Tomas Bata University in Zlín
Faculty of Technology

Doctoral Thesis

Preparation and Study of Photoprotective and Antimicrobial Properties of Novel Materials Based on 1,2,3-Triazole

Příprava a stadium fotoprotektivních a antimikrobiálních vlastností nových látek na bázi 1,2,3-triazolu

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Key words: *1,2,3-triazole – quinoline-2,4(1H,3H)-dione – synthesis – antimicrobial activities – photoprotective properties – metal-to-ligand coordination – NMR spectroscopy*

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ABSTRACT

A class of novel 1,2,3-triazole functionalised quinoline-2,4-diones was synthesized using multi-step reaction approach, starting with the synthesis of suitable organic azides that served as precursors for introduction of the first 1,2,3-triazole ring to the quinoline-2,4-dione framework.

Afterwards, desirable bis-triazole esters were obtained by acetylation of mono-triazole alcohols, subsequent introduction of propargyl group to the position N1 of quinolone heterocycle, and finally employment of copper(I)-catalysed »click« reaction using three different organic azides. Resulted bis- as well as mono-triazole acetates were then deprotected using acidic alcoholysis, while provided alcohols were further oxidized to suitable aldehydes and carboxylic acids. While crystallization of synthesized compounds was normally performed in case of mono-triazoles, it was seldom successful for bis-triazole species. Consequently, quinolones with two 1,2,3-triazole rings were purified mostly by silica-gel column chromatography. During the fulfilment of outline transformation scheme, various reaction conditions and synthetic routes were tested, monitored, and finally optimised. Apart from mainstream reaction pathway, some focus was also devoted to a few accompanying transformations that either highlighted interesting behaviour of the studied systems (quinoline-2,4-dione ring cleavage), or could be exploited as an alternative approach to anthranilic acid derivatives preparation.

Several synthesized materials were also evaluated for their potential ligand-to-metal coordination abilities, as well as antimicrobial activities against ten microbial strains, including bacteria, yeast and fungi. Additionally, their potential photoprotective characteristics were also briefly examined. Regrettably, no interesting physical properties or biological activities were detected for any of the tested compounds.

The vast majority of results obtained throughout my doctoral studies and presented in this dissertation, have already been published or will be published in scientific journals with the impact factors.

ABSTRAKT

V rámci disertační práce byla vícestupňovou syntézou, jež vycházela z vhodných organických azidů, připravena skupina nových chinolin-2,4-dionů substituovaných 1,2,3-triazolovými kruhy.

Bis-triazolové estery byly po acetylaci mono-triazolových alkoholů získány zavedením propargylové skupiny do polohy N1 chinolonového heterocyklu a následnou "click" reakcí s třemi různými organickými azidy za katalytického účinku měďných kationtů. Z výsledných bis-triazolových, stejně jako z mono-triazolových acetátů byly poté kyselou alkoholýzou odstraněny chránící skupiny a získané alkoholy byly dále oxidovány na příslušné aldehydy a karboxylové kyseliny. Zatímco krystalizace syntetizovaných mono-triazolových sloučenin byla prakticky vždy úspěšná, u bis-triazolových derivátů byla úspěšná pouze zřídka, a proto byly chinolony se dvěma 1,2,3-triazolovými kruhy purifikovány převážně chromatografií na sloupci silikagelu. V průběhu řešení podle naplánovaného schématu byly testovány, sledovány a nakonec optimalizovány reakční podmínky jednotlivých syntetických kroků. Kromě hlavních produktů reakcí byla věnována také pozornost několika vedlejším přeměnám výchozích látek, které buď zdůraznily zajímavé chování studovaných systémů (štěpení chinolin-2,4-dionového kruhu), nebo by mohly být využity jako alternativní přístup k přípravě derivátů kyseliny anthranilové.

U několika syntetizovaných derivátů byla sledována jejich potenciální schopnost koordinovat kovy, a také byly testovány jejich antimikrobiální účinky vůči deseti druhům mikroorganismů zahrnujících zástupce bakterií, kvasinek a hub. Navíc byly okrajově zkoumány jejich potenciální fotoprotektivní vlastnosti. Bohužel nebyly zjištěny žádné zajímavé fyzikální vlastnosti nebo biologické aktivity u žádné z testovaných sloučenin.

Naprostá většina výsledků získaných v rámci doktorského studia, které jsou prezentovány v této disertační práci, byla již publikována v impaktovaném vědeckém časopisu nebo je obsažena v rukopisu publikace zaslaném do redakce impaktovaného časopisu.

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ABBREVIATIONS

ACN – acetonitrile
ACP – acyl carrier protein
Bn – benzyl
CCM – Czech collection of microorganisms
COD – 1,5-cyclooctadiene
COSY – correlation spectroscopy
Cp – cyclopentadiene
Cp* – 1,2,3,4,5-pentamethylcyclopentadiene
CuAAC – copper(I)-catalysed azide-alkyne cycloaddition
dba – dibenzylideneacetone
DBU – 1,8-diazabicyclo[5.4.0]undec-7-ene
DCM – dichloromethane
DIPEA – *N*,*N*-diisopropylethylamine
DMF – dimethylformamide
DMSO – dimethyl sulfoxide
dpephos – bis[(2-diphenylphosphino)phenyl] ether
DPPH – 2,2-diphenyl-1-picrylhydrazyl
EA – elemental analysis
HBTST – 6-hydroxybutyltriazole-6-deoxy starch
HDC – Huisgen 1,3-dipolar cycloaddition
HETST – 6-hydroxyethyltriazole-6-deoxy starch
HIV – human immuno-deficiency virus
HMBC – heteronuclear multiple bond correlation
HMTST – 6-hydroxymethyltriazole-6-deoxy starch
HOMO – highest occupied molecular orbital
HPTST – 6-hydroxypropyltriazole-6-deoxy starch
HRMS – high resolution mass spectrometry
HSQC – heteronuclear single quantum correlation
IC_{50} – half maximal inhibitory concentration
InhA – *Mycobacterium tuberculosis* 2-*trans*-enoyl-ACP reductase
IR – infrared (spectroscopy)
LC – liquid crystal
LCST – lower critical solution temperature
LUMO – lowest unoccupied molecular orbital
MbtA – adenylating enzyme from *Mycobacterium tuberculosis*
Me – methyl
MIC – minimum inhibitory concentration
MRSA – methicillin-resistant *Staphylococcus aureus*
μM – micromolar
NBD – norbornadiene
NMR – nuclear magnetic resonance

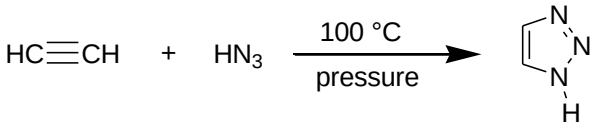
OAc – acetoxy
OLED – organic light emitting diode
OTf – trifluoromethanesulfonate
PCC – pyridinium chlorochromate
PEG – polyethylene glycol
Ph – phenyl
pKa – negative base-10 logarithm of the acid dissociation constant of a solution
PNIPAA – poly(*N*-isopropylacrylamide)
ppb – parts per billion
ppm – parts per million
ppt – 1-(2-picolyl)-4-phenyl-1*H*-1,2,3-triazole
ptmp – 2-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)pyridine
PVA – poly(vinyl alcohol*)*
Py – pyridyl
RBV – ribavirin
rt – room temperature
RuAAC – ruthenium(II) complexes catalysed azide-alkyne cycloaddition
Ru–Cym – (cymene)ruthenium dichloride dimer
SEM – scanning electron microscope
SPAAC – strain-promoted azide-alkyne coupling
TBA – tetrabutylammonium
TBTA – tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine
t-BuOH – *tert*-butyl alcohol
TEA – triethanolamine
THF – tetrahydrofuran
TLC – thin-layer chromatography
TMS – trimethylsilane
TOAF – tetraoctylammonium formate
TOF – time of flight
Ts – tosyl
TSG – tryptone–soya peptone–glucose (broth)
UV-VIS – ultraviolet-visible
V/*V* – volume/volume percent
xantphos – 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

1. INTRODUCTION

1,2,3-Triazole species are five-membered heterocyclic compounds consisting of three consecutive linked nitrogen and two carbon atoms. They can be derived from three conceivable tautomeric basic compounds: 1*H*-1,2,3-triazole, 2*H*-1,2,3-triazole, and 4*H*-1,2,3-triazole. They possess strong dipole moment that polarizes the proton on carbon to such a rate that it can act as a hydrogen-bond donor.[1-3] However, because of their low expressed basic character, protonation of 1,2,3-triazoles at physiological pH is suppressed.[1,2] Furthermore, they are practically inert even at elevated temperatures and stable in oxidizing, reducing, as well as hydrolytic media.[2,4] Even though, 1,2,3-triazoles exhibit a large variety of desirable biological activities and physical properties, they do not occur in nature and thus can be obtained only synthetically.[5]

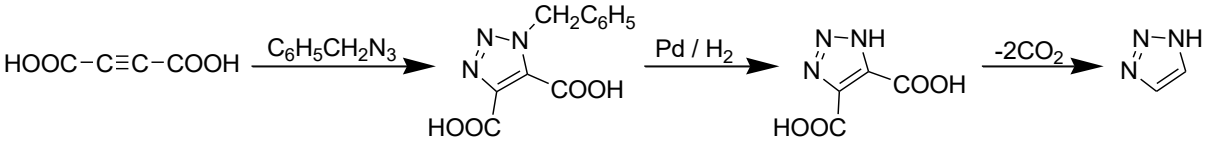
At the end of 19th century, alkyne-azide [3+2] cycloaddition was established by Michael,[6] as he carried out the reaction between dimethyl but-2-ynedioate and phenyl azide to gain 1,2,3-triazole derivative. Reaction took place in a sealed tube and at elevated temperature for the extended time period. Similar reaction approach was also utilized in 1910, when Dimroth and Fester[7] combined acetylene dissolved in acetone and hydrazoic acid in absolute alcohol (Scheme 1), as well as acetylene and phenyl azide in acetone.[7,8] In the same year, reactions of substituted ethynes, namely phenylpropiolic acid and acetylenedicarboxylic acid, with hydrogen azide were published.[9]

Scheme 1



Almost four decades after Michael's discovery,[6] Curtius and Raschig[10] reported two novel 1,2,3-triazole derivatives, synthesized by the same experimental procedure. Additionally, in the forties and fifties of previous century, there were another two worth mentioning tries of 1,2,3-triazole species preparation, carried out by Huttel and Gebhardt[11] in 1947, as well as Willey and co-workers[12] in 1956 (Scheme 2), who characterised 1,2,3-triazole synthesis as a complex and demanding task.[12]

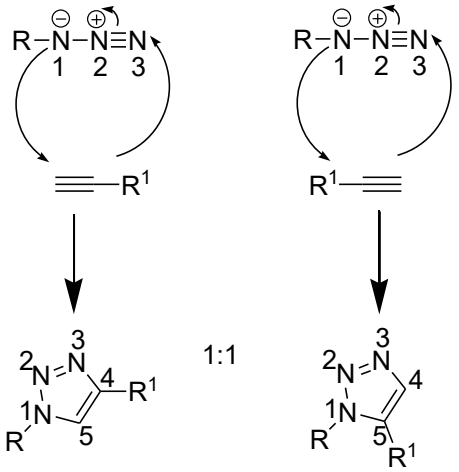
Scheme 2



Finally, during the years 1961–1967, Huisgen et al.[13-16] published four articles, focusing on detailed studies of addition reaction between acetylenic compounds and organic azides, and also introduced the designation Huisgen 1,3-dipolar cycloaddition (HDC), which has been preserved until today.[17]
However, high toxicities of reactants, elevated reaction temperatures, inconvenient manipulation, low to moderate yields and extended reaction times are the main reasons why all mentioned transformations are nowadays recognised as unpractical, irrational, old-fashioned and hazardous, especially in larger scales.[8,12]

Even though, the cyclisation reaction between the triple-bond compounds and azides was established more than 125 years ago,[6] the synthesis of 1,2,3-triazoles and their characterization had remained considerably unexplored for more than a century.[18] Relatively limited interest in the last-mentioned reaction was due to the fact that traditional Huisgen 1,3-dipolar cycloaddition not only requires severe reaction conditions but also results in hardly separable mixture of 1,4- and 1,5-disubstituted 1,2,3-triazole species.[4,18,19] The 1:1 blend of both compounds (Scheme 3) appears because of their comparable HOMO and LUMO energy levels, and therefore practically equal probability of 1,4- and 1,5-disubstituted adducts emergences.[20-22]

Scheme 3

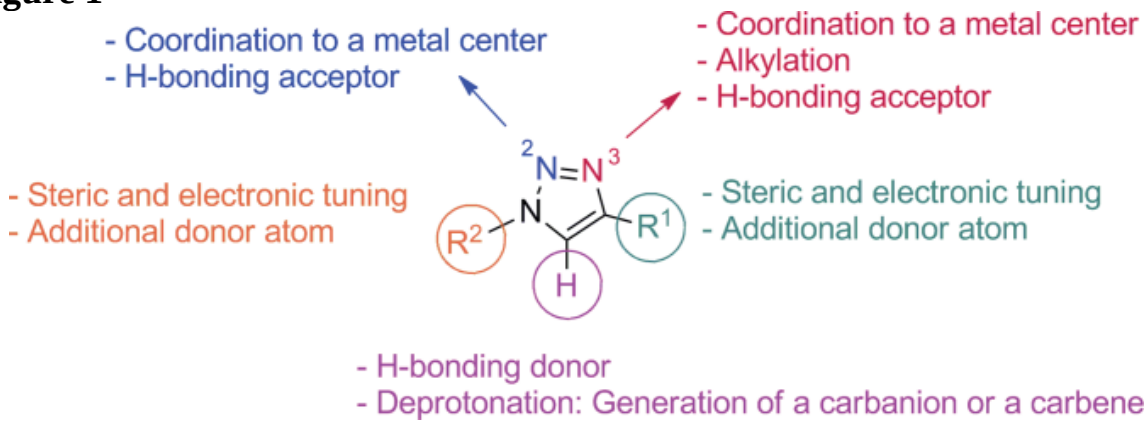


However, the situation dramatically changed in 2002, when Sharpless[19] and Meldal[23] independently discovered and published copper(I) catalysed alkyne-azide cycloaddition (CuAAC) as a 1,2,3-triazoles preparation approach. At the same time, Sharpless introduced and precisely defined the expression

»click chemistry«[24] to designate a series of reactions that are simple to perform, stereoselective, wide in scope, highly-yielding, generate solely inoffensive products (purification limited to crystallization or distillation) and use only readily accessible reagents.[24,25] Furthermore, transformations should proceed in environmentally friendly conditions and they need to be thermodynamically favourable.[21,25] The most common »click reaction« types are additions to carbon-carbon multiple bonds, carbonyl chemistry of the non-aldol type, nucleophilic substitution chemistry and cycloadditions of unsaturated hydrocarbons.[26]

Although, more than 15 years passed from the Sharpless and Meldal's discovery,[19,23] scientists all around the world still admire desirable characteristics of copper catalysed 1,3-dipolar cycloaddition – an effective synthetic pathway for 1,2,3-triazole species preparation. Sarkar et al. emphasized the rarity in chemistry that so much attention is devoted to one single reaction approach, as it is obvious in the case of last-mentioned transformation.[27] At the first sight, simple heterocyclic compound 1,2,3-triazole possesses many versatile properties (Figure 1) that could be effectively exploited in the fields of synthetic,[27-29] medicinal,[28] physical,[30] organometallic,[27] and coordination[27,31] chemistry, as well as in polymer[30] and life[32,33] science.

Figure 1[27]

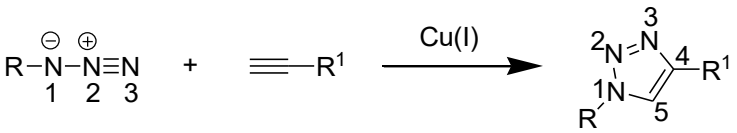


2. SYNTHETIC APPROACHES

2.1 Copper catalysed synthesis

Copper catalysed 1,3-dipolar (Huisgen) cycloaddition is a greatly appreciated and well-investigated method for 1,4-disubstitued 1,2,3-triazoles preparation (Scheme 4),[20,34] and therefore a representative example of a »click reaction«.[19,23,29]

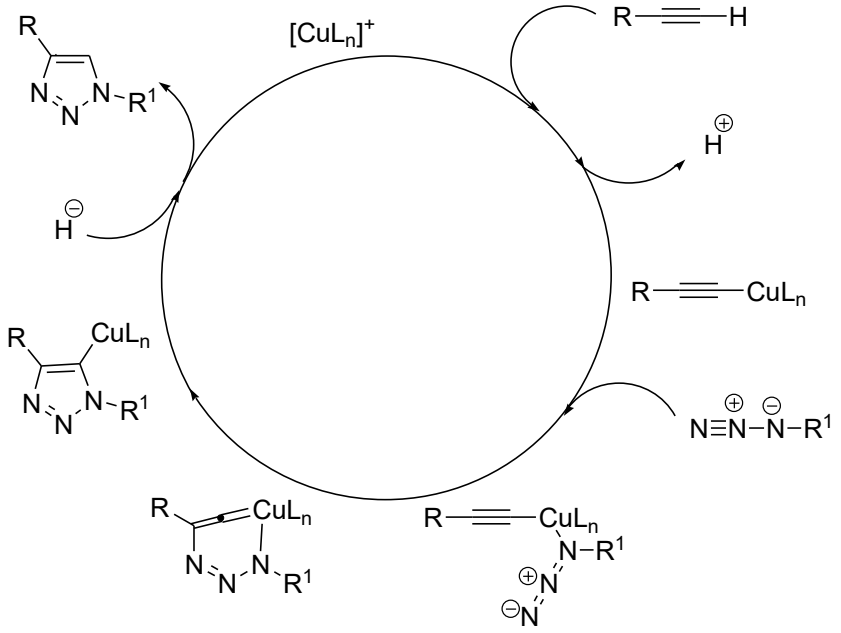
Scheme 4



Fully converted and highly pure products could be obtained in various solvents including *N*,*N*-dimethylformamide,[23,34] acetonitrile,[23] *N*-ethyldiisopropylamine,[23] dichloromethane,[23] toluene[23] tetrahydrofuran[23] and *tert*-butyl alcohol solution in water.[19,35] Even though, Cu(I) cations as a conversion driving force could be utilized directly from the copper monovalent sources such as copper(I) chloride, copper(I) iodide or copper(I) bromide dimethyl sulphide complex, it is more convenient to prepare them *in situ* by the reduction of Cu(II) salts that are frequently more pure and less expensive than their univalent counterparts.[19,23] Some simple reducing agents including metallic copper,[36-38] glucose in the presence of Fehling's reagent[39], sodium ascorbate[40] or cuprous cyanide obtained by the NaCN reduction of copper(II) sulphate,[34] are regularly used. The acceleration rates of 10^5–10^8 in comparison to non-catalysed transformation, quantitative regioselectivity, high degree of oxygen and water tolerance, as well as smooth and simple realisation are just few of numerous advantages that make CuAAC reaction widely popular,[20,34] and consequently »the best click reaction to date«.[41] Furthermore, the stability of resultant 1,2,3-triazole species under many reaction conditions and their compatibility with a broad range of functional groups enable formation of triazole consisting peptides, oligosaccharides and other macromolecules.[21]

An acknowledged mechanism of copper catalysed reaction (Scheme 5) starts with the formation of a copper acetylide between Cu(I) and a terminal alkyne. As a result, pKa of alkyne is lowered enough to be able to get deprotonated in aqueous solution. This copper complex undergoes azido-compound attack that is followed by intramolecular cyclisation reaction and further formation of copper-including triazole. Finally, an adduct is protonated, resulting in formation of 1,4-disubstitued 1,2,3-triazole and regeneration of a catalyst.[21,34]

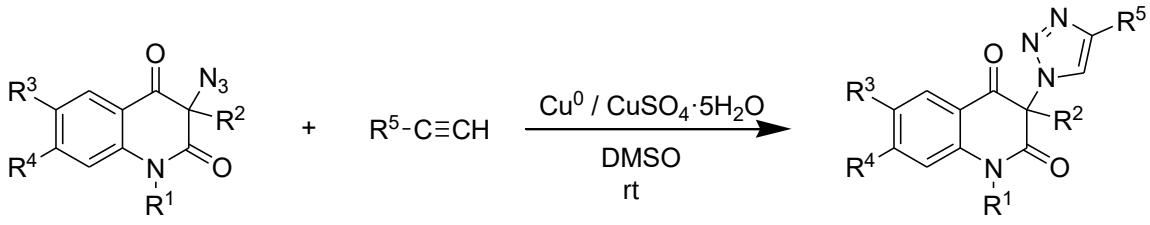
Scheme 5



After establishing a role of univalent copper in CuAAC transformation, different types of Cu species were further examined for their catalytic properties. Similar to the Sonogashira cross-coupling reaction, the Huisgen cycloaddition is also a heterogeneously catalysed process, as it takes part on the surface of copper particles.[38,42] Considering four different metal copper sources, their catalytic activities were diminished in the row Cu(0) clusters > Cu(0) powder > Cu(0) shavings > Cu(II)/ascorbate.[38] Consequently, copper clusters with the surface-to-mass ratio of 168 m^2/g, were found the most potent catalyst in the series.[38]

Kafka and co-workers published synthetic pathway of 1,2,3-triazole incorporating variously substituted quinoline-2,4(1*H*,3*H*)-diones, where Cu^{2+}/Cu^0 system was used as a catalyst (Scheme 6). The conversion was carried out in the presence of metal copper and catalytic quantities of $CuSO_4 \cdot 5H_2O$ in DMSO. The target compounds were obtained in moderate to excellent yields.[43]

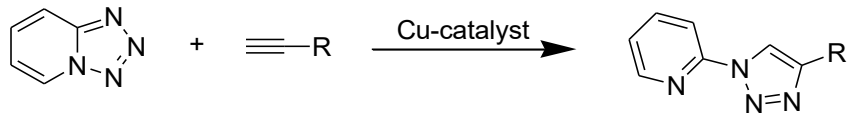
Scheme 6



Next attempt was made by the Gevorgyan's group that presented an imaginative approach of replacing standard organic azides with pyrido (Scheme 7), pyrazino, quinolino and quinoxalino tetrazoles. Their specialty is

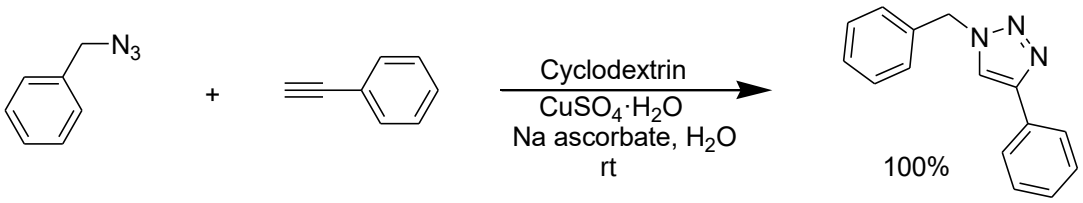
appearance in two equilibrium fashions, where the closed form is strongly prevalent at the standard conditions, in comparison with the opened one. While copper(I) catalysed cycloaddition was effective for combination of all four tetrazoles with a broad scope of alkynes providing 1,4-disubstituted adducts, ruthenium catalysed synthesis of 1,5-counterparts was unsuccessful in case of pyridotetrazoles used as a source of azide. The reason might be possible deactivation of ruthenium catalyst.[44]

Scheme 7



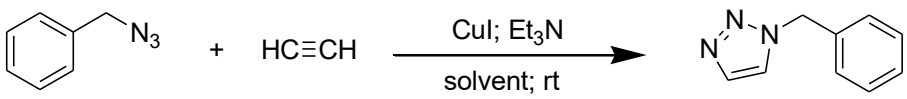
Further modification of classical copper catalysed [3+2] cycloaddition approach was revealed by Shin et al.[45] The reaction between benzyl azide and phenyl acetylene was carried out at room temperature in water in the presence of Cu(II) salt and sodium ascorbate. Almost quantitative transformation rate of 99.5% was accomplished in 330 minutes. Afterwards, the same experiment was repeated with the addition of α-, β- and γ-cyclodextrin, respectively (Scheme 8). In all three cases, reactions were terminated in 10 minutes providing 100% transformation yields. Dramatic increases of reaction rates after addition of cyclodextrins were induced by their properties.[45] While a hydrophilic outer-shell provides an excellent contact with water, a hydrophobic inner cyclodextrin cavity comprises non-polar molecules, allowing effective phase-transfer catalysis.[45,46]

