazolo[3,4-*b*]quinoline (**10e**) cream powder. mp 183-184 °C. yield 61%. IR (solid, KBr, ν_{max}, cm^{-1}): 3130, 2926, 2161, 1736, 1615, 1492. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.99 (1H, s, H-4), 8.68 (1H, s, H-15), 8.49 (1H, s, H-3), 8.17 (1H, d, *J* = 7.6 Hz, H-8), 8.08 (1H, d, *J* = 8.7 Hz, H-5), 7.83 (1H, ddd, *J* = 7.6, 6.9, 1.5 Hz, H-7), 7.71 (2H, d, *J* = 8.5 Hz, H-2'/6'), 7.52 (1H, ddd, *J* = 8.7, 6.9, 1.0 Hz, H-6), 7.34 (1H, d, *J* = 8.3 Hz, H-3'/5'), 5.91 (2H, s, H-10), 2.34 (3H, s, H-16). ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.0 (C-9a), 148.0 (C-8a), 144.5 (C-11), 138.8 (C-1'), 134.7 (C-4'), 134.4 (C-3), 131.9 (C-4), 131.4 (C-7), 130.6 (C-3'/5'), 130.1 (C-8), 128.2 (C-5), 124.6 (C-4a), 124.1 (C-6), 122.2 (C-15), 120.4 (C-2'/6'), 116.9 (C-3a), 42.1 (C-10), 21.0 (C-16). HRMS: (ESI$^+$-MS, *m/z*) calcd for $C_{20}H_{16}N_6Na$ (M + Na)$^+$: 363.1334 found 363.1344.

1-((1-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrazolo[3,4-*b*]quinoline (**10f**) white powder. mp 185-186 °C. yield 59%. IR (solid, KBr, ν_{max}, cm^{-1}): 3138, 2934, 2242, 1731, 1614, 1518. ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.06 (1H, s, H-4), 8.72 (1H, s, H-15), 8.57 (1H, s, H-3), 8.24 (1H, d, *J* = 8.3 Hz, H-8), 8.15 (1H, d, *J* = 8.7 Hz, H-5), 7.88 (1H, dd, *J* = 8.3, 7.1 Hz, H-7), 7.82 (2H, d, *J* = 9.0 Hz, H-3'/5'), 7.56 (1H, dd, *J* = 7.8, 7.1 Hz, H-6), 7.14 (2H, d, *J* = 9.0 Hz, H-2'/6'), 5.89 (2H, s, H-10), 3.86 (3H, s, H-16). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.7 (C-4'), 150.1 (C-9a), 148.1 (C-8a), 144.4 (C-11), 134.4 (C-3), 131.9 (C-4), 131.3 (C-7), 130.4 (C-1'), 130.1 (C-8), 128.2 (C-5), 124.7 (C-4a), 124.1 (C-6), 122.3 (C-15), 122.2 (C-3'/5'), 116.9 (C-3a), 115.2 (C-2'/6'), 56.0 (C-16), 42.1 (C-10). HRMS: (ESI$^+$-MS, *m/z*) calcd for $C_{20}H_{16}N_6ONa$ (M + Na)$^+$: 379.1283 found 379.1286.