Scheme 8



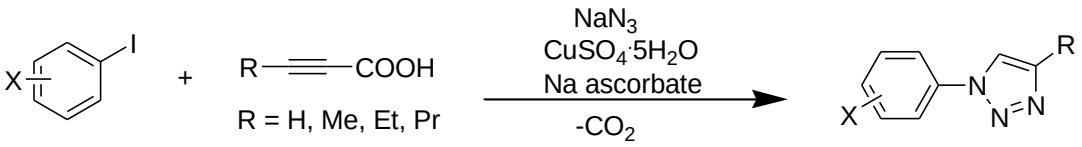
The copper(I) catalysed transformation could be also carried out by the utilization of a reactant in a gaseous state. Wu's research group performed last-mentioned reaction using benzyl azide and acetylene in the presence of copper(I) species and triethylamine at laboratory temperature (Scheme 9). The best results were obtained when DMSO or acetonitrile were used as a solvent.[47]

Scheme 9



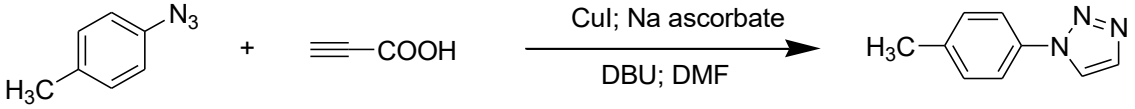
Because of the fact that simple alkynes have low boiling points, they could be pretty unpractical for handling. As a solution, Kolarovič et al. suggested replacing short-chained triple-bond species with their analogous alkynoic acids. Firstly, an efficient method for catalytic decarboxylation in the presence of Cu(I) salt and Et_3N at slightly elevated temperature was developed.[48] That approach was then successfully upgraded to three-step »one-pot« procedure for 1,2,3-triazole compounds synthesis. (Scheme 10).[49]

Scheme 10



In the same year, Xu's group independently established an alternative preparation of 1-monosubstituted 1,2,3-triazoles, where no rigorous experimental conditions or extended time periods are needed.[50] Reaction pathway for synthesis of *p*-tolyl-1*H*-1,2,3-triazole from 1-azido-4-methylbenzene and propiolic acid was optimised by varying different reaction parameters. It turned out that the presence of copper(I) iodide (0.2 equiv.), sodium ascorbate (0.4 equiv.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 0.5 equiv.) as a base in *N*,*N*-dimethylformamide exhibit optimal reaction performance, resulting in yield of 93%. (Scheme 11).[50]

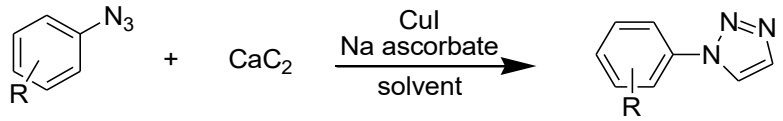
Scheme 11



Moreover, »carboxylic-acid-promoted« reaction under similar transformation conditions was published by the Shao's research group. Eleven out of twelve tested carboxylic acids provided excellent yields in the range of 94% to 98%.[51]

Finally, Jiang's laboratory reported copper(I) catalysed cycloaddition, where calcium carbide was used instead of hydrocarbon triple bond species (Scheme 12). Differently substituted aryl-azides reacted with CaC_2 in the presence of CuI and reductive agent sodium ascorbate in water solution of acetonitrile or tetrahydrofurane. Aryl-triazoles were isolated in yields ranging from 70% to 95%.[52]

Scheme 12



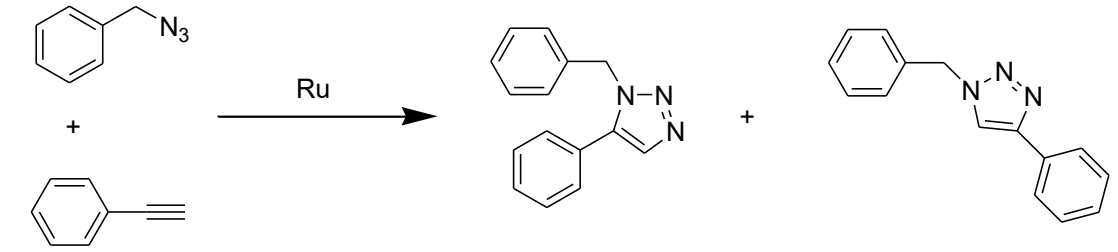
Besides the many benefits that copper catalysed formation of triazoles possesses, it also has one bothersome disadvantage. After the isolation of obtained product, there is always some copper contamination left in a sample.[53,54] However, one of the simplest and most practical transition metal species removal approach was developed by Macdonald and co-workers using Fe_xO_y@Fe nanoparticles to reduce the amount of catalytic impurities in the product from the level 100 ppm to the approximately 40 ppb.[54] Encouraged with the effectiveness of presented »copper-on-iron« (Cu/Fe) catalyst, Kovács' group evolved bimetallic Cu/Fe catalysis of 1,3-dipolar cycloaddition between alkyne and azide.[53,55] Authors correctly assumed that iron actually possesses two very important roles in this catalytic process. It not only serves as the surface for copper nanoparticles, and consequently forms highly effective catalyst, but also acts as a »copper-scavenger«, and therefore drastically reduces content of copper species in the synthesized product.[53]

2.2 Ruthenium catalysed synthesis

During the last decade, pretty much attention has been devoted to the development of »copper-free« synthetic procedures, where ruthenium species have been used as the most common and efficient alternatives.[29,56-58]

Because of well-known catalytic activities of ruthenium complexes, Fokin and co-workers evaluated the ruthenium-catalysed cycloaddition (RuAAC) approach as preparation pathway of 1,5-disubstitued 1,2,3-triazole adducts.[20,59,60] In all cases, benzyl azide and phenylacetylene were utilized as reactants, while $Ru(OAc)_2(PPh_3)_2$,[59] $CpRuCl(PPh_3)_2$,[59,61] $Cp^*RuCl(PPh_3)_2$[59] and Cp*RuCl(NBD)[59] complexes were tested as catalysts. The first mentioned complex gave exclusively 1,4-disubstituted compound, while the second ruthenium species resulted in mostly 1,5-disubstituted adduct (85%). $Cp^*RuCl(PPh_3)_2$ and Cp*RuCl(NBD), respectively caused in formation of pure 1,5-disubstitued 1,2,3-triazole compounds (Scheme 13). Furthermore, it was established that a wide range of solvents, including dioxane, 1,2-dichloroethane, toluene, benzene and tetrahydrofuran, is suitable for the above described transformation.[59,61]

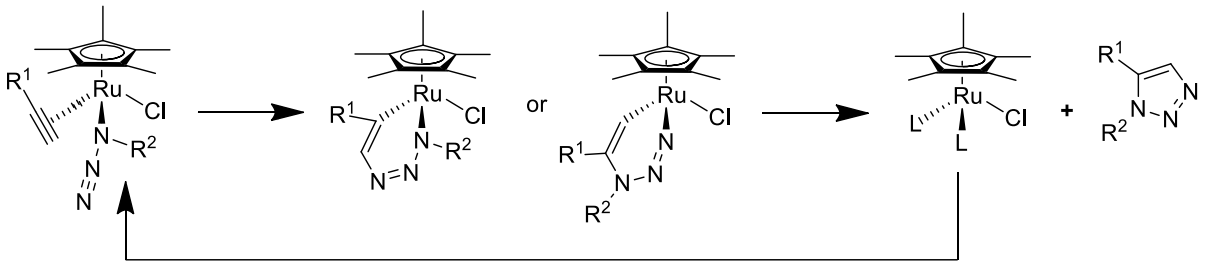
Scheme 13



$Ru(OAc)_2(PPh_3)_2$	/	100%
$CpRuCl(PPh_3)_2$	85%	15%
$Cp^*RuCl(PPh_3)_2$	100%	/
Cp*RuCl(NBD)	100%	/

Fokin's lab[59] additionally extended the range of catalysts that provide only 1,5-disubstitued derivatives (Scheme 14). Beside already mentioned $Cp^*RuCl(PPh_3)_2$ and Cp*RuCl(NBD) counterparts, Cp*RuCl(COD) and [Cp^*RuCl_4] were also utilized.[59] In contrast to copper based reaction, ruthenium catalysed 1,3-dipolar cycloaddition is fully functional also when non-terminal alkynes are used, and consequently 1,4,5-trisubstituted 1,2,3-triazole adducts can be successfully synthesized.[20,59]

Scheme 14



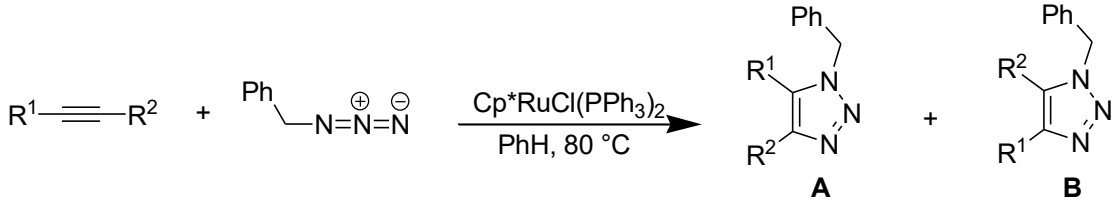
Even though one of the first discovered ruthenium catalyst, $Cp^*RuCl(PPh_3)_2$ shows desirable catalytic properties in alkylazide-alkyne reaction and selectively provides only 1,5-disubstitued 1,2,3-triazole species, it was found relatively ineffective when arylazides were used.[59,60] As a response to a given situation, pentamethylcyclopentadienyl ruthenium(II) chloride was developed. Using the series of reactions in different solvents and temperatures, the transformation in DMF in temperature range between 90–110 °C was recognised as the most suitable.[60]

Due to the fact that very little has been reported about 1,2,3-triazole moieties containing amino or carboxylic groups and practically nothing about those groups attached directly to the positions 4 and 5 of a five-membered

1,2,3 triazole ring, Ferrini et al.[57] focused on ynamides-derived 5-amino-1,2,3-triazole-4-carboxylate preparation using [Cp*$RuCl_4$] ruthenium complex as a catalyst. Various aminotriazoles, as well as dipeptide compounds that were synthesized in moderate to good yields, were further investigated for their biological activities.[57]

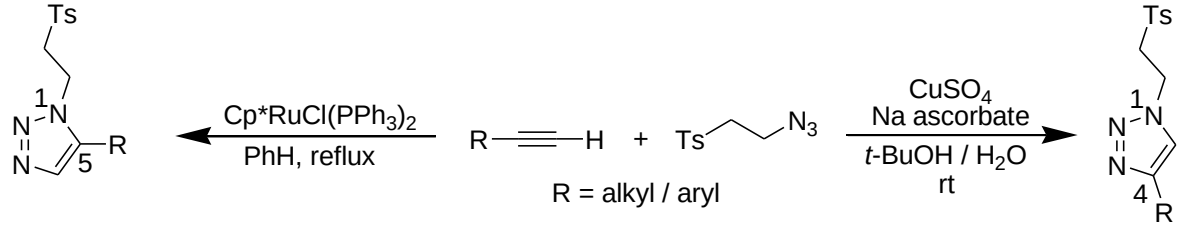
Moreover, Majireck and Weinreb considered Ru-catalysed [3+2] cycloaddition of benzyl azide with numerous non-symmetrical and internal alkynes. It was established that dialkyl and phenyl-alkyl acetylenes result in a mixture of both **A** and **B** forms of 1,2,3-triazoles, whereas unsymmetrical acetylene species substituted by carboxylic group at position R^2 give fully regioselective products **A** (Scheme 15).[61]

Scheme 15



Finally, Weinreb and co-workers[62] compared both widely-utilized metal catalysed approaches. 2-Tosylethylazide and various alkynes were combined in the presence of copper(I) and ruthenium catalysts, respectively. The former resulted in 1,4-disubstitued 1,2,3-triazoles, while the latter expectedly provided 1,5-disubstitued adducts (Scheme 16).[21,62]

Scheme 16



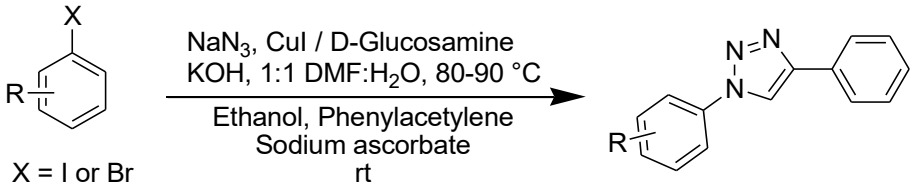
2.3 »One-pot« synthetic approach

Even though organic azides, mostly prepared by nucleophilic substitution from sodium azide and organic halides,[63] are considered as hazardous and highly toxic compounds, they play an indispensable and unique role in »click chemistry«.[19,64] Some of them are pretty stable towards oxygen, water and vast majority of conventional synthesis conditions, while others, especially those of small molar masses or with more N_3 groups, are extremely unstable as well as explosive.[19,64,65] Consequently, handling with these species could be problematic and dangerous.[66,67] As a response, »one-pot« multi-step mechanism was

developed, where an alkyne, organic halide and sodium azide are mixed together and no intermediate step including organic azido compound isolation and its manipulation is assumed. Moreover, »one-pot« transformation approach also proceeds in high yields and considerably simplifies, as well as accelerates the synthetic route.[49,63,66]

In the last two decades, an interest in »one-pot« synthesis is on the rise, which is visible from the numerous attempts for the establishment, modification and finally realization of this procedure. Murthy's lab[68] published a series of »one-pot« three-component transformations in various solvents, resulting in 1,4-disubstitued 1,2,3-triazoles in high yields, obtained by the combination of different aryl halides with phenyl acetylene and sodium azide in the presence of base. It was established that reaction conditions played an important role in this case, as formation of azido derivative was considerably suppressed at the temperatures above 90 °C.[68] Additionally, electron withdrawing groups (R = NO_2, $COCH_3$ or CN) bonded to aryl halides appreciably improved the yields (85% or higher) and also reduced the reaction times (less than 20 hours), in comparison with electron donating groups (R = C_6H_5, NH_2 or CH_3) that resulted in yields of 70–80%, while their reaction times mostly exceeded 20 hours (Scheme 17).[68,69]

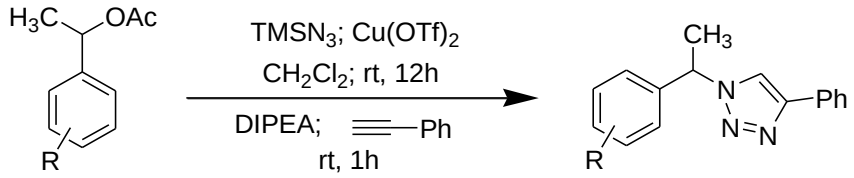
Scheme 17



Similarly, Feldman et al.[66] also reported »one-pot« two-step procedure that was an improvement of previously published prescription[70] that provided considerably lower yields, while heating for an extended time period was necessary.[66,]

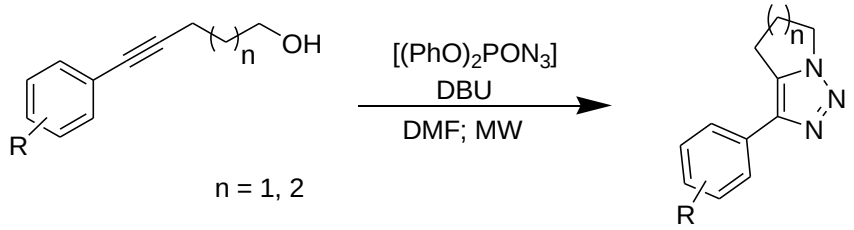
Fukuzawa with co-workers[63] went a step forward as they developed doubly-catalysed »one-pot« method for direct triazole target compounds preparation from easily accessible benzyl acetates, without transforming them firstly to organic halides and then to azide compounds. In the first step, azidotrimethylsilane ($TMSN_3$) and copper(II) trifluoromethanesulfonate ($Cu(OTf)_2$) in dichloromethane were used to obtain azide intermediate that was further directly combined with phenylacetylene in the presence of diisopropyl ethyl amine, and consequentially transformed to the 1,2,3 triazole derivative (Scheme 18).[63]

Scheme 18



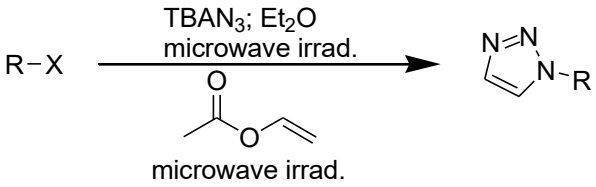
Modified metal-free »one-pot« synthetic approach was efficiently utilised for the preparation of bicyclic[1,2,3]triazoles from suitable yne-ols (Scheme 19), as highly energetic source of microwave irradiation was used instead of copper-based catalysis. Resulting 5,6-dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazole and 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyridine derivatives were produced in moderate to very good yields. When electron withdrawing groups were attached to the *ortho*, *meta* or *para* positions of corresponding precursors, the obtained yields were slightly lower than in the case of electron donating groups.[71]

Scheme 19



Hansen and co-workers also succeeded in synthesis of N-linked C-unsubstituted 1,2,3-triazoles, using »one-pot« procedure carried out under microwave irradiation. Firstly, traditional two-step reaction approach was utilized, as some alkyl azides were combined with vinyl acetate, resulting in appropriate 1,2,3-triazole species in good to excellent yields (up to 99%). Afterwards, the same transformations were carried out in »one-pot« mode. Suitable alkyl halides were transformed *in situ* to organic azides that were subsequently subjected to the reaction with vinyl acetate (Scheme 20), providing expected products in moderate yields (64–70%).[72]

Scheme 20

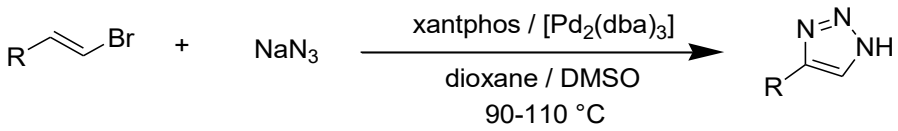


However, taking into account all advantages of described »one-pot« reaction approach, the transformation can be fully successful only in case that nucleophilic substitution of halide proceeds in smoothly and quantitative way. Otherwise, formation of undesired N–H triazole by-product occurs.[66]

2.4 Miscellaneous synthetic approaches

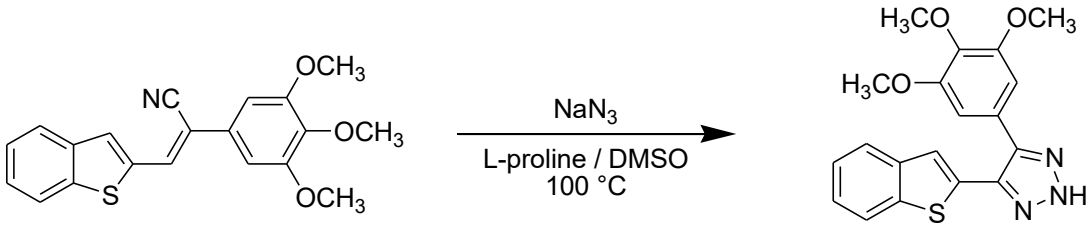
Barluenga's group developed a new approach to 1*H*-1,2,3-triazoles, using organopalladium compound as a catalyst.[73] The reaction between *β*-bromostyrene and sodium azide was carried out in the presence of palladium source [$Pd_2(dba)_3$], dioxane and various ligands. Transformation was successful only in cases when »large-bite« angle chelators such as xantphos or dpephos were utilized. In contrast to aryl-substituted bromoethylenes, their alkyl analogues should be treated under slightly harsher reaction conditions to be able to provide 1*H*-1,2,3-triazoles in good to excellent yields. Elevated temperature (90–110 °C) and larger catalyst loading, as well as replacement of dioxane with DMSO were found mandatory for the synthesis of alkyl-substituted 1,2,3-triazoles. (Scheme 21).[73]

Scheme 21



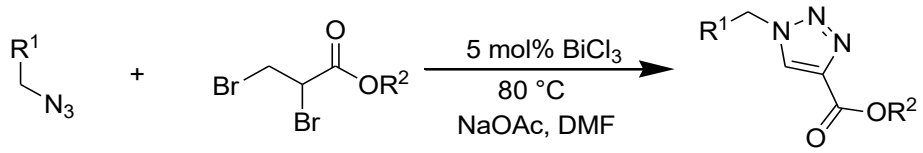
Similarly, 4,5-disubstitued-2*H*-1,2,3-triazole species were synthesized using L-proline as a Lewis base and sodium azide in DMSO. In the proposed mechanism, an azide group N_3^- is introduced by Michael addition, and consequently a carbanion is formed. Afterwards, a triazole bridge is constructed as intramolecular cyclisation took place. Finally, after the cyanide group expulsion, 2*H*-1,2,3-triazole is developed using L-proline catalysed proton transfer. (Scheme 22).[74]

Scheme 22



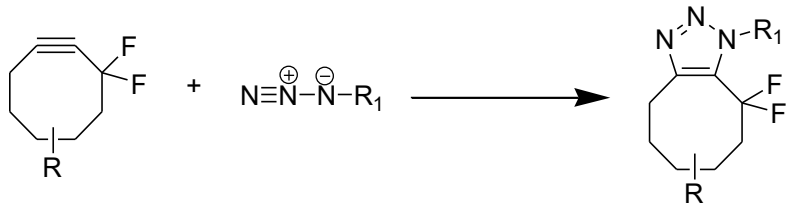
Hong-bin Sun et al. additionally expanded the diversity of triazole target compounds preparation, as they recently published the catalytic cyclisation of 2,3-dibromopropionates with benzyl azides in the presence of a nontoxic bismuth catalyst (Scheme 23).[29]

Scheme 23



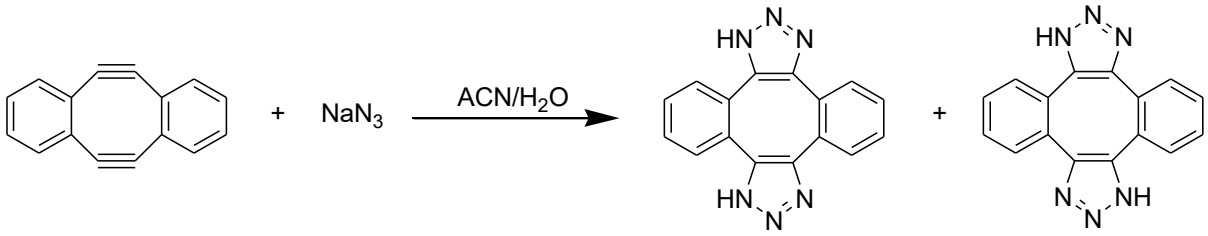
Instead of using some catalysts, Bertozzi et al. focused on activation of alkyne as a driving force of a catalyst-free [3+2] cycloaddition.[75] The strain in cyclooctyne ring results in higher energy levels of reactants, and therefore accelerates so called »strain-promoted« azide-alkyne coupling (SPAAC).[69,75-77] This effect is even more expressed when cyclooctyne derivatives are additionally difluorinated (Scheme 24).[69,76]

Scheme 24



Just a few years later, Wang and co-workers also utilized SPAAC-based metal-free preparation approach to synthesize condensed bis-triazole system (Scheme 25). Reaction was carried out in aqueous acetonitrile at room temperature and it was completed in 30 minutes. As no mono-triazole product was detected even when less than 1 equivalent of sodium azide was used, it was undoubtedly confirmed that the second cyclisation reaction is considerably faster than the first one.[78]