1-((1-(4-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrazolo[3,4-*b*]quinoline (**10g**) brown powder. mp 228-230 °C. yield 55%. IR (solid, KBr, ν_{max}, cm^{-1}): 3147, 2924, 2182, 1733, 1618, 1498. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.05 (1H, s, H-4), 9.00 (1H, s, H-15), 8.56 (1H, s, H-3), 8.44 (2H, d, *J* = 9.1 Hz, H-3'/5'), 8.23 (3H, d, *J* = 9.2 Hz, H-8,2'/6'), 8.13 (1H, d, *J* = 8.7 Hz, H-5), 7.87 (1H, ddd, *J* = 8.7, 7.0, 1.3 Hz, H-7), 7.56 (1H, dd, *J* = 8.7, 7.0 Hz, H-6), 5.99 (2H, s, H-10). ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.1 (C-9a), 148.1 (C-8a), 147.2 (C-4'), 145.4 (C-11), 141.2 (C-1'), 134.5 (C-3), 131.9 (C-4), 131.4 (C-7), 130.2 (C-8), 128.2 (C-5), 125.9 (C-3'/5'), 124.7 (C-4a), 124.1 (C-6), 122.8 (C-15), 121.1 (C-2'/6'), 116.9 (C-3a), 42.0 (C-10). HRMS: (ESI$^+$-MS, *m/z*) calcd for $C_{19}H_{13}N_7O_2Na$ (M + Na)$^+$: 394.1028 found 394.1020.

Synthesis of substituted 1-((1-(4-benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrazolo[3,4-*b*]quinolines (11a-f). Substituted benzyl chlorides (2.5 mmol) were dissolved in EtOH:H_2O (8:1 ml) (18 mL), and sodium azide (244 mg, 3.75 mmol) was added before stirring at room temperature for 16 h. On completion, the product was extracted with dichloromethane (20 mL), dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo* to obtain the benzyl azides in yields of 58-89%. They were then dissolved in dichloromethane (0.425 mmol in 2.5 mL), added to a mixture of the propargylated pyrazoloquinoline (**4**) (80 mg, 0.386 mmol) dissolved in DCM:H_2O (1:1) (10 mL) with $CuSO_4.5H_2O$ (25 mg, 0.100 mmol) and sodium ascorbate (42 mg, 0.212 mmol). The reaction was stirred at room temperature for 6 h and monitored by TLC. Upon completion, the product was extracted with dichloromethane (20 mL), dried over anhydrous $MgSO_4$, and the solvent removed *in vacuo*. The product was purified using column chromatography with a mobile phase of ethyl acetate: hexane (2:3) to produce the products **11a-f** in yields between 61-99%.

1-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrazolo[3,4-*b*]quinoline (**11a**) white powder. mp 190-192 °C. yield 61%. IR (solid, KBr, ν_{max}, cm^{-1}): 3134, 2919, 2166, 1726, 1615, 1497. ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.01 (1H, s, H-4), 8.49 (1H, s, H-3), 8.18 (1H, d, *J* = 7.7 Hz, H-8), 8.12 (1H, s, H-15), 8.06 (1H, d, *J* = 8.6 Hz, H-5), 7.83 (1H, ddd, *J* = 8.7, 6.7, 1.4 Hz, H-7), 7.55 (1H, ddd, *J* = 8.3, 6.7, 1.0 Hz, H-6), 7.27-7.35 (5H, m, H-2'/6', 3'/5',4'), 5.83 (2H, s, H-10), 5.54 (2H, s, H-16). ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.0 (C-9a), 148.1 (C-8a), 143.8 (C-11), 136.5 (C-1'), 134.2 (C-3), 131.9 (C-4), 131.4 (C-7), 130.2 (C-8), 129.2 (C-2'/6'), 128.6 (C-5), 128.4 (C-3'/5'), 128.1

(C-4'), 124.6 (C-4a), 124.2 (C-15), 124.1 (C-6), 116.8 (C-3a), 53.2 (C-16), 42.3 (C-10). *An accurate mass could not be determined due to poor ionisation.