Scheme 25



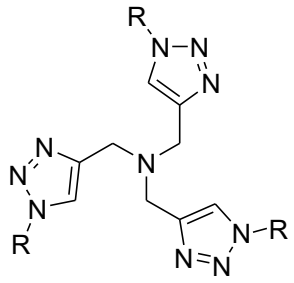
3. PRACTICAL APPLICATIONS

Approximately half a century ago, a strong tendency to connection between the synthetic organic chemistry and biosciences, such as biology, medicine and biophysics appeared. As a result, many theoretical findings and facts got applicable values that resulted in sudden upswing of preliminary and practically oriented studies that have been continuously and exponentially growing until today.[79]

3.1 Coordination properties and catalytic activities

Several journals reported that nitrogen based compounds, such as triethylamine,[80,81] proline,[80,82] diisopropylethylamine,[80,83] 2,6-lutidine[19,35,80] and many others not only stabilize copper(I) species but also quicken the catalytic process. Consequently, various tris((1,2,3-triazolyl)methyl)amines (Figure 2) were confirmed as versatile and promising ligands.[35,80,84,85]

Figure 2

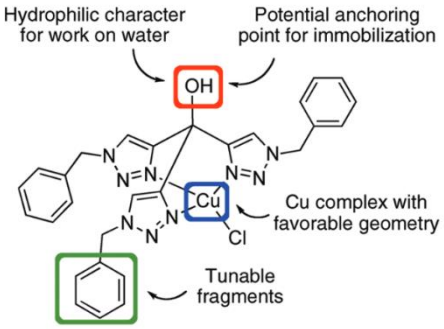


Tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine, shortly TBTA (Figure 2; R=CH_2Ph) that is also the most widely used amine-ligand, was prepared by Chan et al.[35] Tertiary nitrogen and 1,2,3-triazole building blocks make TBTA oligotriazole an efficient catalyst. Its activity was proved by cyclic voltammetry, exhibiting a drastic increase in Cu(I)/Cu(II) redox potential.[35]

Similarly, Özçubukçu and co-workers developed copper(I) tris(triazolyl)methanol complex as a promising ligand for reactions in water environment or neat (Figure 3).[84] Furthermore, the catalytic activity of prepared copper complex was tested in sixteen cycloaddition reactions between different organic azides and alkynes. Transformations mostly resulted in good to excellent yields with one single exception – the reaction between benzyl azide and propargylamine emerged in a conversion rate of 47%.[84] Normally, due to the affection for complexation of amine group with copper(I) ions and subsequent deactivation of the catalyst, the CuAAC reactions are generally unsuccessful. However, when copper(I) tris(triazolyl)methanol complex is used, the catalyst

remains active, and therefore transformation provides a product in a moderate yield.[84,85]

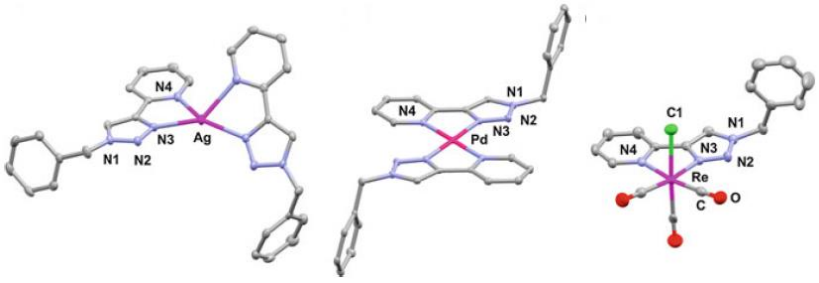
Figure 3[84]



Late transition metal complexes, including monodentate and tuneable 1,2,3-triazole based ligands that could act as Lewis bases, were introduced by van Koten and co-workers.[86] The obtained platinum and palladium complexes exhibited high diversity in electronic and steric characteristics that make these compounds potent species in coordination, materials and catalysis chemistry.[27,86]

A series of 2-pyridyl-1,2,3-triazole (Figure 4) ligands have been considered by various scientists. By combining versatile ionic metals and pyridyltriazole ligands in different stoichiometric ratios, the coordination complexes of miscellaneous geometrical structures such as tetrahedral, square-planar and octahedral have been formed.[87-90]

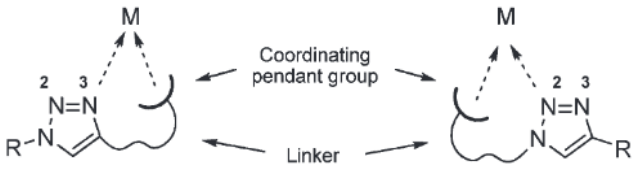
Figure 4[87]



In addition, Košmrlj and co-workers[91] studied the bidentate chelating properties of differently substituted 1,2,3-triazole species, depending on the position of the binding triazole nitrogen and the pendant group (Figure 5). It was concluded that pyridine group, in comparison with primary amine, attached to the N1 nitrogen atom preferable enhanced chelator's binding properties to the metal centre. Furthermore, it was also proven that stable 1,2,3-triazole coordination complexes could be achieved by the complexation through the N2 triazole nitrogen. As binding properties were successfully considered on cations of various transition metals including Ag^{+}, Pt^{2+}, Pd^{2+}, Ru^{2+} and Cu^{2+}, it is quite

possible that observed characteristics could be actual for a wide scope of metallic ions.[91]

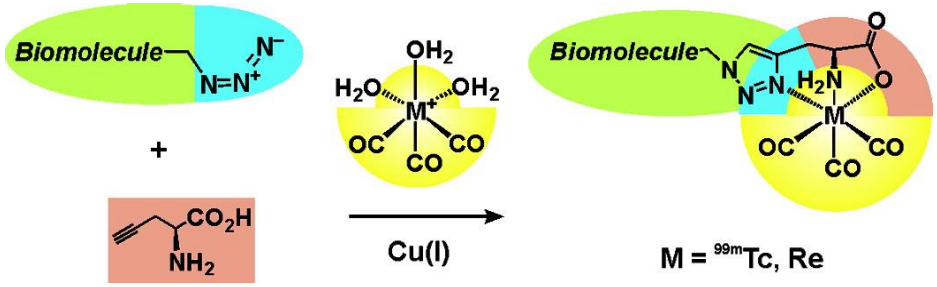
Figure 5[91]



Furthermore, a set of four metal complexes with 2-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)pyridine (ptmp) scaffolds was also developed. The last-mentioned ligands could be attached in monodentate manner or act as multidentate ligands that are able to bond through several available electron-rich binding sites to the versatile cationic centres. While in the neutral medium $PdCl_2$ is bidentately coordinated by the ptmp ligand through the N2 and N4 nitrogen atoms, under the acidic conditions the basic nitrogens are protonated, resulting in monodentate coordination of palladium centre through the electron rich N3 nitrogen of ptmp ligand.[92]

Approximately one decade ago, Schibli et al.[93] introduced »click-to-chelate« approach by combining numerous alkyne and azide compounds with propargyl and azide modified L-glycine and L-alanine, resulting in 1,2,3-triazole building blocks (Scheme 26). Those, attached to the metal centre through the more basic N3 nitrogen, were labelled as »regular«, while rarer N2-coordinated were designated as »inverse« chelators.[93]

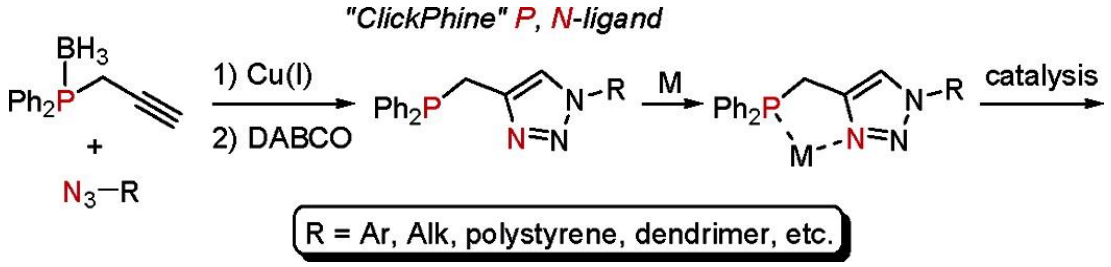
Scheme 26[93]



By preparation of a class of bidentate P,N-type ligands, a new term »clickPhine«[94] was introduced into the »click chemistry«. In addition, it was also the first known study that reported usage of triazoles as nitrogen donors in P,N ligands. The authors emphasize the desirable properties of last-mentioned compounds, including easy synthetic accessibilities and great tuning capabilities of their electronic and steric characteristics. Prepared chelators were further immobilised to the coordination centre. Obtained palladium(II)-allyl complexes could be either bonded in monodentate way only through the P-donor or in the

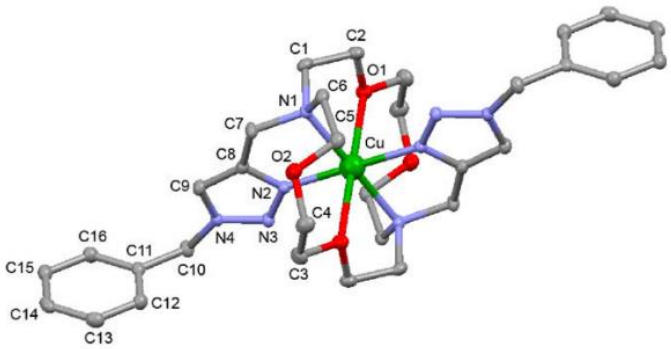
chelate fashion through the N3 nitrogen of 1,2,3-triazole scaffold and phosphor (Scheme 27). Finally, high catalytic activities and selective properties of synthesized ligands, resulting in higher initial rates, were also observed.[94]

Scheme 27[94]



Taking into account only polydentate ligands containing 1,4-disubstituted-1,2,3-triazole scaffolds, Lewis' group published various methods for the bifunctional ligands preparation that could be used during the »click-conjugation« to the peptides.[95] Similarly, Joly and co-workers reported diaza-crown ether based species, modified by two 1,2,3-triazole units as sidearms. The triazole bridges were attached through the position 4 to the nitrogen atoms of last-mentioned crown ether (Figure 6).[96]

Figure 6[96]

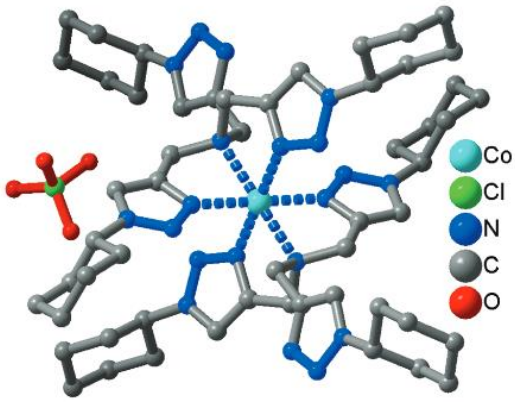


Lammertsma's group[97] developed a series of scorpion-like ligands containing three P-substituted 1,2,3-triazole units. The phosphate based scorpionate ligands were prepared by Huisgen cycloaddition between tris(ethynyl)phosphine oxide and phenyl azide compound. What is more, phosphorous pinnacle is able to bond also on additional metal centre, when two cations are presented. The achieved compounds could be potentially used in the field of homogenous catalysis.[97]

In addition, four types of tripodal 1,2,3-triazole »click-ligands« were synthesized and further utilized for the formation of various cobalt(II) complexes. According to authors' statement, it was also the premier known usage of tridentate »click-derived« 1,2,3-triazole based ligands for spin-crossover compounds preparation. Cobalt(II) centre was octahedrally coordinated with two tridentate

molecules through the central amine nitrogen and two 1,2,3-triazole N-atoms (Figure 7). Desirably, ligands' structural flexibility results in simple alteration of coordination and therefore contributes to system's bistability, which makes »click-based« ligands desirable and versatile species.[98]

Figure 7[98]



What is more, various tetradentate ligands based on ethylene diamine were bonded to Mn(II), Fe(II), Ni(II) and Zn(II) metallic centres through the two N3 triazole nitrogen and two amine nitrogen atoms. Obtained manganese complexes were additionally tested for their catalytic activities during the epoxidation of different terminal and aliphatic alkenes.[99]

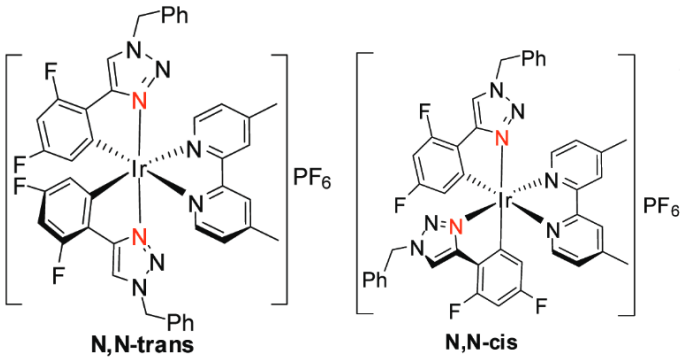
Finally, another attempt of tetradentate ligand formation was realised by Mascal's group,[100] which introduced phenyltriazole units to the azatriquinacene scaffold. Synthesized ligands were then attached to the Zn(II) and Co(II) metal centres resulting in trigonal bipyramidal coordination through the azatriquinacene central nitrogen and three N3 1,2,3-triazole nitrogen atoms.[100]

3.2 Photophysical and electrochemical characteristics

Because of well-known highly potential utilization of various cyclometalated complexes in sensor applications, as well as display and light-emitting diode (OLED) devices,[101,102] Schubert's group focused on preparation of »bis-cyclometalated iridium(III) complexes with 4-phenyl-1*H*-[1,2,3]triazole« using copper(I) catalysed »click reaction«.[103] Moreover, iridium(III)-1,2,3-triazole moieties also exhibit strong phosphorescence at standard conditions and spectral blue-shifting behaviour. In accordance to the studies of several ligand systems, the iridium(III) bis- and tris-species were recognised as greatly promising in the field of optical and electrical applications.[103]

In addition, 4-(2,4-difluorophenyl)-1,2,3-triazole derivatives (Figure 8) were independently prepared by De Cola[104] and Colman[105] groups. In both cases, cationic cyclometalated iridium(III) complexes were additionally stabilised by fluorine electron-withdrawing groups and exhibited blue-shift behaviour.[102,104,105] While De Cola reported colour change in the range from yellow to sky-blue as a result of ligands tuning, Colman compared photophysical properties of cis and trans geometric isomers.[104,105] The former showed higher luminance in electroluminescent devices than the latter.[104]

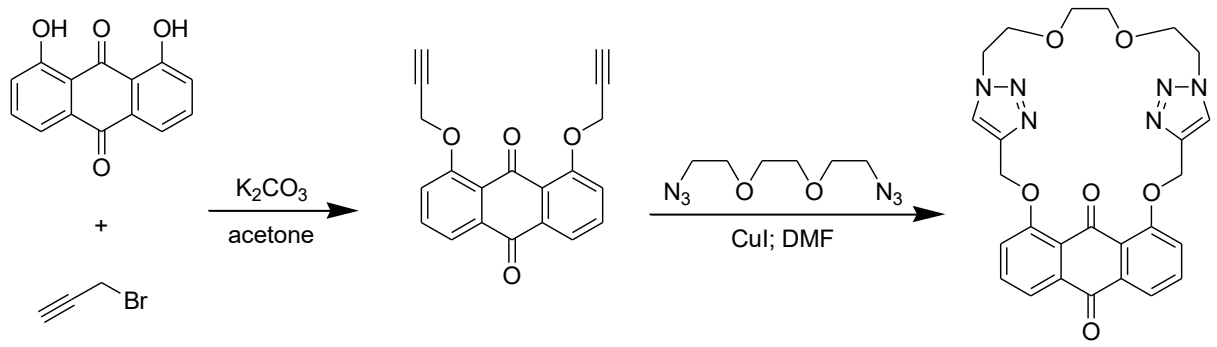
Figure 8[104]



Apart from iridium(III) metallic centre, ruthenium(II) ion was also used for preparation of several other cyclometallated complexes.[27,101] Yang and co-workers synthesized several bis-tridentate and tris-bidentate ruthenium(II) complexes consisted of 1,2,3-triazoles as ligands. Their electronic properties are easily regulated in accordance to the absence or presence of other ligands bonded to the metallic centre. In addition, »metal-to-ligand« charge transfer absorption maximums were measured for both, bidentate and tridentate types of cyclometallates. It was established that absorption maximums for the former appears at lower energy than those for the latter.[106]

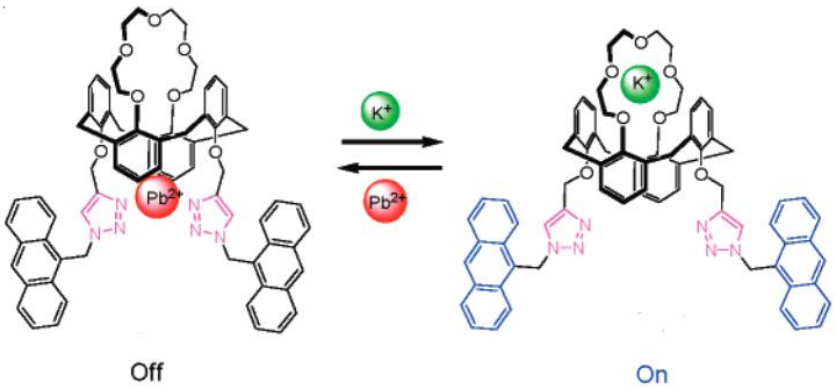
Kim's group[107] developed a photoactive 1,2,3-triazole based cyclic ligand (Scheme 28) that was coordinated to several metal centres. While most cations exhibited no photo-activity, Al^{3+} ion coordinated with two molecules of prepared ligand showed intensive band at wavelength of approximately 565 nm, indicating its possible utilisation as an effective chemosensor for the aluminium(III) species.[107]

Scheme 28



Moreover, Chung's laboratory[108] reported a novel type of chemophore with two cationic binding places, one of which was a triazole unit (Figure 9). Binding properties of 15 different metals ions were examined. It was established that one group of ions (Pb^{2+}, Cr^{3+}, Hg^{2+} and Cu^{2+}) greatly suppress the fluorescence activity of chemosensors, while the other (K^{+}, Zn^{2+} and Ba^{2+}) reactivate it.[108]

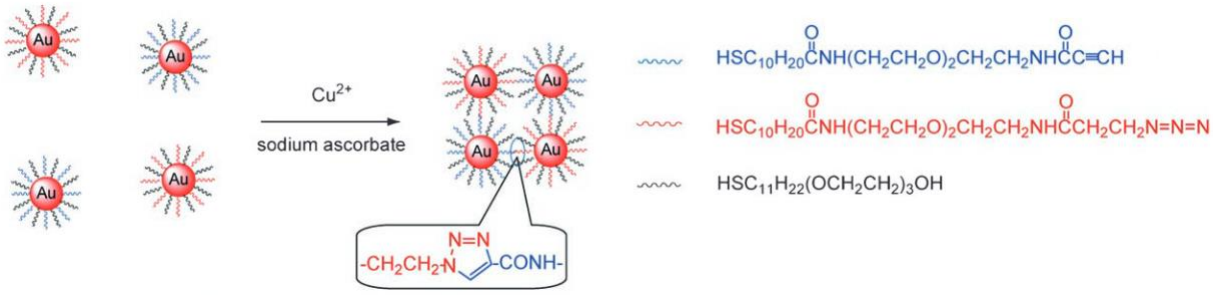
Figure 9[108]



Similarly, Yang's[109] and Vicens'[110] groups independently developed the triazole based calyx[4]arenes chemoreceptors with single and double pyrene units, where triazole moieties acted as bridge linkages and also as cation binding sites.[109,110] Yang established that the mono-pyrene substrate shows affinity only to Cu^{2+} ions, while compound containing two pyrene subunits forms coordination complexes with a wide range of heavy metals.[109] On the other hand, Vincens focused mostly on preparation and properties interrogation of Zn^{2+} and Cd^{2+} calyx[4]arenes complexes, proving their indisputable usefulness as selective chemophores.[110]

Golden nano-particles aggregates (Scheme 29) for sensitive and accurate detection of Cu^{2+} ions were developed by Zhou and co-workers.[111] In the presence of bivalent copper, the pink solution of chemophore was immediately discoloured. It was recognised as exceedingly selective even in the presence of high quantities of other interfering metal ions.[111]

Scheme 29[111]



Analogously, bifunctionalized triazole-carboxyl silver nanoparticles (Figure 10) were prepared and tested over the several metal cations, obtaining a characteristic response only for Co^{2+} ions. Apart from the colour change from yellow to red, a redshift in UV-VIS spectra was also detected. This chemosensor could be efficiently exploited in detection of Co^{2+} species in water till the concentration of 10^{-5} mol/L.[112]

Figure 10[112]

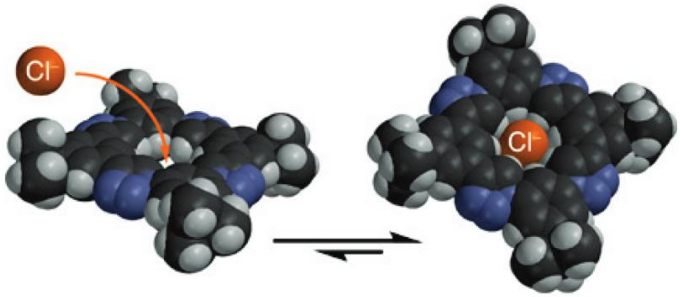
Besides the cations' receptors, numerous supramolecular species for anions' detection have also been developed during the last decade. The interactions between anions and sensors base on hydrogen bonds, ion pairs, Coulomb forces and coordinative as well as π-stacking interactions.[113]

Approximately a year after preparing a chemophore for detection of Hg^{2+} species, the Pandey's group[114] also developed a selective colorimetric detector for iodine I^- anions determination based on bile-acid polymeric compound in the presence of silver nano-particles. Afterwards, a series of anions have been interrogated for their optical activities, however only iodine species caused in visible change, resulting in a discolouration of the testing solution.[114]

Bachas et al.[115] reported preparation of halide-selective ionophore, containing a macrocyclic cavity (Figure 11) that enables interaction with spherical chlorine and bromine anions through the eight H-bonds. This sensor belongs to the group of triazolophanes and has been successfully used in poly(vinyl chloride)

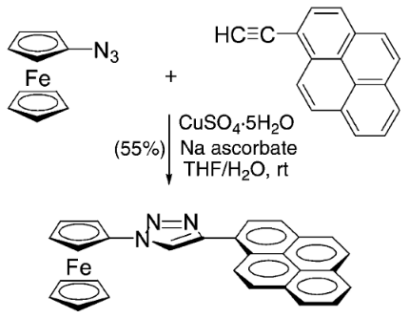
membrane electrodes during determination of Cl^- and Br^- species in horse serum.[115]

Figure 11[115]



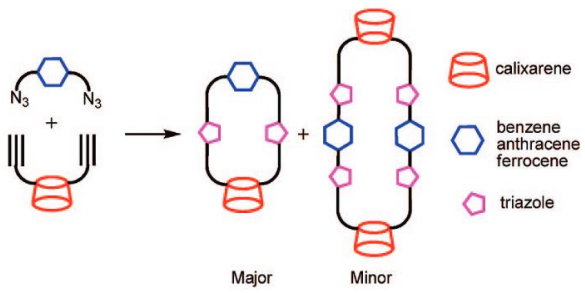
An effective and highly selective chemosensor for pyrophosphate ($HP_2O_7^{3-}$) determination was developed by combining ferrocene and pyrene units through the 1,2,3-triazole building blocks (Figure 12). The obtained 2:1 ligand-to-metal ratio complex exhibited a change in electrochemical behaviour and a considerable increase in fluorescence in comparison with the ligand monomer. Even though, ferrocene dyad has been tested on several negative species, the cathodic shift was observed only during the step-wise addition of $HP_2O_7^{3-}$.[116]

Figure 12[116]



During the attempts of nano-tubes and cavitands preparation from calyx[4]arenes, the chemophores possessing bis-1,2,3-triazole segments (Figure 13) were prepared by copper(I) catalysed cycloaddition between bis-azide and bis-alkyne species. The obtained cavitand was able to interact with bromine and iodine anions, resulting in slight stiffening of fluorescence intensity.[117]

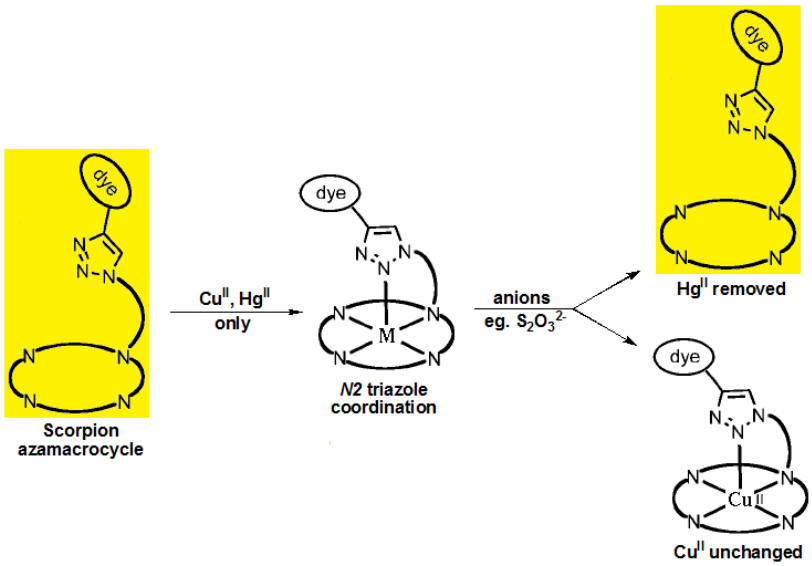
Figure 13[117]



Although, cation-anion chemophores are pretty rare, a few systems of that type have already been developed.[113]

Rutledge et al.[118] prepared a fluorescent 1,2,3-triazole based detector for detection of Cu(II) and Hg(II) species (Figure 14). It demonstrated high selectivity in the presence of other competing cations and also great performance in neutral, as well as saline water. What is more, prepared complexes with copper(II) and mercury(II) ions are the first known species that have been coordinated to the electron-deficient N2 atom of triazole ring. When Hg^{2+} or Cu^{2+} metal ions are added to the ligand, a considerable decrease in fluorescence intensity is detected. However, during the following addition of thiosulfate or iodine anions, the fluorescence is recovered in the case of mercury(II) cations, but not also in the case of bivalent copper. This observation could be advantageously utilized in distinguishing between the former and the latter.[118]

Figure 14



Finally, Yamato's group[119] focused on preparation of fluorescence active sensors containing pyrenes and triazoles building blocks and acting as a ratiometric selective detector for Zn^{2+} and $H_2PO_4^-$ species, simultaneously.[119]

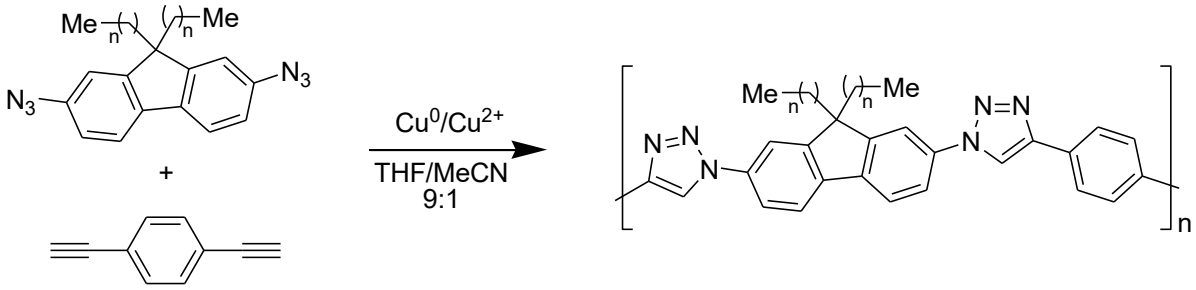
3.3 Polymerization and gelation

The 1,2,3-triazole scaffolds could also serve as bridging blocks and connectivity units in the process of polymerization. Dimitrov-Raytchev and co-workers[120] published a step-growth polymerization of α-azide-ω-alkyne monomeric units containing terminal alkyne and azide groups. Afforded 1,4-disubstituted poly(1,2,3-triazole) was further investigated and modified by iodomethane, obtaining poly(3-methyl-1,2,3-triazolium iodide) as a

poly(ionic liquid) that possesses extraordinary combination of properties such as thermal, mechanical and chemical stability, durability and ionic conductivity.[120,121]

Another appearance of 1,2,3-tiazole species in polymeric conjugated systems (Scheme 30) was described by van Steenis et al.[122] as diazide and dialkyne compounds were used in step-growth polymerization. The reaction was carried out in 9:1 THF/MeCN solvent mixture in the presence of metal copper and source of Cu^{2+} ions as a catalyst.[122]

Scheme 30



Versatile usefulness in numerous applications, enviable biocompatibility and preferable water-swelling characteristics make hydrogels promising and potentially exploitable materials.[123] Poly(N-isopropylacrylamide) based thermosensitive hydrogels (PNIPAA) were prepared *in situ* by cross-linking concept using copper(I) catalysed cycloaddition. The obtained materials were considered by scanning electron microscope (SEM) and as a result, swelling behaviour in dependence with temperature was monitored. According to the observations, all tested hydrogels were in the swollen form when the temperature was below the lower critical solution temperature (LCST), while its rising caused in hydrogels' shrinkage.[124]

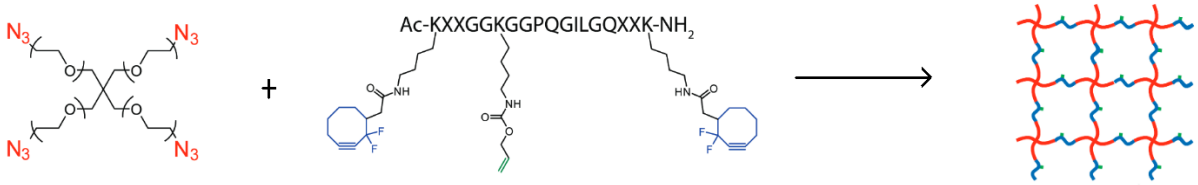
Ossipov and Hilborn[125] developed polyvinyl hydrogel (PVA), where azide and acetylene counterparts were joined together forming a triazole-binding crosslinked system. It was established that bi-terminal diazide shows a tendency to a single-end binding, and consequently reduces the rate of cross-linking and gelation capacity.[123,125] This study[125] is also known as the first one, where »click chemistry« concept was used for preparation of hydrogels. A novel approach of cross-linking was immediately accepted, as it was recognised an efficient and high-yielding reaction pathway.[125]

Due to the fact that residues of univalent copper species have been recognised as cell toxic and hardly removable, a new reaction approach of a great usefulness, including copper-free »click chemistry« mechanism, was presented.[123,126] Apart from strain-induced azide-alkyne cycloaddition,[76-78]

modification of cross-linking materials could also be used as an alternative copper-free synthetic road.[126] As a result, Clark and Kiser[126] reported *in situ* cross-linking hydrogel formation by copper-free catalysed Huisgen cycloaddition, based on combination of electron-deficient dialkynes with polymers that contain azide functional groups. Even thought, the desirable products were successfully prepared, the obtained yields at room temperature were quite low (10–34%), while the reactions times exceeded 48 hours.[126]

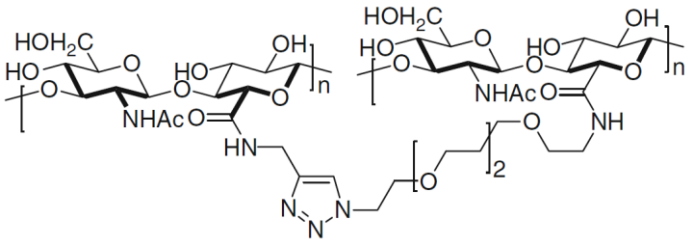
Similarly, the cytotoxicity of copper(I) species was also noted by the Anseth's group[127] and as a result, »strain-promoted« [3+2] Huisgen cycloaddition (SPAAC) was utilized as a tool for the peptide-functionalized step-growth cross-linked networks preparation (Scheme 31). Polyethylene glycol (PEG) tetraazide and bifunctional cyclooctyne-modified peptide were used as starting materials. The obtained network properties were considered and tuned by the varying in cross-linking density and connectivity as they were utilized for the purpose of dynamic 3D cell behaviour studies.[127]

Scheme 31[127]



Crescenzi and co-workers[128] synthesized a hyaluronic acid based hydrogels, obtained by the combination of azide and alkyne-modified hyaluronic acid (Figure 15). The achieved cross-linked networks, consisting of 1,2,3-triazole bridge blocks, could capture small molecules such as doxorubicin, and consequently act as controlled drug releasers.[128]

Figure 15[123]

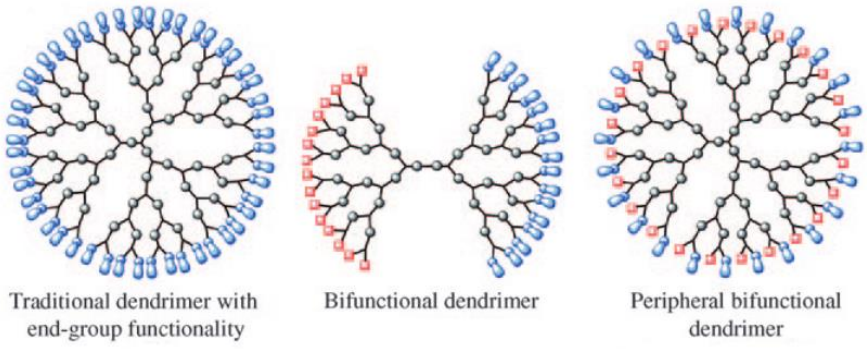


One of the most important properties of drug delivery agents is their biodegradability. Frequently, larger molecular structures are decomposed to smaller species using acid-base or enzymatic catalysed hydrolytic processes. Consequently, several degradable, practically-applicable hydrogels, based on polyester, polysaccharide or polypeptide skeletons, have already been prepared.[123]

In addition, De Geest[129] reported a novel concept of biodegradable drug-delivery microcapsules, based on 1,2,3-triazole moieties. Propargyl and azide modified dextran species were combined in the presence of Cu(II) ions and sodium ascorbate. The synthesized adducts could be potentially exploited for the labile biological drugs encapsulation, as only non-severe and harmless reaction conditions are used during their preparation.[129]

A new class of bifunctional dendritic species containing both, internal and peripheral functional groups, was developed (Figure 16). They could be further used for the dendritic nano-particles production or as multifunctional hydrogel cross-linkers. By selecting the efficient copper(I) catalysed transformation pathway, harsh reaction conditions were successfully circumvented.[130]

Figure 16[130]



Finally, the integrity of crystal's orderliness and polymer's elasticity led the scientists to join both qualities in so called liquid crystal (LC) gels. They could be used in numerous applications as they exhibit noticeable changes concerning their forms, cross-linking rates and optical characteristics. Consequently, Grubbs and co-workers[131] prepared a set of LC gels by crosslinking of the azide-terminated telechelic liquid crystals and triacetylenes. Taking into consideration electro-optical characteristics, it was established that unconstrained gels display rapid and fully-reversible switching properties. Furthermore, liquid crystal networks, processed from longer polymer sets, showed higher switching rate than those prepared from the shorter strands.[131]

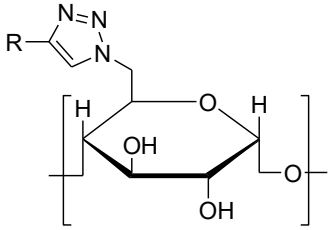
3.4 Antioxidant activities

In addition, 1,2,3-triazole species exhibit high stability towards reductive, oxidative, acidic and also basic environments. Because of their well-expressed dipole moments, they are able to take part in π-stacking and dipole-dipole interactions, and consequently facilitate their potential bindings to the target molecules.[132]

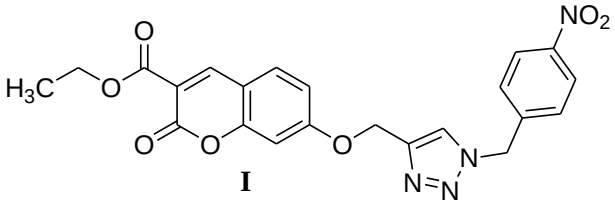
Chemical modification of starch could considerably improve its antioxidant characteristics. Polymeric 6-azido-6-deoxy starch in DMSO was combined with terminal alkyne derivatives in the presence of copper(I) catalyst to provide corresponding water soluble HMTST, HETST, HPTST and HBTST starch counterparts (Figure 17). Obtained species were tested for their antioxidant activities against superoxide, DPPH and hydroxyl radicals. It was concluded that strong electron-donating groups remarkably improve starch antioxidant properties.[133]

Figure 17

R	Abbrev.
OH	HMTST
OH	HETST
OH	HPTST
OH	HBTST

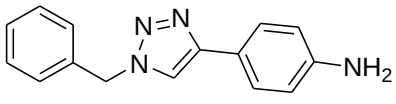


Shingate's group[134] synthesized a novel class of coumarin derivatives including 1,2,3-triazole scaffolds. The resulted compounds were screened for their antioxidant activities using DPPH radical scavenging essay. According to the results, derivative **I** was recognised as the most potent antioxidant in the series.[134]

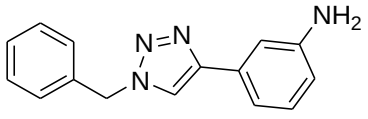


I

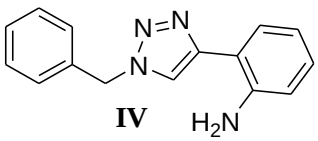
Similarly, Montes-Ávila[135] et al. described a modified method of DPPH scavenging activities assessment. Various 1-benzyl-1,2,3-triazole counterparts were mixed with DPPH solution in methanol. In accordance to derogation in measured absorbance value, potential antioxidant activities of interrogated compounds were evaluated, while bellow mentioned derivatives **II**–**IV** were highlighted.[135]



II

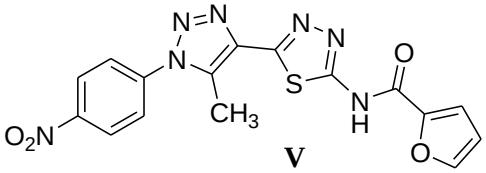


III



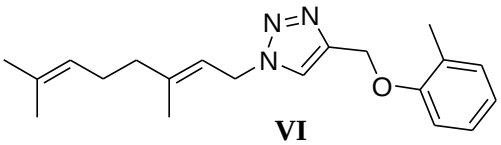
IV

Furthermore, a small library of 1,2,3-triazole bearing amides was examined for their free-radical scavenging characteristics. Three species from the series showed potent behaviour, while the best antioxidant properties were observed for the compound **V**.[136]

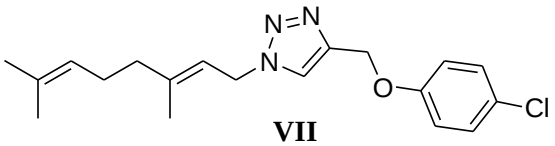


V

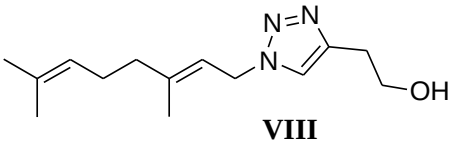
Finally, Dubey et al.[137] synthesized 1,2,3-triazole based compounds that were screened for their antioxidant properties. The DPPH free radicals scavenging activities of tested species were established according to their inhibitory concentration values (IC_{50}), and compared with the antioxidant standard. It turned out that compounds **VI**–**IX** possess excellent antioxidant characteristics.[137]



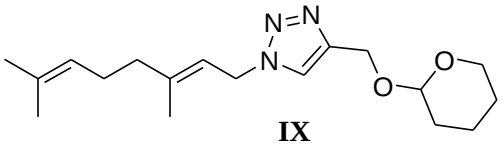
VI



VII



VIII



IX

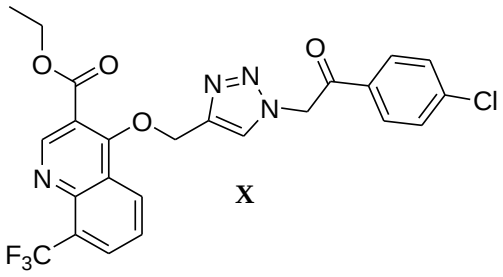
3.5 Medical activities

The primary clues of 1,2,3-triazole examination in medicinal purposes dated back in the first half of 20th century, when 1,2,3-triazolo[4,5-*d*] pyrimidine was mentioned as potential anticancer and anti-malignant agent. Because of its desirable and perspective biological activities, 1,2,3-triazole based heterocyclic chemistry was labelled as »the corner stone« of the medicinal chemistry.[132] Until nowadays, numerous 1,2,3-triazole based species have been prepared and examined for their biological activities. Consequently, a wide range of antimicrobial, antiviral, anti-inflammatory, anti-tubercular, anticancer and antitumor, as well as anti-Alzheimer's disease characteristics were detected and successfully evaluated for the tested compounds.

3.5.1 Antimicrobial and antiviral activities

Multi-step reaction approach was used for the preparation of three novel classes of 1,2,3-triazole-based 8-trifluoromethylquinoline species. As expected,

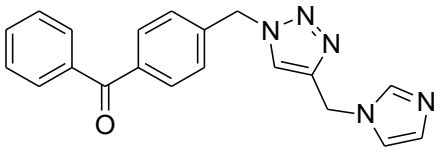
derivatives including electron withdrawing groups on 1,2,3-triazole frameworks were prepared in higher yields than those with electron donating substituents.[138] Obtained final compounds were additionally screened for their antimicrobial activities against *Escherichia coli*, *Pseudomonas aeruginosa* and *Bacillus subtilis* bacteria using ciprofloxacin as a standard. Taking into account inhibition zones' diameters and their appearance, the compounds' activities were examined quantitatively as well as qualitatively. Bellow presented derivative **X** was recognised as the most active against the *E. coli* bacterial strain.[138]



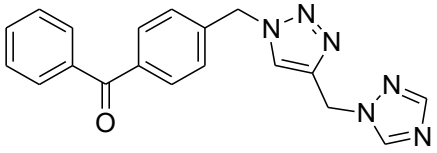
X

Different counterparts were further tested for antifungal activities against *Candida albicans*, *Aspergillus flavus* and *Chrysosporium keratinophilum* utilizing fluconazole as a standard. For approximately two-thirds of all examined samples, the inhibition zones were detected.[138]

Analogously, a new set of 1,2,3-triazolyl methylbenzophenones was screened against Gram-positive bacteria (*Staphylococcus aureus, Bacillus subtilis*), Gram-negative bacteria (*Escherichia coli*) and yeast (*Candida albicans*). Although, compounds **XI** and **XII** exhibited minor resistance against *E. coli*, they were highly effective inhibitors in all other cases, and therefore confirmed as promising antimicrobial species.[139]

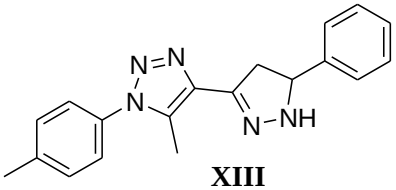


XI

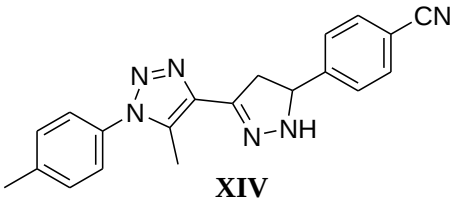


XII

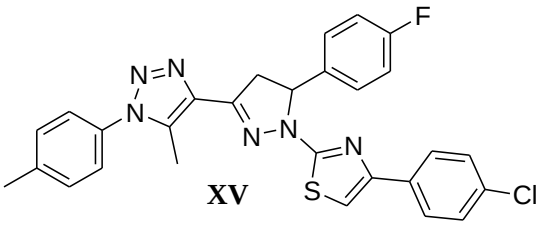
Newly prepared pyrazolyl-1,2,3-triazoles and 1,2,3-triazol-4-yl-pyrazolylthiazol compounds were also tested for their antimicrobial properties and minimum inhibitory concentrations (MIC) against Gram-positive bacteria (*Bacillus megaterium*, *Staphylococcus aureus*, *Sarcina lutea*, *Bacillus subtilis*), Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebseilla pneumonia*), as well as yeast (*Candida albicans*, *Saccharomyces cerevisiae*). While most of synthesized counterparts showed desirable antimicrobial activities, bellow mentioned four species (**XIII**–**XVI**) performed extraordinary characteristics.[140]



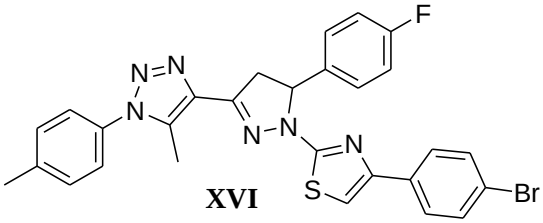
XIII



XIV

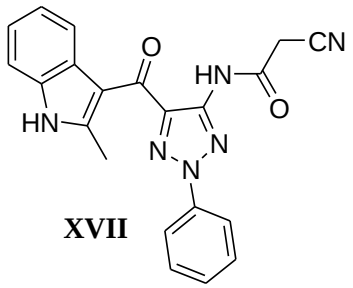


XV



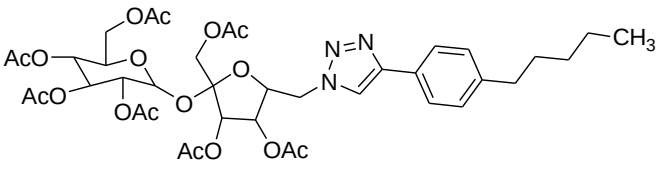
XVI

Furthermore, various target species including pyrazole and pyrazolo[1,5-*a*]-pyrimidine frameworks were synthesized and screened for their activities against Gram-positive (*Staphylococcus aureus*, *Bacillus subtilis*), Gram-negative bacteria (*Escherichia coli*) and yeast (*Candida albicans*). Widely known antibacterial agent ampicillin was used as a reference. According to the obtained results, different derivatives exhibited promising antimicrobial characteristics, among which the counterpart **XVII** is a standout example with the inhibition zone of 9.3 mm against *Bacillus subtilis*.[141]

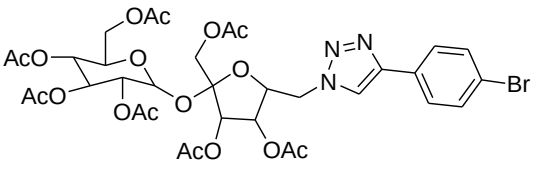


XVII

Several 1,2,3-triazole based sucrose derivatives were also examined for antifungal, antibacterial and cytotoxic activities. Compounds **XVIII** and **XIX** were detected as the most promising in the series. While the former was the strongest antibacterial agent, the latter exhibited the most potent antifungal characteristics.[142]



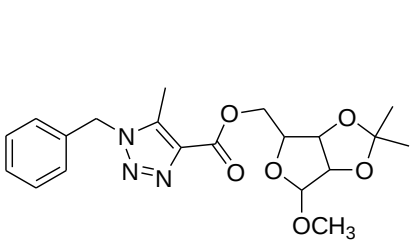
XVIII



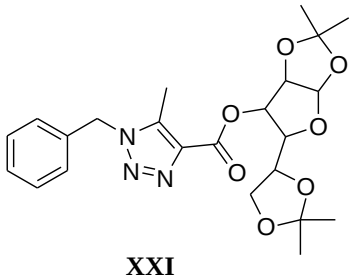
XIX

After the appearance of the human immuno-deficiency virus (HIV) that has already killed over 35 million people around the world, a strong tendency of