1-((1-(4-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrazolo[3,4-*b*]quinoline (**11b**) white powder. mp 201-202 °C. yield 62%. IR (solid, KBr, ν_{max}, cm^{-1}): 3130, 2921, 2182, 1728, 1616, 1498. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.99 (1H, s, H-4), 8.49 (1H, s, H-3), 8.18 (1H, d, *J* = 8.2 Hz, H-8), 8.12 (1H, s, H-15), 8.06 (1H, d, *J* = 8.6 Hz, H-5), 7.83 (1H, dd, *J* = 7.3, 7.1 Hz, H-7), 7.52 (1H, dd, *J* = 7.6, 7.2, Hz, H-6), 7.35 (2H, dd, *J* = 8.8, 5.6 Hz, H-2'/6'), 7.17 (2H, dd, *J* = 8.8, 8.8 Hz, H-3'/5'), 5.81 (2H, s, H-10), 5.52 (2H, s, H-16). ^{13}C NMR (150 MHz, DMSO-d_6): δ 162.3 (d, *J* = 242.8 Hz, C4'), 150.0 (C-9a), 148.1 (C-8a), 143.8 (C-11), 134.2 (C-3), 132.7 (C-1'), 131.9 (C-4), 131.3 (C-7), 130.7 (d, *J* = 8.5 Hz, C-2'/6'), 130.2 (C-8), 128.2 (C-5), 124.6 (C-4a), 124.1 (C-6, C-15), 116.8 (C-3a), 116.0 (d, *J* = 21.2 Hz, C-3'/5'), 52.4 (C-16), 42.3 (C-10). HRMS: (ESI$^+$-MS, *m/z*) calcd for $C_{20}H_{15}N_6FNa$ $(M + Na)^+$: 381.1240 found 381.1245.

1-((1-(4-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrazolo[3,4-*b*]quinoline (**11c**) cream powder. mp 196-198 °C. yield 77%. IR (solid, KBr, ν_{max}, cm^{-1}): 3134, 2945, 2172, 1727, 1617, 1492. ^{1}H-NMR (600 MHz, DMSO-d_6): δ 8.97 (1H, s, H-4), 8.48 (1H, s, H-3), 8.17 (1H, d, *J* = 8.3 Hz, H-8), 8.13 (1H, s, H-15), 8.06 (1H, d, *J* = 8.7 Hz, H-5), 7.82 (1H, dd, *J* = 8.3, 7.2 Hz, H-7), 7.52 (1H, dd, *J* = 8.7, 7.2 Hz, H-6), 7.40 (2H, d, *J* = 8.3 Hz, H-3'/5'), 7.30 (2H, d, *J* = 8.3 Hz, H-2'/6'), 5.83 (2H, s, H-10), 5.54 (2H, s, H-16). ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.0 (C-9a), 148.1 (C-8a), 143.8 (C-11), 135. 4 (C-4'), 134.2 (C-3), 133.3 (C-1'), 131.8 (C-4), 131.3 (C-7), 130.3 (C-3'/5'), 130.1 (C-8), 128.6 (C-2'/6'), 128.2 (C-5), 124.6 (C-4a), 124.3 (C-15), 124.1 (C-6), 116.9 (C-3a), 52.4 (C-16), 42.3 (C-10). HRMS: (ESI$^+$-MS, *m/z*) calcd for $C_{20}H_{15}N_6Cl$ $(M + Na)^+$: 397.0944 found 397.0934.

1-((1-(4-Bromobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrazolo[3,4-*b*]quinoline (**11d**) white powder. mp 202-204 °C. yield 60%. IR (solid, KBr, ν_{max}, cm^{-1}): 3135, 2921, 2165, 1723, 1616, 1489. ^{1}H-NMR (600 MHz, DMSO-d_6): δ 8.99 (1H, s, H-4), 8.48 (1H, s, H-3), 8.17 (1H, d, *J* = 8.3 Hz, H-8), 8.12 (1H, s, H-15), 8.06 (1H, d, *J* = 8.6 Hz, H-5), 7.83 (1H, dd, *J* = 8.3, 8.3 Hz, H-7), 7.54 (2H, d, *J* = 8.3 Hz, H-3'/5'), 7.52-7.54 (1H, m, H-6), 7.23 (2H, d, *J* = 8.3 Hz, H-2'/6'), 5.82 (2H, s, H-10), 5.52 (2H, s, H-16). ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.0 (C-9a), 148.1 (C-8a), 143.8 (C-11), 135.8 (C-1'), 134.2 (C-3), 132.1 (C-3'/5'), 131.8 (C-4), 131.3 (C-7), 130.7 (C-2'/6'), 130.1 (C-8), 128.2 (C-5), 124.6 (C-4a), 124.2 (C-15), 124.1 (C-6), 121.9 (C-4'), 116.9 (C-3a), 52.5 (C-16), 42.3 (C-10). HRMS: (ESI$^+$-MS, *m/z*) calcd for $C_{20}H_{15}N_6BrNa$ $(M + Na)^+$: 441.0439 found 441.0430.