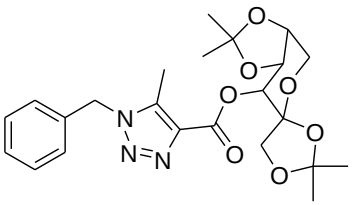
development of an effective anti-HIV drug arose. One of the numerous attempts of its preparation was carried out by Silva and co-workers,[143] who synthesized two classes of various 1-benzyl-1*H*-1,2,3-triazole frameworks bonded to different carbohydrate scaffolds. Afterwards, obtained species were tested for their HIV reverse transcriptase abilities. In accordance with the results, the protected carbohydrate 1,2,3-triazole-based compounds exhibited higher inhibitive effectiveness than the unprotected ones. Out of all screened samples, three bellow presented derivatives (**XX**–**XXII**) were recognised as the most potent and promising counterparts in the series.[143]



XX

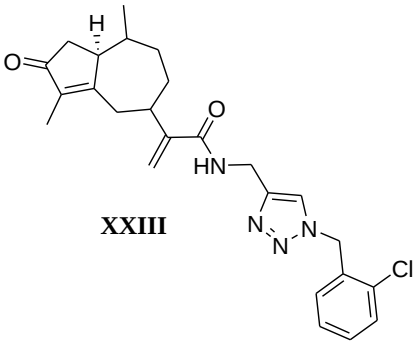


XXI

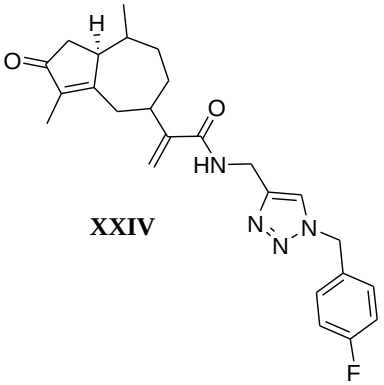


XXII

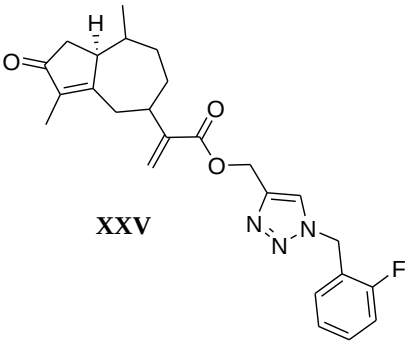
He et al.[144] reported synthesis of two classes of rupestonic acid derivatives including (1-substituted-1*H*-1,2,3-triazol-4-yl)methyl esters and N-(1-substituted-1*H*-1,2,3-triazol-4-yl)methyl amides that were further examined for their antiviral properties against the viruses influenza A and B. It was concluded that compounds **XXIII**–**XXV**, tested in a plaque essay experiment, were recognised as better inhibitors than ribavirin (RBV) standard drug, and therefore highly potent antiviral candidates.[144]



XXIII



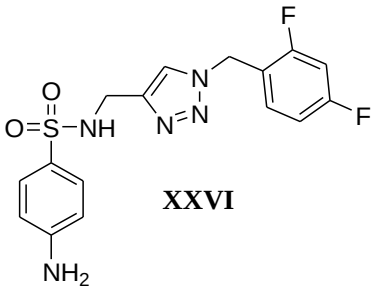
XXIV



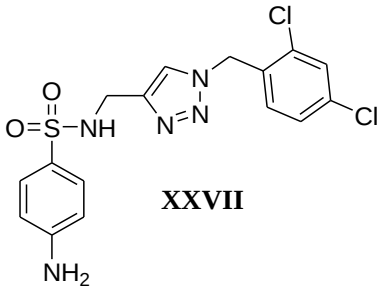
XXV

A novel class of sulphanilamide derivatives, differing in alkyl chain lengths and benzyl framework substitution position, was screened against a wide range of microorganisms including *E. typhosa*, *B. subtilis*, *S. aureus*, *E. coli*, MRSA, *C. albicans*, *P. aeruginosa*, *C. mycoderma* and *S. dysenteriae*. Most of the tested species exhibited moderate to good activities against all considered organisms, while compounds **XXVI**–**XXVIII** performed as highly potent inhibitors. Furthermore, it was proved that 1,2,3-triazole scaffolds, introduced into the

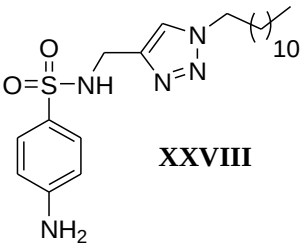
sulphonamide moieties, play a key role in microorganisms' inhibition processes.[145]



XXVI



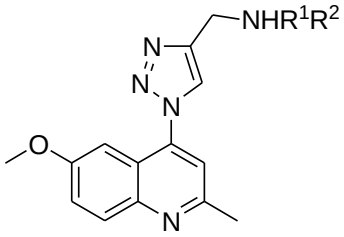
XXVII



XXVIII

Finally, a set of quinoline frameworks (Figure 18) was screened for antimicrobial characteristics. All derivatives were firstly examined against *Staphylococcus aureus, Klebsiella pneumonia, Escherichia coli, S. Pyogenes,* and *Pseudomonas aeruginosa*. In most cases, moderate to very good inhibition activities were detected. Similarly, the same compounds were tested for their antifungal properties against *Aspergillus fumigatus, Trichophyton mentagrophytes, Aspergillus flavus, Candida albicans* and *Penicillium marneffei*. By evaluating the zone inhibition diameters and subsequent comparison with standard antifungal drug ciclopirox olamine, it was concluded that most synthesized counterparts exhibit good to excellent antifungal inhibition activities.[146]

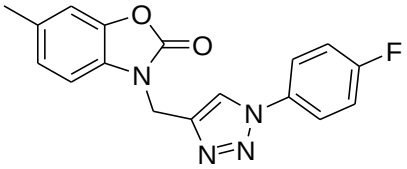
Figure 18



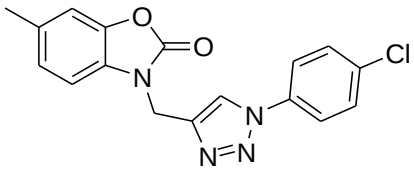
NHR^1R^2 ---> 25 different amines

3.5.2 Anti-inflammatory activities

Numerous 1,2,3-triazole based benzoxazolinone derivatives were examined for their anti-inflammatory characteristics. Vigorous *in vivo* anti-inflammatory activities were detected in cases of compounds **XXIX** and **XXX**. While former showed inhibition rate of 81.4% after three-hour and 80.6% after five-hour post-carrageenan administration, the latter exhibited 74.0% and 76.7% inhibition in the time periods of three and five hours, respectively. Attained results were compared with the activity of well-known anti-inflammatory drug indomethacin representing 79.1% and 82.3% inhibition after three-hour and five-hour post-carrageenan administration, respectively.[147]



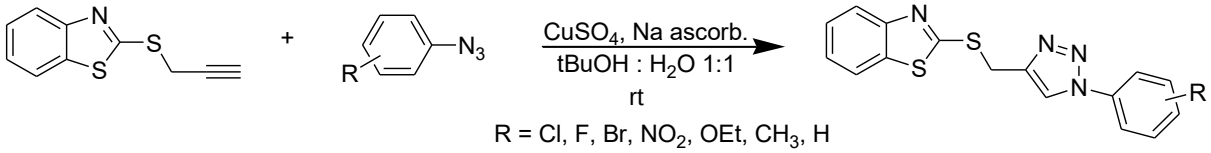
XXIX



XXX

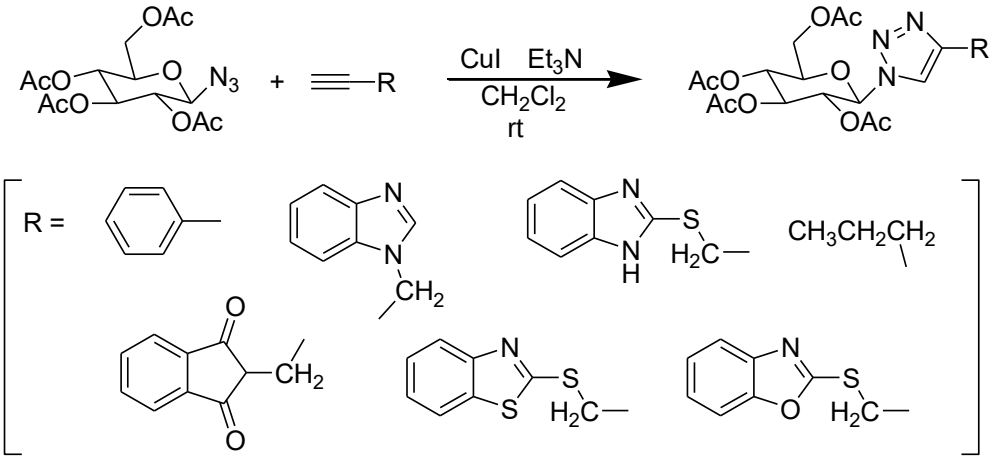
In addition, a group of 2-mercaptobenzothiazole bis-heterocycles (Scheme 32) was prepared and tested for anti-inflammatory properties and derived results were evaluated using the ibuprofen standard drug. According to the scientific findings, the most potent anti-inflammatory activities were exhibited by the species, where electron-withdrawing groups were bonded to the *para* position of the aromatic ring.[148]

Scheme 32



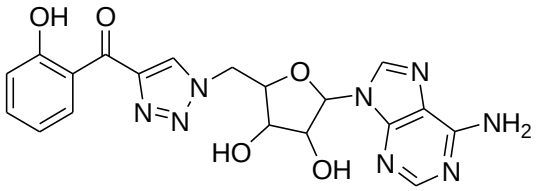
Finally, Oliveira and co-workers[149] published a new set of 1,4-disubstituted N-*β*-D-glucopyranosyl-1,2,3-triazole compounds, obtained by combining 2,3,4,6-tetra-O-acetyl-*β*-D-glucopyranosyl azide with seven different terminal alkynes (Scheme 33). The reactions were carried out under the ultrasound radiation and in the presence of copper(I) iodide and triethylamine resulting in yields up to 99%. Desirable anti-inflammatory properties were observed in the cases of glycoconjugates including benzoheterocyclic scaffolds.[149]

Scheme 33



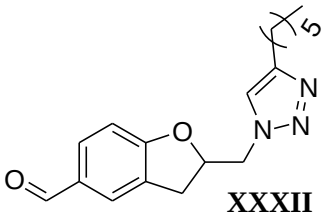
3.5.3 Antitubercular activities

A novel potent inhibitor of adenylate-forming MbtA enzyme was developed by Somu and co-workers.[150] What is more, prepared acylsulfamide compound **XXXI** showed inhibition activity against *Mycobacterium tuberculosis*, and consequently promising properties that could be potentially exploited for antibiotics preparation.[150]



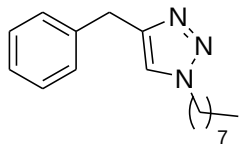
XXXI

Similarly, different 2-(azidomethyl)-dihydronaphtho(benzo)furans were also screened against last-mentioned *M. tuberculosis* strain using agar microdilution method. The best anti-tubercular characteristics were observed for the compound **XXXII**.[151]

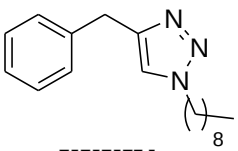


XXXII

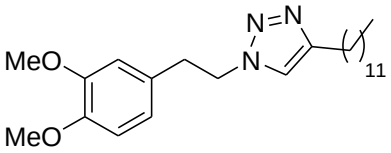
Menendez and co-workers[152,153] focused on 1,2,3-triazole scaffolds as potential InhA and *M. tuberculosis* inhibitors. Numerous substituents were introduced to the 1,2,3-triazole skeleton, resulting in a large variety of compounds that were later interrogated for antitubercular activities. Furthermore, effects of the substituents nature, alkyl chains length and triazole-frame linking positions were taken into consideration. All prepared species were appraised for minimal inhibitory concentrations (MIC) on *Mycobacterium tuberculosis* and tested for their activities against InhA. The obtained results were further compared with the activity of well-known antibacterial and antifungal agent triclosan. Even though, several prepared compounds exhibited desirable properties against InhA, the best inhibiting activities were established for the counterparts **XXXIII** and **XXXIV** that contained a single carbon atom between aromatic and triazole frames. On the other hand, the derivative **XXXV**, which showed the lowest minimal inhibitory concentration value, was completely inactive towards InhA.[152,153]



XXXIII

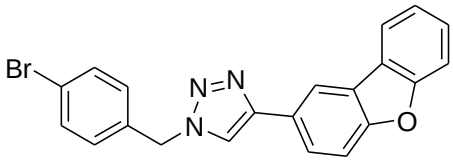


XXXIV



XXXV

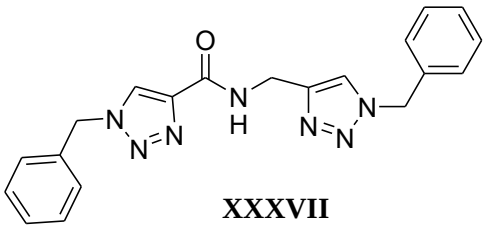
Finally, a class of dibenzo[*b*,*d*]furan-1,2,3-triazole compounds was examined against *Mycobacterium tuberculosis* (H37Rv) strain. It turned out that the derivative **XXXVI** exhibited the superior combination of its antitubercular activity and the mildest cytotoxicity.[154]



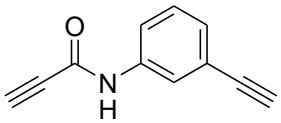
XXXVI

3.5.4 Anticancer and antitumor activities

Various bis-alkyne amides and their mono- and bis-triazole derivatives were synthesized and screened against highly invasive melanoma B16 cell line. Apart from bis-triazole species that showed anticancer activities in micromolar and nanomolar ranges, bis-alkyne compounds, containing phenyl ring between both triple bonds, surprisingly also exhibited antitumor characteristics. Especially, compounds **XXXVII** and **XXXVIII** were recognised as the most potent materials against B16 melanoma cells, and therefore representative examples of both last-mentioned functional groups classes.[155]

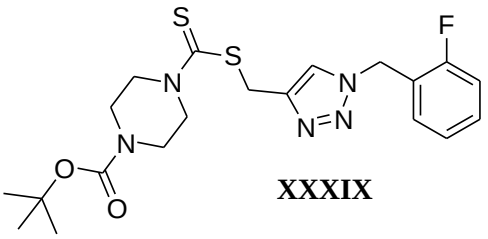


XXXVII

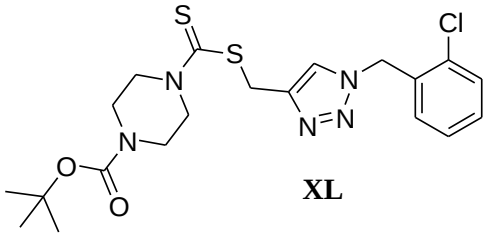


XXXVIII

In addition, Liu's group[156] reported preparation of novel 1,2,3-triazole-dithiocarbamate hybrids that were examined for their potential antitumor properties against C-803, MCF-7, PC-3 and EC-109 human cancer cells. Most of the tested derivatives exhibited at least moderate anticancer activities, while the counterparts **XXXIX** and **XL** were recognised the most potent in the series.[156]

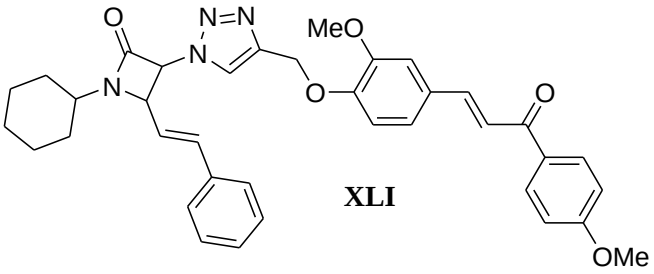


XXXIX



XL

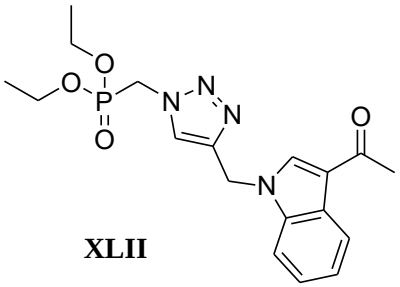
Several *β*-lactam-chalcone bifunctional hybrids were screened against different cancer cell lines such as A-549(lung), PC-3(prostate), THP-1(leukemia), and Caco-2(colon). The most potent properties were observed for the counterpart **XLI**.[157]



XLI

Moreover, 1-(2-picolyl)-4-phenyl-1*H*-1,2,3-triazole (ppt) derivatives, also utilized as ligands in ruthenium(II) complexes, were examined for their potential antitumor and anticancer activities. Surprisingly, almost all investigated compounds were less cytotoxic than already several decades well-established cisplatin. The exception was one of the tested species, exhibiting selective cytostatic activity against human lung carcinoma cells.[158]

Finally, acyclonucleotide analogues containing 1,2,3-triazole bridging blocks were screened against human *T-lymphocyte* (CEM), *murine leukaemia* (L1210) and *human cervix carcinoma* (HeLa) cells. The compound **XLII** grabs attention due to its low half maximal inhibitory concentration (IC_{50}) value of only 2.78 μM for CEM cell line.[159]

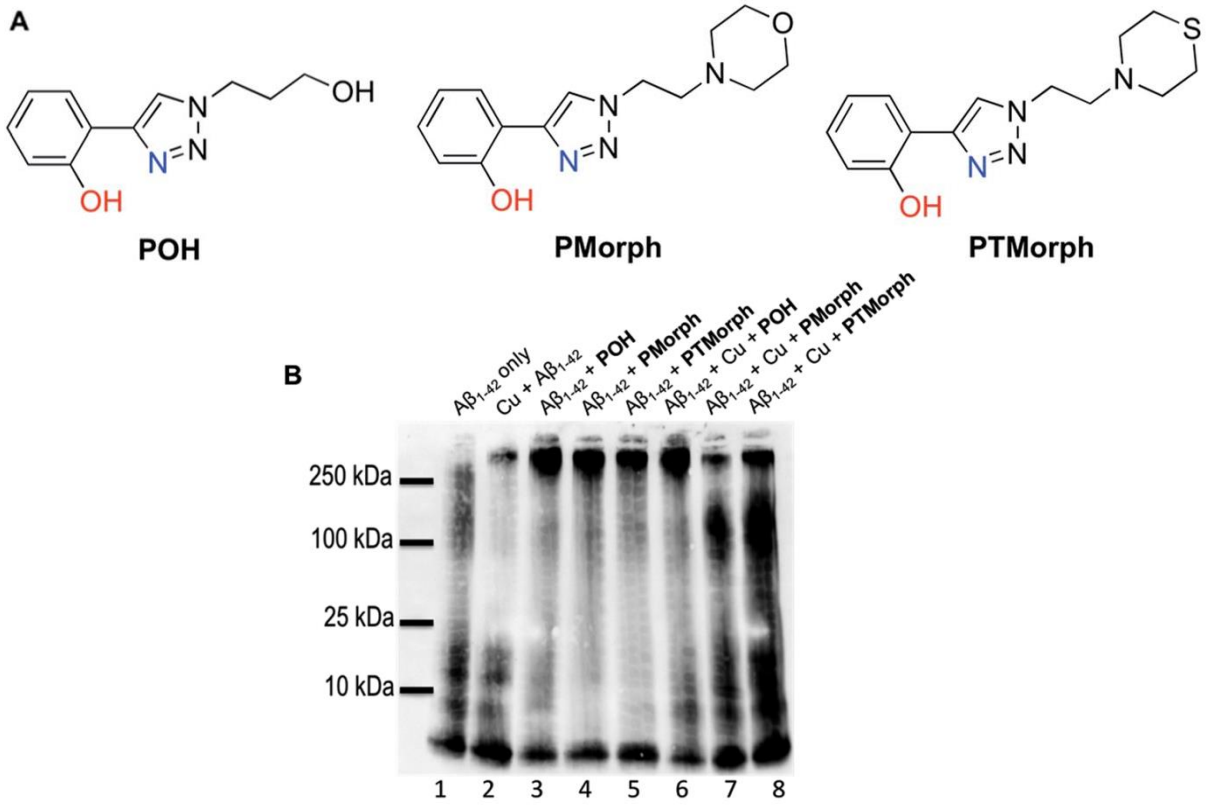


XLII

3.5.5 Anti-Alzheimer's disease activities

Three phenol-triazole-based »multi-target-directed« ligands were synthesized using well-known 1,3-dipolar cycloaddition and screened for several applications, including copper-binding affinities, possible interactions with Aβ peptide and modulation of its aggregation.[160] Due to the fact that toxic Aβ oligopeptides cause neuronal cell apoptosis, they were recognised as one of the main contributors to Alzheimer's disease. The idea was to confine Aβ oligopeptides creation, and consequently encourage formation of harmless aggregates with higher molecular masses. As binding affinities of copper species to Aβ peptide are comparable with those to phenol-triazole systems, competitive interaction process, and consequently alteration of Aβ peptide aggregation was expected. POH, PMorph and PTMorph phenol-triazole chelators (Figure 19A) were individually incubated with Aβ peptide in the absence and presence of copper ions, respectively. While all three novel ligands were highly effective during the first essay, POH exhibited the most potent modulating abilities for Aβ peptide aggregation throughout the second experiment (Figure 19B).[160]

Figure 19[160]

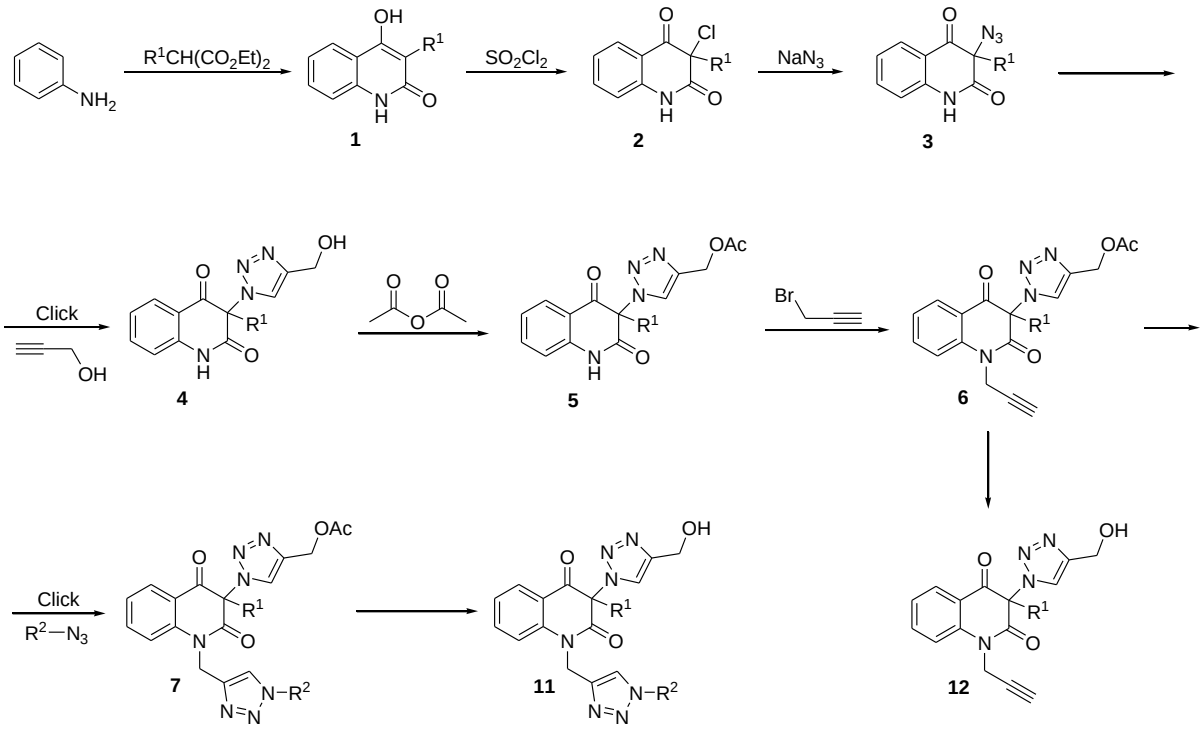


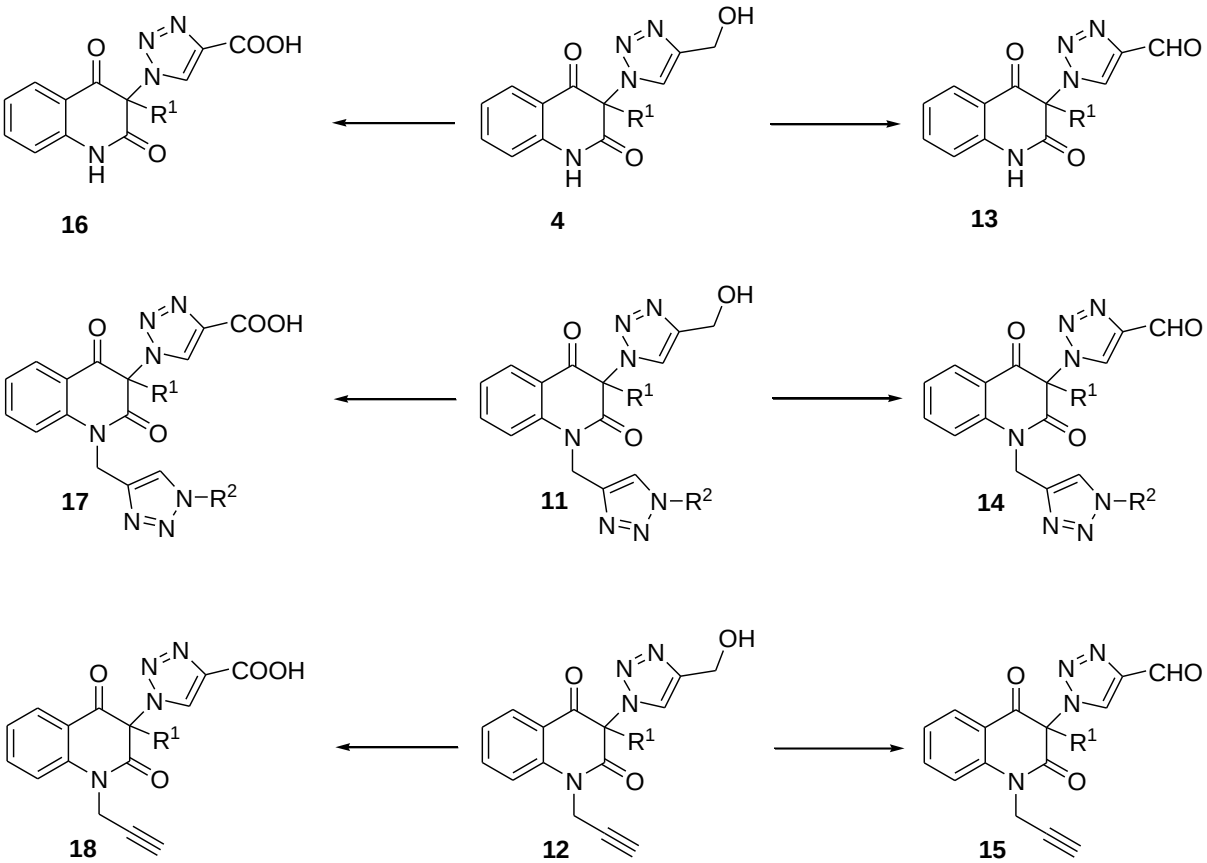
4. AIMS AND OBJECTIVES

As it is already summarized in the title, the primary consideration of my doctoral studies was preparation of various 1,2,3-triazole functionalised quinoline-2,4-dione derivatives, and according to possibilities, evaluation of their potential antimicrobial activities and photoprotective properties.