1-((1-(4-Methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrazolo[3,4-*b*]quinoline (**11e**) yellow powder. mp 198-199 °C. yield 69%. IR (solid, KBr, ν_{max}, cm^{-1}): 3124, 2920, 2091, 1725, 1615, 1491. ^{1}H-NMR (600 MHz, DMSO-d_6): δ 8.98 (1H, s, H-4), 8.48 (1H, s, H-3), 8.17 (1H, d, *J* = 8.2 Hz, H-8), 8.07 (1H, s, H-15), 8.06 (1H, d, *J* = 8.5 Hz, H-5), 7.82 (1H, dd, *J* = 8.2, 7.3 Hz, H-7), 7.52 (1H, dd, *J* = 8.5, 7.3 Hz, H-6), 7.17 (2H, d, *J* = 7.9 Hz, H-3'/5'), 7.12 (2H, d, *J* = 7.8 Hz, H-2'/6'), 5.81 (2H, s, H-10), 5.47 (2H, s, H-16), 2.25 (3H, s, H-17). ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.0 (C-9a), 148.1 (C-8a) 143.8 (C-11), 137.9 (C-4'), 134.2 (C-3), 133.4 (C-1'), 131.8 (C-4), 131.3 (C-7), 130.2 (C-8), 129.7 (C-3'/5'), 128.5 (C-2'/6'), 128.2 (C-5), 124.6 (C-4a), 124.2 (C-6), 124.0 (C-15), 116.9 (C-3a), 53.0 (C-16), 42.3 (C-10), 21.1 (C-17). HRMS: (ESI$^+$-MS, *m/z*) calcd for $C_{21}H_{18}N_6Na$ $(M + Na)^+$: 377.1491 found 377.1483.

1-((1-(4-Nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-pyrazolo[3,4-*b*]quinoline (**11f**) cream white powder. mp 234-236 °C. yield 98%. IR (solid, KBr, ν_{max}, cm^{-1}): 3114, 2920, 2104, 1738, 1615, 1510. ^{1}H-NMR (600 MHz, DMSO-d_6): δ 8.99 (1H, s, H-4), 8.49 (1H, s, H-3), 8.16-8.20 (4H, m, H-15, H-8, H-3'/5'), 8.06 (1H, d, *J* = 8.7 Hz, H-5), 7.82 (1H, ddd, *J* = 8.6, 7.8, 1.3 Hz, H-7), 7.53 (1H, ddd, *J* = 8.7, 7.8, 1.0 Hz, H-6), 7.49 (2H, d, *J* = 8.7 Hz, H-2'/6'), 5.85 (2H, s, H-10), 5.72 (2H, s, H-16). ^{13}C NMR (150 MHz, DMSO-d_6): δ 150.0 (C-9a), 148.1 (C-8a), 147.7 (C-4'), 143.9 (C-11), 143.8 (C-1'), 134.3 (C-3), 131.9 (C-4), 131.3 (C-7), 130.1 (C-8), 129.4 (C-3'/5'), 128.2 (C-5), 124.7 (C-15), 124.6 (C-4a), 124.3 (C-2'/6'), 124.1 (C-6), 116.8 (C-3a), 52.3 (C-16), 42.3 (C-10). HRMS: (ESI$^+$-MS, *m/z*) calcd for $C_{20}H_{15}N_7O_2Na$ $(M + Na)^+$: 408.1185 found 408.1183.