The fundamentals of dissertation topic date back in 2011, when premiere merging of 1,2,3-triazole scaffold with quinoline-2,4-dione framework was published.[43] The idea was to upgrade mono-triazole species to the appropriate bis-triazoles by the introduction of propargyl group to quinolone nitrogen, and subsequent formation of the second 1,2,3-triazole ring. As anticipated, three different organic azides were synthesized and further combined with mono-triazole propargyl derivatives, providing novel bis-triazole counterparts. According to plan, that way obtained collection of mono- and bis-triazole species was efficiently extended by preparation of different functional derivatives bearing hydroxymethyl, formyl or carboxylic group in the position four of the first 1,2,3-triazole scaffold. Establishment and optimisation of reaction conditions for alcohols deprotection and their subsequent oxidation to suitable aldehydes and carboxylic acids were also intended. The main synthetic route is presented in Scheme 34.

Scheme 34. *Synthesis of (1,2,3-triazole)-functionalised quinoline-2,4-diones.*





R^1 = Me, Ph R^2 = Bn, Ph, 2-Py

5. RESULTS AND DISCUSSION

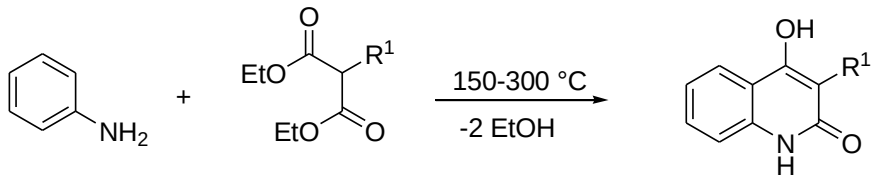
The synthesis of 1,2,3-triazole-functionalised quinolone derivatives was carried out in two parallels, performing each reaction step on both, 3-methyl and 3-phenyl quinoline-2,4-dione counterparts.[161] 3-Azidoquinoline-2,4-dione species were obtained throughout three-step,[161-163] slightly modified literature procedure, and were utilised as precursors for the following »click« reactions. The obtained yields of particular compounds are collected in tables or could be found in schemes. In addition, some accompanying experiments were carried out, to either highlight interesting properties of studied structures or to suggest and evaluate alternative synthetic ways for target compounds acquisition.

5.1 Synthesis of mono-triazole compounds

5.1.1 Precursors

The reaction sequence started with the known condensation reaction between aniline and diethyl methylmalonate or diethyl phenylmalonate, providing 4-hydroxy-3-methylquinolin-2(1*H*)-one[161] (**1a**) and 4-hydroxy-3-phenylquinolin-2(1*H*)-one[161] (**1b**), respectively. At the beginning, the reaction temperature was kept relatively low (up to 150 °C) to avoid distillation of malonate, especially in the case of diethyl methylmalonate (b.p. 200 °C / 760 mm Hg).[164] For this reason, appropriate ester was also added in 10% excess to the reaction mixture. When more than 50% of theoretical mass of ethanol was collected, and therefore amide bond between both reactants was formed, the temperature was gradually raised up to 300 °C. The yields of prepared compounds **1** are given in Scheme 35. Due to the fact that considerably lower yield was observed in the case of methyl derivative (**1a**), the transformation was also performed in the presence of nitrogen, however the obtained yield (53%) was not improved.

Scheme 35. *Preparation of compounds **1a** and **1b**.*

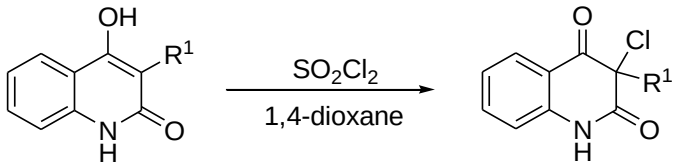


1a (R^1 = Me), 59%
1b (R^1 = Ph), 83%

Synthesized materials were then subjected to chlorination at slightly elevated temperature (40–50 °C), using sulfuryl chloride as a source of chlorine in 1,4-dioxane. During the addition of sulfuryl chloride to the reaction mixture,

white suspension of insoluble starting compound was gradually transformed into vivid yellow solution, indicating formation of 1,4-dioxane soluble chlorinated product. Desired compounds **2** were prepared in excellent yields during the time period of 30 minutes. (Scheme 36).

Scheme 36. *Preparation of compounds **2a** and **2b**.*

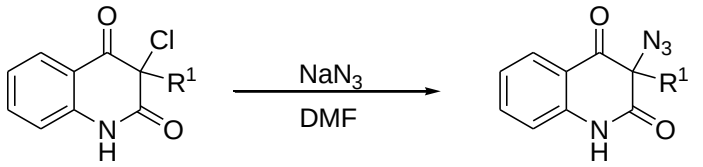


1a (R^1 = Me)
1b (R^1 = Ph)

2a (R^1 = Me), 91%
2b (R^1 = Ph), 93%

Organic azides are widely recognised as valuable partners to acetylenic compounds in 1,3-dipolar cycloaddition reactions. Although, they are assigned as hazardous and harmful species, they play an irreplaceable role in 1,2,3-triazole preparation process.[19] 3-Aziodquinoline-2,4-diones **3** were synthesized by nucleophilic displacement, where chlorine atom of a particular chloro-derivative was exchanged with the azido group. The transformation and isolation processes were carried out in darkness, as organic azides are quite unstable on light. The reactions were completed in approximately three hours, providing yields presented in Scheme 37.

Scheme 37. *Preparation of compounds **3a** and **3b**.*



2a (R^1 = Me)
2b (R^1 = Ph)

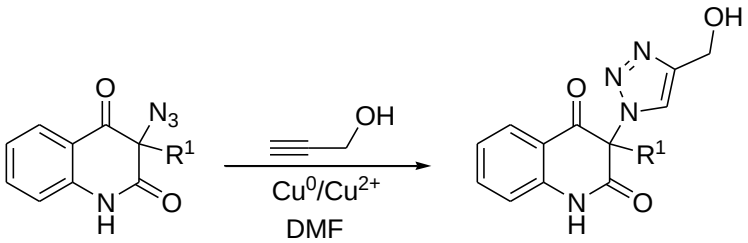
3a (R^1 = Me), 95%
3b (R^1 = Ph), 97%

5.1.2 First 1,2,3-triazole ring

Synthesized organic azides served as precursors in the reaction scheme, as they were further combined with propargyl alcohol to give suitable mono-triazoles. The transformations were carried out in the presence of metal copper and $CuSO_4 \cdot 5H_2O$ in DMF (Scheme 38) and were completed within 30 minutes. Although, relatively large quantities of copper species were added to the reaction mixtures, their residues were in most cases successfully eliminated using filtration through the silica-gel column, subsequent extraction with saturated aqueous solution of NH_4Cl, and finally crystallization from the suitable solvent.

In addition, DMF was efficiently removed by multiple dilutions with toluene and following co-distillations *in vacuo* at 50 °C. Yields of pure compounds **4** could be found in Scheme 38.

Scheme 38. *Preparation of compounds **4a** and **4b**.*

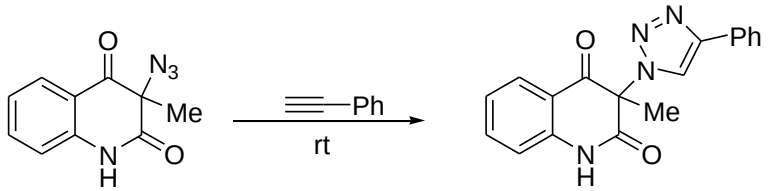


3a (R^1 = Me)
3b (R^1 = Ph)

4a (R^1 = Me), 99%
4b (R^1 = Ph), 98%

Even though, sodium ascorbate or L-ascorbic acid in the presence of Cu^{2+} ions in *t*-BuOH/H_2O 1:1 (*V*/*V*) solvent mixture is the most commonly utilised system for the purpose of 1,2,3-triazole preparation, Cu^0/Cu^{2+} catalytic pair in DMF was recognised as more convenient method for the synthesis of 1,2,3-triazole functionalised quinoline-2,4-diones. To confirm the hypothesis, 3-azido-3-methylquinoline-2,4(1*H*,3*H*)-dione was combined with phenyl acetylene in the presence of Cu^{2+} ions and L-ascorbic acid in CH_2Cl_2/H_2O 1:1 (*V*/*V*) solvent system. Although, the reaction mixture was stirred nearly 100 times longer (48 hours) than in case of Cu^0/Cu^{2+} (30 min), the obtained yield of the former (83%) was still obviously lower than in case of the latter (95%) (Table 1). Taking into account results from 2011,[43] where DMSO was also successfully used as a solvent, it was concluded that the main drawback of quinoline-2,4-dione based materials is their very low solubility in most organic solvent–water systems.

Table 1. *Preparation of compound **4c**.*



3a **4c**

Entry	Time (h)	Yield of **4c** (%)[a]
1	0.5	95[b]
2	48	83[c]

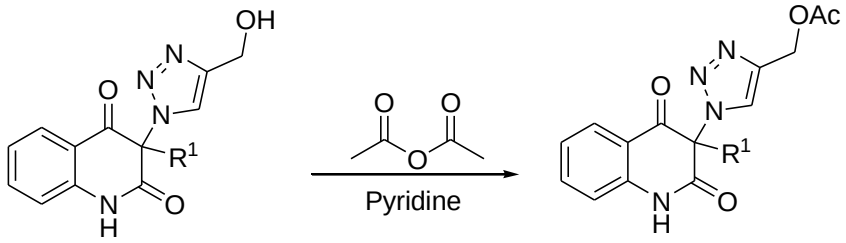
[a] Refers to percent yield of pure (by TLC and IR) isolated product. [b] Employing DMF / Cu^0 / $CuSO_4 \cdot 5H_2O$ conditions. [c] Employing CH_2Cl_2 / water / $CuSO_4 \cdot 5H_2O$ / L-ascorbic acid conditions.

5.2 Synthesis of bis-triazole compounds

5.2.1 Acetylation and propargylation

After mono-triazole alcohols were successfully synthesized, introduction of the second 1,2,3-triazole segment was taken into consideration. The idea was to introduce a propargyl group to the quinolone N1 nitrogen. Even though, *N*-alkylation of the lactam group takes place predominantly, *O*-alkylation has also been reported for similar systems.[165] To avoid formation of undesirable ethers, primary alcohol group was protected using acetic anhydride in pyridine and appropriate acetates were formed. Pyridine not only served as a solvent, but also acted as a base that neutralized the formed acidic by-product, namely acetic acid. After completion of reaction, the content of the flask was poured onto ice-cooled water to remove all inorganic impurities. In case of phenyl derivative, precipitated sand-like solid product was simply collected by filtration through the sintered glass filter, while methyl counterpart (in a contact with water) turned into a sticky material that was firstly exposed to the temperature of 4 °C to partially solidify and then filtered. The yields of pure products are given in Scheme 39.

Scheme 39. *Preparation of compounds **5a** and **5b**.*

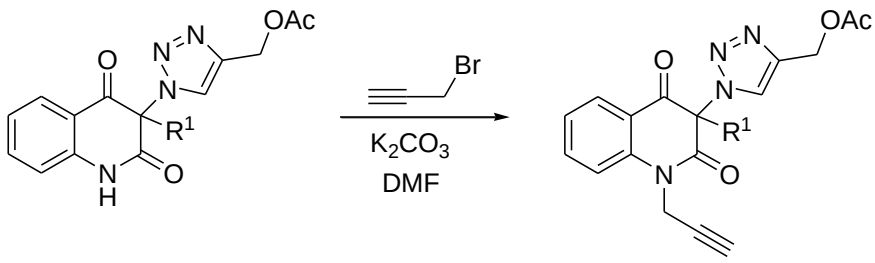


4a (R^1 = Me)
4b (R^1 = Ph)

5a (R^1 = Me), 84%
5b (R^1 = Ph), 85%

Obtained esters **5** were then exposed to nucleophilic displacement with propargyl bromide. Apart from the last-mentioned reactants and DMF as solvent, K_2CO_3 (3 equiv.) was also added to the reaction mixture. Using basic potassium carbonate, relatively acidic proton from the position one of quinoline-2,4-dione framework was extracted, and thus quinolone nitrogen became more nucleophilic. Afterwards, propargyl bromide (1.5 equiv.) was added and SN2 nucleophilic substitution took place, resulting in gradual disappearance of starting compound and arising of more non-polar propargyl derivative **6**. The reactions were completed within 45 minutes, providing moderate to very good yields (Scheme 40).

Scheme 40. *Preparation of compounds **6a** and **6b**.*

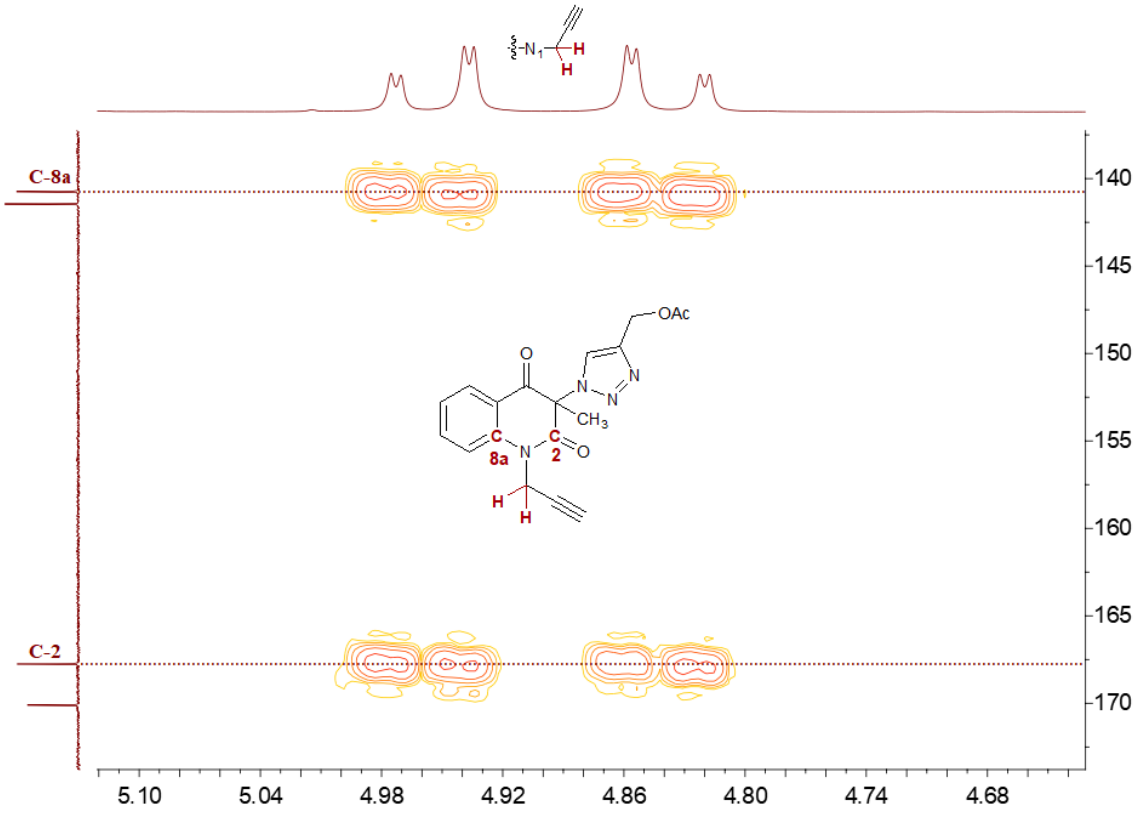


5a (R^1 = Me)
5b (R^1 = Ph)

6a (R^1 = Me), 81%
6b (R^1 = Ph), 63%

Expected products were further confirmed by 2D NMR, more precisely, ^{1}H–^{13}C *gs*-HMBC and ^{1}H–^{15}N *gs*-HMBC. As can be seen in Figure 20, two hydrogen atoms from N_1-CH_2 group strongly correlate with C-8a and C-2 carbons of quinolone scaffold, and therefore unambiguously determine the proposed structure of synthesized compounds **6**.

Figure 20. *^{1}H–^{13}C gs-HMBC NMR spectrum of propargyl derivative.*

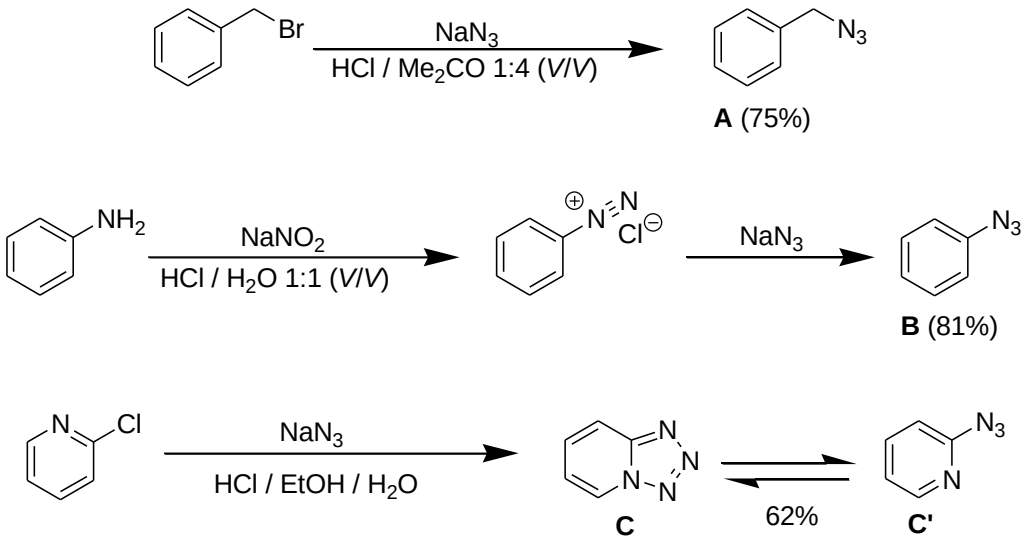


5.2.2 Organic azides

In the next step, each of both last-mentioned propargyl derivatives was combined with three different organic azides, namely benzyl azide **A**, phenyl azide **B** and tetrazolo(1,5-*a*)pyridine **C** to gain bis-triazole counterparts. All three

A, **B** and **C** azido compounds were synthesized from benzyl bromide, aniline and 2-chloropyridine, respectively. While for liquid azides **A** and **B** no additional purification was needed, solid tetrazolo(1,5-*a*)pyridine was chromatographed on silica-gel column using chloroform as mobile phase, and subsequently crystalized from acidified ethanol. Purity above 95% for all three azido compounds was established by gas chromatography (**A** and **B**) or ^{1}H NMR spectroscopy (**C**). Obtained yields are presented in Scheme 41.

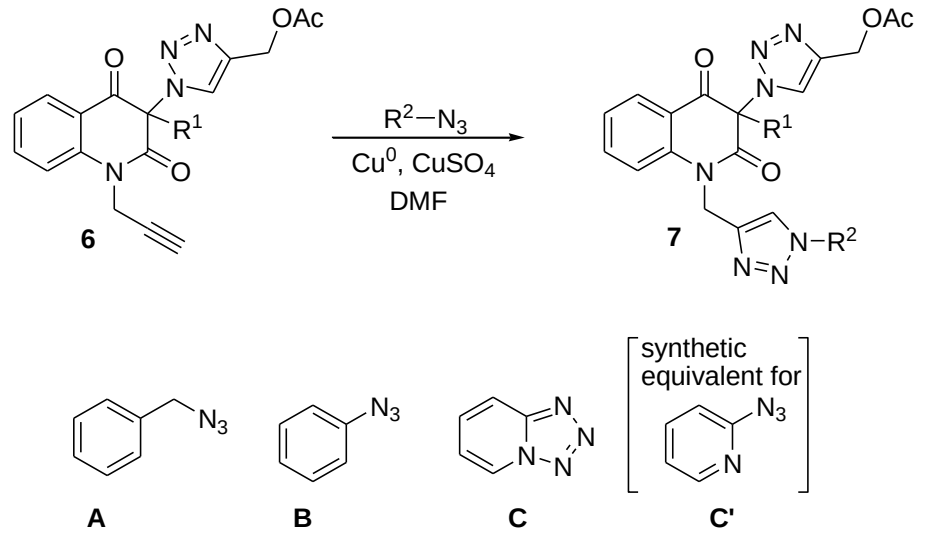
Scheme 41. *Preparation of compounds **A**, **B** and **C**.*



5.2.3 Second 1,2,3-triazole ring

Synthesis of bis-triazole species was carried out using very similar conditions than in case of the first »click«. Both, benzyl and phenyl azides (**A** and **B**) were combined with acetylenic compounds **6** at the laboratory temperature, however elevated temperature was utilized in case of the tetrazolo(1,5-*a*)pyridine **C**, which is a synthetic equivalent and an equilibrium form of 2-azidopyridine **C'**. While the former is »click-inactive« and predominant at laboratory temperature, the latter could be acquired at elevated temperature and readily used as an azide partner for preparation of 2-pyridyl substituted 1,2,3-triazoles. Consequently, transformations with tetrazolo(1,5-*a*)pyridine (**C**) were performed at 100 °C under inert atmosphere. Apart from traditional heating on oily bath, syntheses in microwave reactor were also carried out and yields of isolated compounds from both synthetic approaches were compared. While in the case of phenyl derivative, a bit higher yield was obtained from the reaction in microwave reactor, an opposite trend was observed for methyl counterpart, exhibiting slightly better performance when conventional heating was utilised. Nevertheless, all yields of isolated 2-pyridyl derivatives **7c** and **7f** were quite similar, and therefore comparable. (Table 2).

Table 2. *Preparation of compounds* ***7a–f****.*

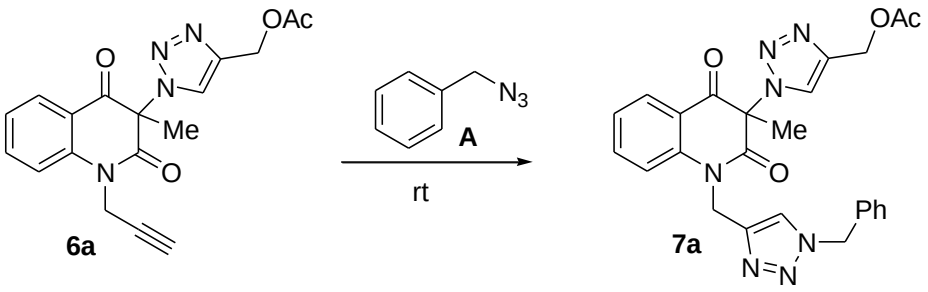


Entry	**6**	R^1	R^2	T (°C)	Time (h)	Yield of **7** (%)[a]
1	**a**	Me	Bn	23	0.5	96
2	**b**	Me	Ph	23	2	92
3	**c**	Me	2-Py	100	1	85
4	**c**	Me	2-Py	90	0.25	79[b]
5	**d**	Ph	Bn	23	2	97
6	**e**	Ph	Ph	23	0.5	93
7	**f**	Ph	2-Py	100	0.5	85
8	**f**	Ph	2-Py	90	0.25	92[b]

[a] Refers to percent yield of pure (by TLC and IR) isolated product. [b] Transformation was carried out in a microwave reactor T = 90 °C, t = 15 min, P = 150 W.

Apart from $Cu^0/CuSO_4 \cdot 5H_2O$ in *N*,*N*-dimethylformamide, some more standard solvent systems in the presence of sodium ascorbate or L-ascorbic acid, as well as $CuSO_4 \cdot 5H_2O$ were further investigated. In these experiments, compound **6a** and benzyl azide (**A**) were used as dienophile and diene, respectively. Three different solvent mixtures, namely *t*-BuOH/H_2O, *t*-BuOH/H_2O/CH_3CN and CH_2Cl_2/H_2O were studied. In comparison with Cu^0/Cu^{2+} in DMF, the reactions times were significantly longer, while the yields of isolated compounds were considerably lower for all of three organic solvent/water combinations. (Table 3). As the main reason, highly hydrophobic nature of both, reactants and products was established. The presence of water in the reaction mixture, especially in the case of *t*-BuOH/H_2O 1:1 (*V*/*V*), turned compounds into sticky resin-like materials that stuck to the magnetic stirring bar as well as flask walls, and therefore prevented reaction from proceeding to the completion.

Table 3. *Preparation of compound **7a**.*



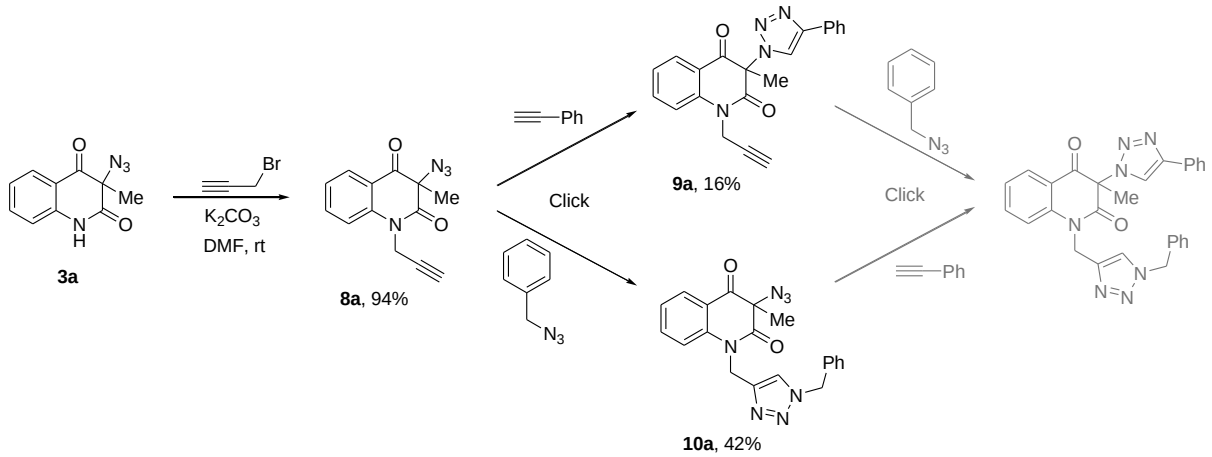
Entry	Time (h)	Yield of **7a** (%)[a]
1	0.5	96[b]
2	45	45[c]
3	48	81[d]
4	4	85[e]

[a] Refers to percent yield of pure (by TLC and IR) isolated product. [b] Employing DMF / Cu^0 / $CuSO_4 \cdot 5H_2O$ conditions. [c] Employing *t*-BuOH / water / $CuSO_4 \cdot 5H_2O$ / L-ascorbic acid conditions. [d] Employing *t*-BuOH / water / CH_3CN / $CuSO_4 \cdot 5H_2O$ / Na-ascorbate conditions. [e] Employing CH_2Cl_2 / water / $CuSO_4 \cdot 5H_2O$ / Na-ascorbate conditions.

5.2.4 Alternative reaction pathway

Apart from already presented »click-propargylation-click« synthetic approach, »propargylation-click-click« strategy was also briefly examined. As a result, 3-azido-3-methylquinoline-2,4(1*H*,3*H*)-dione (**3a**) was exposed to the *N*-alkylation reaction using propargyl bromide and K_2CO_3 in DMF, providing 3-azido-3-methyl-1-(prop-2-ynyl)quinoline-2,4(1*H*,3*H*)-dione (**8a**) as a desired product. The transformation proceeded smoothly, providing an excellent yield, however, manipulation of obtained product was not very convenient due to its tendency to be in an oily state. Expectedly, all attempts of its crystallization failed, and therefore silica-gel column chromatography was performed as a purification method, giving pure oily material. After several additions of diethyl ether and its subsequent evaporation using rotary evaporator, the compound was somehow transformed into sticky, kneadable, partially solid state. Obtained azide-propargyl bifunctional species (**8a**) was then combined with phenyl acetylene and benzyl azide (**A**) in two separate experiments, using $Cu^0/CuSO_4 \cdot 5H_2O$ catalytic system in DMF, providing 3-methyl-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1-(prop-2-ynyl)quinoline-2,4(1*H*,3*H*)-dione (**9a**) and 3-azido-1-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-3-methylquinoline-2,4(1*H*,3*H*)-dione (**10a**), respectively. The former was prepared in a poor reaction yield of only 16%, while the latter was obtained in 42% (Scheme 42).

Scheme 42. *Alternative »propargylation-click-click« reaction approach.*



Taking into account all last-mentioned facts, classical »click-propargylation-click« approach is definitely more reasonable and rational than its modification in »propargylation-click-click« form. While throughout the former, only one single product is expected in each transformation step, in case of the latter, competitive reaction of 3-azido-1-propargyl-quinolone derivative self-polymerization takes place. Moreover, light-sensitivity, toxicity and in some cases also explosiveness of organic azides are unwanted characteristics that should be definitely considered during the reaction scheme planning. Consequently, many »one-pot« 1,2,3-triazole synthetic approaches have already been developed and published throughout the last fifteen years.[68,69,71,72] Even though, in this study no »one-pot« reactions were performed and organic azides were prepared, isolated, purified, crystalized, characterized and even chromatographed, minimization of manipulation with the currently mentioned species seems to be prudent decision. As a result, more convenient »click-propargylation-click« strategy was not only found more practical and higher yielding, but also a wise choice when taking into account impacts on health and environment.

5.3 Synthesis of mono- and bis-triazole functional derivatives

5.3.1 Removal of acetyl protecting group

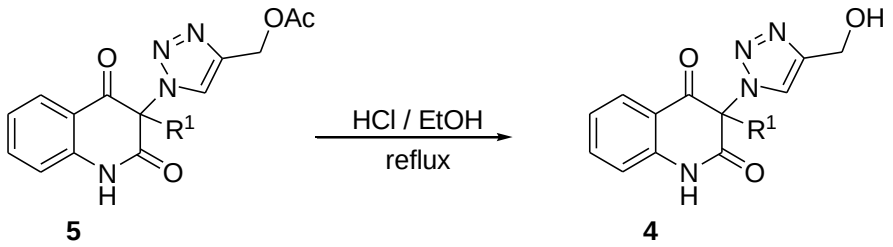
Due to already mentioned well-know and highly applicable physical properties and biological activities of 1,2,3-triazole bearing compounds, as well as quinolone based materials, maximization of number of mono- and bis-triazole functionalised quinoline-2,4-dione counterparts was carried out by the synthesis of different functional derivatives. Consequently, synthesized acetates **6** and **7** were firstly deacetylated to gain alcohols **12** and **11**, respectively. Before the transformations were performed on previously mentioned compounds **6** and **7**,

reaction conditions were studied and optimised on more accessible *N*-unsubstituted mono-triazole functionalised quinoline-2,4-diones (**5**).

Three different re-esterification approaches in basic, as well as acidic environments were tested. The reaction with catalytic quantities of sodium methoxide in dry methanol gave a mixture of products, as undesirable quinolone framework opening took place. Furthermore, cleavage of quinolone scaffold was also observed in case, when transformation was carried out in alkaline ethanol, using potassium hydroxide as a source of base. Finally, acidic alcoholysis resulted in formation of expected derivatives.

Additionally, optimisation of acidic deacetylation conditions was also briefly investigated and obtained results are presented in Table 4.

Table 4. *Re-esterification of compounds **5a** and **5b**.*



5 **4**

Entry	**5**	R^1	HCl/EtOH *V*/*V*(%)	Time (h)	Yield of **4** (%)[a]
1	**a**	Me	2.0	1.5	89
2	**a**	Me	1.0	3	92
3	**a**	Me	0.5	11	76
4	**b**	Ph	1.0	3.5	93

[a] Refers to percent yield of pure (by TLC and IR) isolated product.

The reaction was extremely slow when carried out at laboratory temperature, using 2% (*V*/*V*) solution of concentrated hydrochloride acid in ethanol as a solvent, however at elevated temperature, it proceeded smoothly in the time period of 90 minutes. Keeping the reflux temperature constant, the volume percent of HCl in ethanol was halved twice and reaction times, as well as yields were monitored. While in the case of 1% (*V*/*V*) HCl in ethanol, the transformation was finished in 3 hours, the time period of 11 hours was needed when only 0.5% (*V*/*V*) solution of hydrochloric acid in EtOH was utilised. Taking into account reaction yields, 1% (*V*/*V*) solution of hydrochloric acid in ethanol and reflux temperature were recognised optimal for the primary alcohols preparation.

Propargyl derivatives **6** and bis-triazoles **7** were then subjected to the optimised alcoholysis conditions, providing expected alcohols **12** and **11** within the time period of 4 hours (Table 5).

Table 5. *Preparation of compounds **11a–f**, **12a** and **12b**.*

Entry	Acetate	R^1	R^2	Time (h)	Alcohol	Yield (%)
1	**7a**	Me	Bn	3.5	**11a**	86[a]
2	**7b**	Me	Ph	3.5	**11b**	98[a]
3	**7c**	Me	2-Py	2.5	**11c**	80[a]
4	**7d**	Ph	Bn	4	**11d**	89[a]
5	**7e**	Ph	Ph	3	**11e**	97[a]
6	**7f**	Ph	2-Py	3	**11f**	87[a]
7	**6a**	Me	-	3	**12a**	83[b]
8	**6b**	Ph	-	3	**12b**	87[b]

[a] Refers to percent yield of pure (by TLC and IR) isolated product. [b] Refers to percent yield of crystallized product.

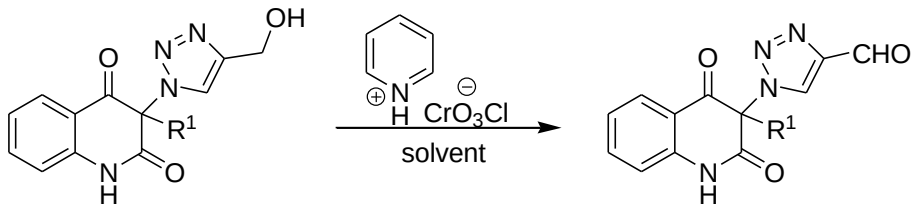
5.3.2 Oxidations

All three groups of alcohols **4**, **11** and **12** were subjected to oxidation reactions in the presence of chromium-based reagents to provide appropriate aldehydes and carboxylic acids. In addition, compounds **4** and **12**, as well as one representative of compounds **11** were further oxidized to corresponding aldehydes, using more benign MnO_2 as an oxidant.

5.3.3 Preparation of aldehydes 13a, 13b, 14a–f, 15a and 15b

A set of reactions (Table 6) was performed, searching for optimal transformation conditions for aldehydes preparation, using well-known pyridinium chlorochromate (PCC) as a reagent. Transformation parameters were again optimised, utilizing more available *N*-unsubstituted mono-triazole species. According to literature, great majority of primary alcohol oxidations with PCC were carried out in dichloromethane, obtaining even quantitative reaction yields in some cases.[166] Due to excellent solubility of phenyl derivative, last-mentioned solvent was assumed as a prime choice for the synthesis of compound **13b**. Conversely, low solubility of counterpart **4a** in dichloromethane was a reason to consider acetone as an alternative.

Table 6. *Preparation of compounds **13a** and **13b** using PCC.*



4 **13**

Entry	**4**	R^1	PCC (eqv.)	Time (h)	T (°C)	Solvent	Yield of **13** (%)[a]
1	**a**	Me	1.7	22	23	Me_2CO	36[b]
2	**a**	Me	1.2	22	23	CH_2Cl_2	31[b]
3	**a**	Me	1.2	MW[c]	40	CH_2Cl_2	16
4	**a**	Me	1.2	1.5	40	CH_2Cl_2	15
5	**a**	Me	1.2	5	56	Me_2CO	23[b]
6	**b**	Ph	1.7	1.5	23	CH_2Cl_2	35
7	**b**	Ph	1.7	22	23	Me_2CO	26[b]
8	**b**	Ph	1.7	0.5	40	CH_2Cl_2	34
9	**b**	Ph	2.0	1	23	CH_2Cl_2	31
10	**b**	Ph	1.5	4	23	CH_2Cl_2	41
11	**b**	Ph	1.2	1.5	40	CH_2Cl_2	44
12	**b**	Ph	1.2	MW[c]	40	CH_2Cl_2	42

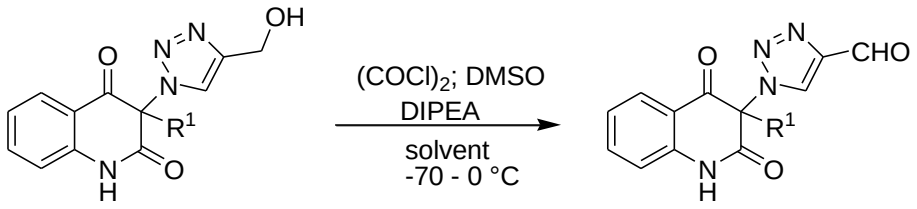
[a] Refers to percent yield of pure (by TLC and IR) isolated product. [b] Complete consumption of **4** was not reached. [c] Transformation in microwave reactor – T = 40 °C, t = 10 min, P = 150 W.

According to collected data, obtained yields for the phenyl analogue (**13b**) were significantly higher, than in the case of its methyl partner (**13a**). In addition, 1.2 equivalents of PCC in refluxing dichloromethane (40 °C) were found optimal reaction conditions for preparation of **13b**. On the other hand, quite opposite is true for the methyl derivative (**13a**). Despite the fact that transformations never proceeded to completion in acetone, slightly higher yields were observed when last-mentioned solvent was used. Similarly, better results were gained when reactions were carried out at lower – laboratory temperature. Apart from conventional heating on oil bath, microwave-induced syntheses of aldehydes **13a** and **13b** were also considered. By comparing both synthetic approaches, it turned out that no worth mentioning difference in reaction yields was observed for methyl (*Entries 3 and 4*), as well as phenyl (*Entries 11 and 12*) analogues.

Additionally, Swern oxidation using oxalyl chloride and *N*,*N*-diisopropylethylamine (DIPEA) in dimethyl sulfoxide (DMSO) was also briefly studied, however obtained results were unsatisfactory for both, phenyl and methyl counterparts (Table 7). While the former resulted in the yield of 33%, no pure product was isolated in case of the latter. The main drawback of this reaction

approach was the presence of hardly removable dimethyl sulfoxide that remained in products, despite the fact that they were intensively washed with ice-cold water. Apparently, utilization of relatively large quantities of water also caused significant loses of target compounds that were much more obvious in the case of methyl analogue. Finally, according to our previous observations, some 1,2,3-triazole bearing quinoline-2,4-dione species are not very stable in DMSO, and therefore usage of last-mentioned solvent could be troublesome also from that point of view.

Table 7. *Preparation of compounds **13a** and **13b** using Swern reaction approach.*



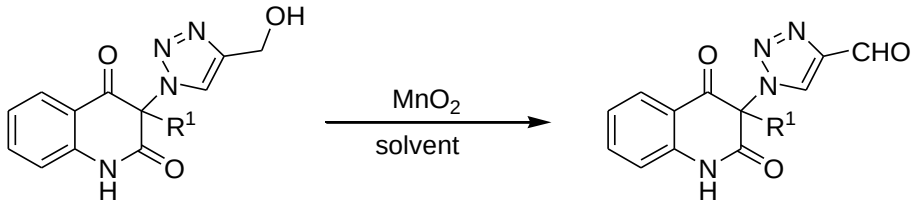
4 **13**

Entry	**4**	R^1	DMSO (eqv.)	Time (h)	Solvent	Yield of **13** (%)[a]
1	**a**	Me	2.6	3.5	Me_2CO	0
2	**b**	Ph	2.6	3.5	CH_2Cl_2	33

[a] Refers to percent yield of pure (by TLC and IR) isolated product.

As the third option, oxidation of primary alcohols **4** with MnO_2 was further examined. Taking into account reaction parameters such as transformation times and quantities of reagent (Table 8), acetone was recognized superior in comparison with dichloromethane, while obtained yields were practically the same in both cases (*Entries 1 and 2*).

Table 8. *Preparation of compounds **13a** and **13b** using MnO_2.*



4 **13**

Entry	**4**	R^1	MnO_2 (eqv.)	Time (h)	T (°C)	Solvent	Yield of **13** (%)[a]
1	**a**	Me	10	1.25	56	Me_2CO	60
2	**b**	Ph	10	1.5	56	Me_2CO	58
3	**b**	Ph	10+5[b]	3	40	CH_2Cl_2	62
4	**b**	Ph	10	96	23	CH_2Cl_2	44

[a] Refers to percent yield of pure (by TLC and IR) isolated product. [b] After 2 hours of stirring in the presence of 10 eqv. of MnO_2, another 5 eqv. of MnO_2 were added.

Optimised reaction conditions were then applied for preparation of aldehydes **14** and **15**. Oxidation of all compounds from the series **11** and **12** was performed by 1.2 equivalents of PCC in refluxing dichloromethane, while materials **14b**, **15a** and **15b** were also synthesized using MnO_2 in acetone. As solubility of *N*-substituted 3-methyl-quinoline-2,4-dione alcohols **11a–c** and **12a** in dichloromethane is significantly better than in the case of *N*-unsubstituted species **4a**, obtained yields for compounds **14a–c** and **15a** were considerably higher (up to 48%) than in the case of **13a**. Poor to moderate yields gained in reactions with PCC are most probably caused by formation of tar-like sediment in the reaction mixture. Even though, chromium sticky material was intensively triturated and washed during the isolation process, non-negligible part of product could still be trapped into the gluey residue, and consequently lost.

Considering toxicity of both utilised oxidants (PCC and MnO_2), as well as achieved yields, MnO_2 was recognised as more convenient reagent for 1,2,3-triazole bearing quinoline-2,4-dione aldehydes preparation. Obtained results are collected in Table 9.

Table 9. *Preparation of compounds **14a–f**, **15a** and **15b**.*

Entry	Alco.	R^1	R^2	Reag.	t (h)	T (°C)	Solv.	Aldeh.	Yield (%)
1	**11a**	Me	Bn	PCC	0.5	40	CH_2Cl_2	**14a**	41[a]
2	**11b**	Me	Ph	PCC	0.5	40	CH_2Cl_2	**14b**	40[a]
3	**11b**	Me	Ph	MnO_2	0.75	56	Me_2CO	**14b**	51[a]
4	**11c**	Me	2-Py	PCC	0.75	40	CH_2Cl_2	**14c**	48[a]
5	**11d**	Ph	Bn	PCC	0.5	40	CH_2Cl_2	**14d**	41[a]
6	**11e**	Ph	Ph	PCC	0.5	40	CH_2Cl_2	**14e**	45[a]
7	**11f**	Ph	2-Py	PCC	0.5	40	CH_2Cl_2	**14f**	41[a]
8	**12a**	Me	-	PCC	1	40	CH_2Cl_2	**15a**	41[b]
9	**12a**	Me	-	MnO_2	1.25	56	Me_2CO	**15a**	40[b]
10	**12b**	Ph	-	PCC	0.75	40	CH_2Cl_2	**15b**	38[b]
11	**12b**	Ph	-	MnO_2	2	56	Me_2CO	**15b**	38[b]

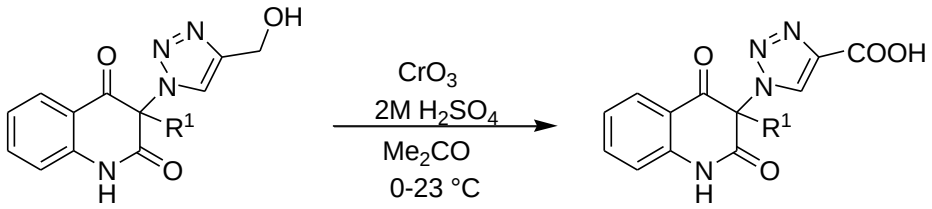
[a] Refers to percent yield of pure (by TLC and IR) isolated product. [b] Refers to percent yield of crystalized product.

5.3.4 Preparation of carboxylic acids 16a, 16b, 17a–f, 18a and 18b

Alcohols (**4**, **11** and **12**) were also transformed to suitable carboxylic acids, using CrO_3 in 2M H_2SO_4 and acetone as a solvent. Although, up to 9-fold molar excess,[167-169] of hexavalent chromium compound is usually added to the reaction mixture, utilization of 24 proportional parts of CrO_3 was found reasonable in our case (Table 10). When only 6 equivalents of CrO_3 were used, the transformation was significantly slower and achieved yield was drastically lower, as mixture of carboxylic acid and appropriate aldehyde was isolated after three hours of stirring

at laboratory temperature. Although, large quantities of potentially toxic chromium species were added to the reaction mixture, performed isolation process enabled efficient separation of desirable carboxylic acids from chromium residues, providing chromatographically pure products.