Antibacterial activity

The synthesized compounds were prepared by dissolving 2.0 mg of compound in 2.0 mL of DMSO (Merck) to make sample solutions with a concentration of 1 mg mL^{-1}. The hybrid compounds were screened for the antibacterial activity against three Gram-negative bacteria (*Enterobacter hormaechei* ATCC 700232, *Pseudomonas aeruginosa* ATCC 27853 and *Escherichia coli* ATCC 35218) and five Gram-positive bacteria (methicillin resistant *S. aureus* (MRSA) ATCC 10069, *Streptococcus pyogenes* ATCC 49247, *Bacillus subtilis* ATCC 12344, *Enterococcus faecalis* ATCC 19434 and *Staphylococcus aureus* ATCC 25923). The initial screening was done using the zone of inhibition method.[43] Initially, the bacterial strains were grown in nutrient broth overnight at 37 °C and diluted with sterile distilled water to achieve a required concentration of 600 nm (OD600). The bacterial strains were inoculated into Mueller Hinton Agar plates (Composition (g L^{-1}): Beef infusion solids 2.0; starch 1.5; Casein hydrolysate 17.5; Agar 17.0; Final pH (at 25 °C) 7.3 ± 0.2) by streaking. The samples were then spotted onto the inoculated plates in triplicate using Ciprofloxacin and DMSO as controls. The plates were incubated for 18 h at 37 °C.

Compounds that had significant zones of inhibition were further tested to determine their Minimum Inhibition Concentration (MIC). Using broth microdilution plates (96 microtiter well plates containing 12 rows), 2 -fold serial dilutions were carried out using 100 µL stock solution diluted with Mueller Hinton broth to get the concentration of the compounds between 250-0.49 µg mL^{-1} (10 wells) with Ciprofloxacin and DMSO as controls in the remaining two wells. The bacterial strain solution (100 µL) was added into all plate wells, sealed and incubated at 37 °C for 18 h. A fluorescent dye, resazurin was then added, which turn the wells with bacterial growth pink showing the lowest concentration that inhibits bacterial growth.

Antitubercular activity

Compounds were dissolved in dimethyl sulfoxide (Merck) to create stock solutions of 1 mg mL^{-1} and stored at -20 °C. Cultures of *Mycobacterium tuberculosis* H37Rv (ATCC 27294) in MiddleBrook 7H9 (Difco) broth supplemented with 0.1% glycerol (Merck) and 10% oleic acid-albumin-dextrose-catalase (OADC) (Becton-Dickinson) were aerobically grown at 37 °C until an optical density $(OD)_{600nm}$ of 1 was attained. This was equivalent to approximately 3 x 10^8 bacilli mL^{-1}.[50] The antitubercular activity of the synthesized compounds against *M. tuberculosis* was tested in 3 biological assays in triplicate using microbroth dilution assays in a BSL-3 laboratory. Microtiter plates were set up using 96 well plates containing 12 rows. Antibiotic stocks, containing 4 × the initial concentration (4 mg mL^{-1}) required for the first row in the plate, were set up and 100 µL of the stock solution was inoculated into the first row. Thereafter, 2-fold serial dilutions were carried out from row 2 to row 12 by transferring 50 µL from one well to the next and diluting it to 100 µL and repeating the process in the next rows.

The *M. tuberculosis* culture inoculum was diluted 10-fold, and a 50 µL aliquot was added to each well. These plates were sealed and incubated at 37 °C for 7 days. Thereafter, 30 µL 0.02% resazurin solution was aliquoted into each well and the plates incubated at 37 °C overnight. Microbial growth was measured by observing the resazurin colour change from blue to pink. In addition to the compounds tested, Erythromycin was included as positive controls and broth and DMSO solvent as negative controls. The minimum inhibitory concentration (MIC) was interpreted as the lowest concentration inhibiting a colour change from blue to pink.

Antidiabetic activity

Samples were prepared by dissolving 2.0 mg of compound in 2.0 mL DMSO (Merck) to make a stock solution with a concentration of 1 mg mL^{-1}.

For the α-Glucosidase inhibition assay, samples were tested using a known method from the literature with slight modifications.[46] Approximately 200 µL aliquots of the compound (1 mg mL^{-1}) or standard acarbose (50 – 400 mg mL^{-1}) was added to the α-glucosidase (1.0 U/mL) solution in 100 mM sodium sulphate buffer at pH 6.8.

The mixture was incubated for 15 min at 37 °C. A volume of 5 mM *para*-nitrophenyl β-D-glucopyranoside (50 µL) was then added and the mixture further incubated for 30 min at 37 °C. The absorbance of the resulting solution was measured at 405 nm and the inhibitory activity of the compounds calculated as the percentage of the control sample using the % inhibition expression below.

$$\% \text{ Inhibition} = \left(1 - \frac{\text{Absorbance of compound}}{\text{Absorbance of control}}\right) \times 100$$

For the α-Amylase inhibition assay, a method from the literature was used with slight modification.[47] Approximately 200 µL aliquots of compound or standard acarbose (50 – 400 mg mL^{-1}) was added to a 200 µL porcine pancreatic amylase solution (0.5 mg mL^{-1}) in 200 mM sodium sulphate buffer at pH 6.9 and incubated for 10 min at 25 °C. Thereafter, approximately 500 µL of 1 % starch solution was added and the mixture further incubated for 15 min at 25 °C. The reaction was terminated by the addition of 1 mL dinitrosalicylate reagent, and then boiled for 10 min. The cooled mixture was diluted with 5 mL distilled water and the absorbance measured at 405 nm. The inhibitory activity of the compound was calculated as the percentage control using the % inhibition expression used above.

Anticancer activity

Stock solutions of the compounds were prepared by dissolving 1 mg in 10% DMSO (Merck) in water to a concentration of 1 mg mL^{-1}. HepG2, HeLa and Caco2 cells were maintained in Eagle's minimal essential medium (EMEM) and supplemented with 10% (v/v) gamma-irradiated FBS and 1% antibiotics (100 U mL^{-1} penicillin, 100 µg mL^{-1} streptomycin) at 37 °C and 5% CO_2, in a HEPA Class 100 Steri-Cult CO_2 incubator (*Thermo-Electron Corporation,* Waltham, Massachusetts, USA).

For the MTT assay, cells were trypsinized and seeded into 96-well microtiter plates at a seeding density of approximately 3 X 10^4 cells per well and incubated at 37 °C for 24 h to allow for attachment. The medium was then replaced with fresh medium, and the respective compound added to the wells and allowed to incubate for 48 h at 37 °C. Two positive controls were set up, one containing only cells was set as 100% cell survival/viability and another to which 10 µL of 10% DMSO was added (resulting in a final concentration of 0.5% DMSO per well). The DMSO control was used since the samples were prepared in a 10% DMSO solution. All assays were performed in triplicate. After the 48 h incubation period, the spent medium was removed and 100 µL fresh medium and 10 µL MTT reagent (5 mg mL^{-1} in PBS) added to each well. The cells were incubated at 37 °C for a further 4 h, after which the MTT-medium was removed and 100 µL DMSO added to solubilize the formazan crystals. The absorbance was read at 540 nm using a *Mindray* MR-96A microplate reader (*Vacutec*, Hamburg, Germany). The IC_{50} values were obtained from a graph of cell survival *vs*. log of concentration, substituting y=50 for the equation of the graphs to calculate x and getting the antilog of x = IC_{50}.

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Supplementary Material

^1H and ^{13}C NMR, Infrared and High Resolution Mass spectra of all the synthesised target compounds are contained in the Supplementary material.

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