Table 10. *Preparation of compounds **16a** and **16b**.*



4 **16**

Entry	**4**	R^1	CrO_3 (eqv.)	H_2SO_4 (eqv.)	Time (h)	Yield of **16** (%)[a]
1	**a**	Me	24	48	2.75	33
2	**b**	Ph	6	12	3	40[b]
3	**b**	Ph	24	48	3.25	71

[a] Refers to percent yield of crystalized product. [b] Complete consumption of the intermediate (aldehyde) was not reached.

After the establishment of satisfactory reaction conditions, bis-triazoles **11** and *N*-propargyl substituted alcohols **12** were subjected to the oxidation process. Due to excellent solubility of all starting materials in acetone, the transformations proceeded smoothly providing only desirable products. In all cases, oxidations were completed within the time period of three hours, indicating no starting compounds, intermediates or any other impurities according to TLC (Table 11). Carboxylic acids were then isolated in two portions of equal quality, gaining the first crude product by precipitation from the ice-cold water and the second one by extraction from filtrate. It is also worth mentioning that synthesized species possess low solubility in chloroform, however presence of acetone in mostly aqueous filtrate enables facile transition of desirable compound residues into organic ($CHCl_3$) phase. Due to the fact that isolated bis-triazoles **17** were TLC and NMR pure, no silica-gel column purification was performed. While crystallization of mono-triazole species **18** was carried out with the ease, it was unsuccessful in the case of bis-triazole carboxylic acids (**17**).

Table 11. *Preparation of compounds **17a–f**, **18a** and **18b**.*

Entry	Alcohol	R^1	R^2	Time (h)	Carbox. acid	Yield (%)
1	**11a**	Me	Bn	3	**17a**	88[a]
2	**11b**	Me	Ph	2.5	**17b**	92[a]
3	**11c**	Me	2-Py	2.5	**17c**	84[a]
4	**11d**	Ph	Bn	2	**17d**	75[a]
5	**11e**	Ph	Ph	2.25	**17e**	77[a]
6	**11f**	Ph	2-Py	2.5	**17f**	69[a]
7	**12a**	Me	-	3	**18a**	55[b]
8	**12b**	Ph	-	3	**18b**	68[b]

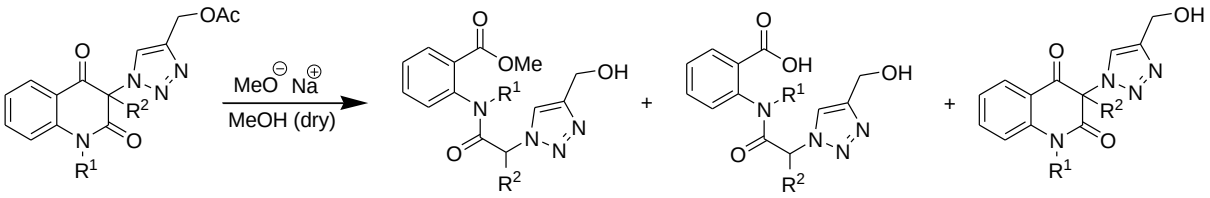
[a] Refers to percent yield of pure (by TLC and IR) isolated product. [b] Refers to percent yield of crystalized product.

5.3.5 Ring-opening studies

As already mentioned, deprotection of synthesized acetates in basic environments resulted in partial or complete quinoline-2,4-dione framework cleavage. Due to the potentially interesting synthetic route for 1,2,3-triazole bearing anthranilic acid derivatives preparation, the quinolone ring opening was also taken into consideration. The transformations were mostly carried out in dry methanol and in the presence of sodium methoxide, however potassium hydroxide in ethanol was also tested as reaction medium. The main difference between phenyl and methyl derivatives is in the nature of both substituents. While the former could be cleaved considerably faster and at laboratory temperature, heating on oil bath is mandatory for ring opening of the latter. The electron-withdrawing character of phenyl group pulls the electrons from C3 carbon of quinolone ring, making it electron-deficient, and therefore more exposed to the nucleophilic attack of methoxide or hydroxide anion. Conversely, electron-donating methyl group increases the electron density on C3 carbon, and consequently harsher reaction conditions are necessary for quinoline-2,4-dione cleavage.

Throughout the study of quinoline-2,4-dione ring opening process, three different acetates **5a**, **5b** and **6b** were deacetylated using sodium methoxide in dry methanol. The transformations were carried out at laboratory temperature (23 °C) or at the temperature of reflux (65 °C). Partial or complete ring-opening, as well as appearance of pure anthranilic acid derivative or mixture with its ester were detected. The reaction conditions are collected in Table 12.

Table 12. *Cleavage of quinoline-2,4-dione using sodium methoxide in methanol.*



5a (R^1 = H, R^2 = Me)
5b (R^1 = H, R^2 = Ph)
6b (R^1 = CH_2CCH, R^2 = Ph)

19a (R^1 = H, R^2 = Me)
19b (R^1 = H, R^2 = Ph)
19c (R^1 = CH_2CCH, R^2 = Ph)

20a (R^1 = H, R^2 = Me)
20b (R^1 = H, R^2 = Ph)
20c (R^1 = CH_2CCH, R^2 = Ph)

4a (R^1 = H, R^2 = Me)

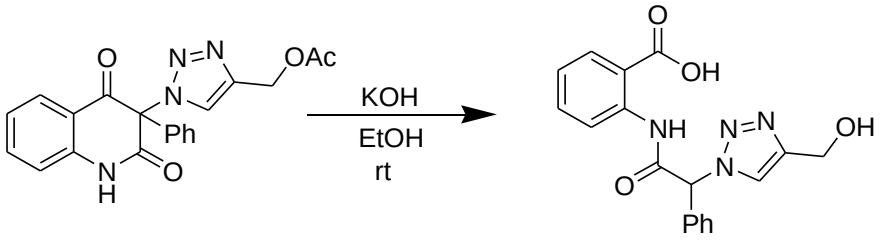
Entry	Acetate	R^1	R^2	Time (h)	Temp. (°C)	Yield (%)[a] **19 20 4**
1	**5b**	H	Ph	10	23	0 + 33 + 0
2	**5b**	H	Ph	0.5	65	26 + 28 + 0
3	**6b**	$CH_2C{\equiv}CH$	Ph	1.5	23	0 + 69 + 0
4	**5a**	H	Me	1	65	23 + <5[b] + 29

[a] Refers to percent yield of crystalized product. [b] No pure compound was isolated.

As can be seen from the collected data, solely open-ring species were isolated in the case of phenyl-bearing quinoline-2,4-dione esters. Conversely, closed form (**4a**) appeared predominantly throughout the methyl derivative deacetylation. During the isolation process, reaction mixtures were neutralised with 1.0 M HCl. Consequently, hydrolysis took place that turned appropriate methyl esters **19a**, **19b** and **19c** into carboxylic acids **20a**, **20b** and **20c**, respectively. According to data in Table 12, the acidic hydrolysis of open-ring phenyl derivatives **19b** and **19c** seems to be considerably faster than for methyl counterpart **19a**. While the major products of the former are carboxylic acids **20b** and **20c**, respectively, no pure derivative **20a** was isolated in case of the latter.

Furthermore, compound **5b** was also subjected to basis alcoholysis using potassium hydroxide in ethanol. Expectedly, complete ring-opening occurred and only one product appeared that was identified as a derivative of anthranilic acid **20b** (Scheme 43).

Scheme 43. *Cleavage of quinoline-2,4-dione using KOH in ethanol.*



5b

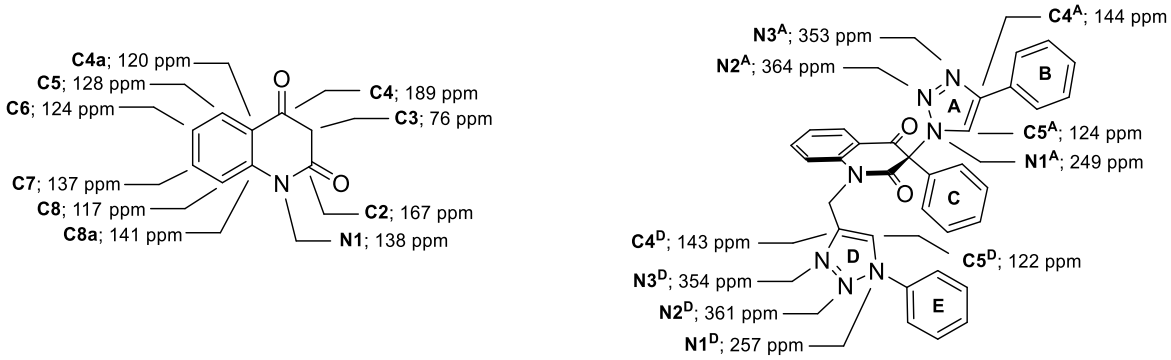
20b (75%)

Beside the preliminary results presented in this chapter, the research on synthesis of 1,2,3-triazole substituted anthranilic acid derivatives could still be significantly broadened by introduction of new substituents on the position 3 of quinoline-2,4-dione molecule, as well as utilization of different bases for intentional ring-opening. Nevertheless, a ratio between obtained esters and carboxylic acids could also be potentially regulated.

5.4 NMR chemical shifts and single-crystal structure

All prepared compounds were assigned by ^{1}H and ^{13}C, while most of them also by ^{15}N NMR spectroscopy. The corresponding resonances were characterized on the basis of gradient-selected 2D NMR experiments including $^{1}H–^{1}H$ gs-COSY, $^{1}H–^{13}C$ gs-HSQC, $^{1}H–^{13}C$ gs-HMBC and $^{1}H–^{15}N$ gs-HMBC. The ring and atom numbering system, as well as their chemical shift data are presented in Figure 21.

Figure 21. *Ring and atom numbering system, including chemical shift data.*



Selected ^{1}H, ^{13}C and ^{15}N NMR chemical shifts of synthesized compounds are presented in Tables 13–17.

Table 13. *Selected ^{1}H, ^{13}C and ^{15}N NMR chemical shifts in ppm for mono-triazoles **4**, **5**, **13** and **16**.*

	4a	**4b**	**5a**	**5b**	**13a**	**13b**	**16a**	**16b**
Quinolone								
N1	–	–	133.5	–	133.4	134.8	133.2	–
C2	168.7	166.8	168.6	166.8	168.3	166.6	168.5	166.8
C3	71.9	79.7	72.4	79.9	73.6	80.7	73.4	80.6
C4	190.8	189.0	190.7	188.8	190.3	188.4	190.5	188.6
C4a	117.5	119.2	117.5	119.3	117.6	119.5	117.7	119.6
C5	127.6	127.5	127.6	127.5	127.6	127.5	127.6	127.4
C6	123.3	123.4	123.3	123.4	123.5	123.5	123.4	123.4

	4a	4b	5a	5b	13a	13b	16a	16b
C7	137.1	136.9	137.1	136.9	137.2	136.8	137.2	136.7
C8	116.9	116.7	116.9	116.7	117.0	116.7	117.0	116.7
C8a	141.6	140.6	141.6	140.5	141.4	140.4	141.5	140.4
Ring A								
$N1^{A}$	–	–	248.7	–	252.0	249.8	250.2	–
$N2^{A}$	–	–	362.9	–	367.9	356.4	367.5	–
$N3^{A}$	–	–	354.1	–	358.6	351.6	357.1	–
$C4^{A}$	147.4	146.8	141.4	140.8	146.6	146.2	139.5	139.2
$C5^{A}$	123.7	124.8	125.8	127.0	129.6	130.7	130.4	131.1
$H5^{A}$	8.26	7.77	8.45	8.07	9.18	8.93	8.99	8.71

Table 14. *Selected ^{1}H, ^{13}C and ^{15}N NMR chemical shifts in ppm for bis-triazoles **7**.*

	7a	7b	7c	7d	7e	7f
Quinolone						
N1	138.7	138.7	135.3	140.4	140.4	138.9
C2	168.2	168.3	168.6	166.6	166.9	166.6
C3	71.6	71.5	73.3	79.6	79.6	79.7
C4	189.4	189.4	189.9	187.9	187.9	187.9
C4a	119.2	119.2	119.4	120.9	120.9	121.0
C5	129.3	129.4	127.9	129.0	129.1	129.1
C6	124.6	124.7	123.8	124.6	124.7	124.6
C7	137.8	137.8	137.0	137.2	137.4	137.2
C8	116.9	116.8	116.5	116.8	116.7	116.6
C8a	141.7	141.7	141.3	141.1	140.9	141.2
Ring A						
$N1^{A}$	248.4	248.8	247.6	249.8	249.9	249.7
$N2^{A}$	361.6	–	363.7	365.1	–	–
$N3^{A}$	355.2	355.5	353.4	356.9	357.2	357.1
$C4^{A}$	142.3	142.3	141.6	140.9	140.9	140.9
$C5^{A}$	124.2	124.1	126.1	126.4	126.4	126.4
$H5^{A}$	7.78	7.86	8.47	7.08	7.14	7.13
Ring D						
$N1^{D}$	250.4	256.3	260.0	250.4	256.3	261.2
$N2^{D}$	362.6	–	361.9	362.9	–	–
$N3^{D}$	350.0	351.9	356.5	350.5	352.9	355.8
$C4^{D}$	142.9	143.2	143.2	142.9	143.2	143.0
$C5^{D}$	123.5	121.7	120.6	123.5	121.8	121.0
$H5^{D}$	7.55	8.10	8.82	7.58	8.05	8.63

Table 15. *Selected ^{1}H, ^{13}C and ^{15}N NMR chemical shifts in ppm for bis-triazoles **11**.*

	11a	**11b**	**11c**	**11d**	**11e**	**11f**
Quinolone						
N1	138.6	138.5	137.7	140.4	139.5	–
C2	168.3	168.4	168.3	166.6	166.9	166.7
C3	71.7	71.6	72.0	79.6	79.6	79.7
C4	189.6	189.5	189.6	188.0	188.0	188.0
C4a	119.2	119.2	119.3	120.9	120.9	121.0
C5	129.0	129.4	129.3	129.0	129.1	129.0
C6	124.6	124.6	124.6	124.5	124.6	124.5
C7	137.7	137.8	137.6	137.2	137.3	137.1
C8	116.9	116.8	116.6	116.8	116.7	116.6
C8a	141.7	141.7	141.6	141.1	140.9	141.2
Ring A						
$N1^{A}$	247.1	247.4	246.7	248.9	249.0	–
$N2^{A}$	362.1	–	–	364.9	–	–
$N3^{A}$	350.4	350.8	350.3	352.8	353.0	–
$C4^{A}$	147.3	147.3	147.4	145.8	145.8	145.9
$C5^{A}$	122.1	122.1	122.3	124.5	124.6	124.5
$H5^{A}$	7.70	7.76	7.76	7.03	7.09	7.09
Ring D						
$N1^{D}$	250.4	256.2	259.9	250.6	256.2	–
$N2^{D}$	361.6	–	–	362.8	–	–
$N3^{D}$	349.3	351.6	355.0	350.0	352.6	–
$C4^{D}$	142.9	143.2	143.0	142.9	143.2	143.0
$C5^{D}$	123.5	121.8	120.9	123.6	121.8	121.0
$H5^{D}$	7.56	8.09	8.58	7.59	8.07	8.61

Table 16. *Selected ^{1}H, ^{13}C and ^{15}N NMR chemical shifts in ppm for bis-triazoles **14**.*

	14a	**14b**	**14c**	**14d**	**14e**	**14f**
Quinolone						
N1	138.4	138.5	137.8	140.0	139.3	139.2
C2	167.7	167.8	167.7	165.9	166.2	165.9
C3	72.6	72.5	72.9	80.1	80.1	80.2
C4	188.9	188.8	189.0	187.3	187.2	187.3
C4a	119.0	119.0	119.1	120.7	120.7	120.8
C5	129.3	129.4	129.4	129.0	129.3	129.1
C6	124.8	124.9	124.8	124.8	124.8	124.8
C7	138.0	138.1	137.9	137.5	137.6	137.4

	14a	14b	14c	14d	14e	14f
C8	117.0	117.0	116.8	117.0	116.8	116.7
C8a	141.5	141.5	141.6	141.0	140.9	141.1
Ring A						
$N1^A$	251.7	251.6	251.1	253.7	254.3	254.0
$N2^A$	361.8	362.2	361.8	–	363.4	363.1
$N3^A$	–	–	–	–	–	–
$C4^A$	147.0	147.0	147.1	145.8	145.8	145.8
$C5^A$	126.3	126.2	126.4	128.4	128.4	128.4
$H5^A$	8.30	8.36	8.35	7.58	7.64	7.63
Ring D						
$N1^D$	250.6	256.2	261.0	250.6	256.1	260.2
$N2^D$	362.6	–	–	362.5	–	–
$N3^D$	350.0	352.0	355.3	350.8	352.7	355.5
$C4^D$	142.7	143.0	142.8	142.7	143.0	142.8
$C5^D$	123.4	121.8	120.8	123.5	121.8	120.9
$H5^D$	7.53	8.05	8.59	7.58	8.06	8.63

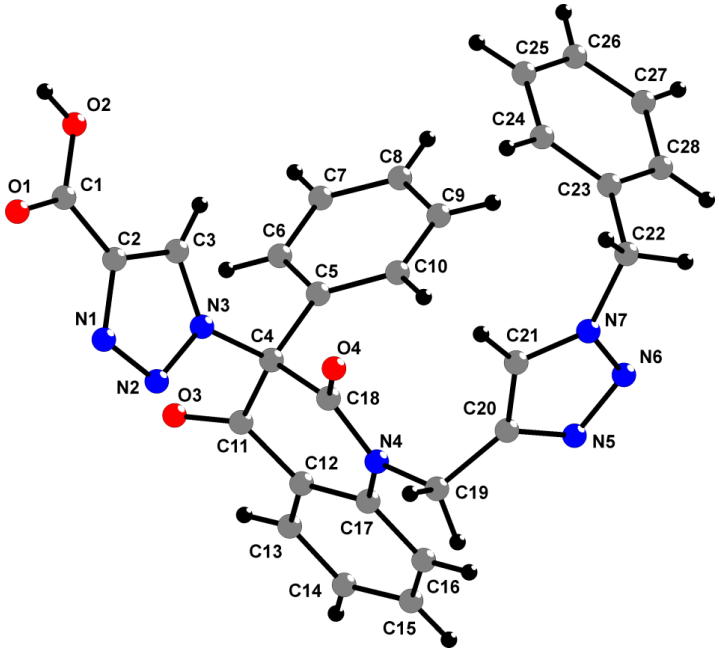
Table 17. *Selected ^1H, ^{13}C and ^{15}N NMR chemical shifts in ppm for bis-triazoles **17**.*

	17a	17b	17c	17d	17e	17f
Quinolone						
N1	136.8	135.9	–	–	139.5	137.8
C2	168.2	168.3	168.5	166.1	166.3	166.7
C3	74.0	74.1	74.2	80.5	80.7	80.8
C4	189.8	189.9	189.8	187.9	188.0	187.9
C4a	119.3	119.4	119.4	121.1	121.1	121.2
C5	128.2	128.0	128.0	127.7	127.8	127.9
C6	123.9	124.0	123.9	124.0	124.1	124.0
C7	137.1	137.2	137.1	136.6	136.8	136.7
C8	116.7	116.8	116.6	116.6	116.7	116.5
C8a	141.4	141.5	141.2	140.8	140.7	140.4
Ring A						
$N1^A$	249.3	249.4	249.2	249.8	249.8	249.7
$N2^A$	367.7	367.8	–	–	372.6	–
$N3^A$	357.4	357.0	–	356.4	357.5	356.8
$C4^A$	139.6	139.7	139.7	139.3	139.3	139.2
$C5^A$	130.6	130.6	130.6	131.2	131.3	131.3
$H5^A$	8.96	8.97	8.99	8.76	8.79	8.86
Ring D						
$N1^D$	251.2	255.7	260.3	250.9	255.6	260.4
$N2^D$	362.4	–	–	362.7	–	–

	17a	17b	17c	17d	17e	17f
$N3^D$	351.1	353.2	–	351.6	354.2	357.1
$C4^D$	142.3	143.3	143.2	141.9	142.9	143.0
$C5^D$	123.9	121.8	120.7	124.3	122.4	120.9
$H5^D$	8.16	8.74	8.83	8.24	8.81	8.83

From solution of **17d** in deuterated chloroform originally intended to NMR measurements, the crystal had grown. Using X-ray diffraction, the structure of solvate **12d**·2$CDCl_3$ was unambiguously determined (Figure 22).

Figure 22. *Crystallographic view of molecule **17d**. $CDCl_3$ molecules are omitted.*



It turned out that compound **17d** crystalize in monoclinic $P2_1/n$ space group. Intermolecular hydrogen bonds of O–H---N type were found in the crystal structure of bis-triazole species **17d**. While O2 atom acts as hydrogen bond donor, N5 atom of symmetry related molecule was recognised as hydrogen bond acceptor. Consequently, two dimensional chain extension along *b*-axis was established (Figure 23). Selected bonds' lengths and angles are presented in Tables 18–20.

Figure 23. *Hydrogen bonding interactions resulting in polymeric chain.*

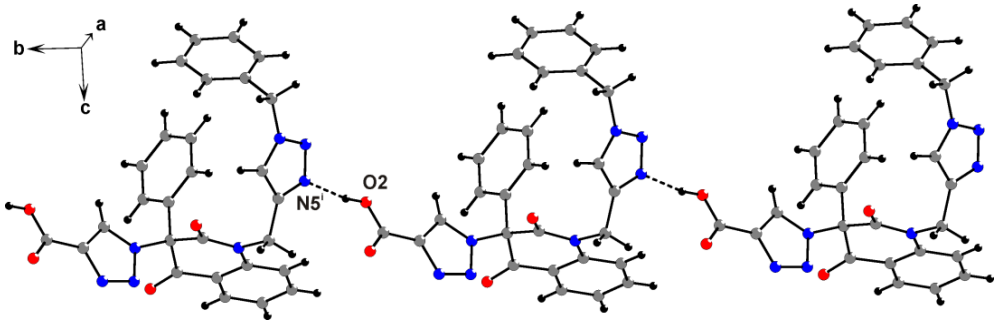


Table 18. *Crystal data and structure refinement details for compound **17d**.*

formula	$C_{30}H_{21}Cl_6D_2N_7O_4$
Fw (g mol–1)	760.29
crystal size (mm)	0.50×0.30×0.10
crystal color	colourless
crystal system	monoclinic
space group	P21/n
a (Å)	13.5462(6)
b (Å)	11.9884(9)
c (Å)	20.8335(10)
β (º)	92.823(4)
V (Å3)	3379.2(3)
Z	4
calcd density (g cm-3)	1.494
F(000)	1544
no. of collected reflns	29191
no. of independent reflns	7754
Rint	0.0563
no. of reflns observed	3853
no. parameters	438
R[I> 2σ (I)]a	0.0974
wR2(all data)b	0.3413
Goof , Sc	1.092

Table 19. *Selected bond lengths and angles for compound **17d**.*

Bond	Length (Å)	Bonds	Angle (°)
N1–N2	1.298(5)	N1–N2–N3	106.8(3)
N2–N3	1.359(5)	N5–N6–N7	106.8(4)
N5–N6	1.310(5)	N2–N3–C3	110.7(3)

Bond	Length (Å)	Bonds	Angle (°)
N6–N7	1.328(6)	N6–N7–C21	111.2(4)
N1–C2	1.353(5)	N1–C2–C3	108.3(4)
N3–C3	1.330(5)	N3–C3–C2	104.9(3)
N3–C4	1.456(5)	N4–C17–C12	119.9(4)
N4–C17	1.424(5)	N4–C18–C4	118.0(3)
N4–C18	1.358(5)	N4–C19–C20	112.1(3)
N4–C19	1.475(5)	N5–C20–C21	107.0(4)
N5–C20	1.348(6)	N7–C21–C20	105.4(4)
N7–C21	1.328(6)	C17–N4–C18	123.2(3)
N7–C22	1.481(6)	C19–N4–C17	121.9(4)

Table 20. *Hydrogen bonding geometry for compound **17d**.*

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)	Sym. code
O2–H2···N5	0.82	1.90	2.700(5)	166.7	x, y+1, z

5.5 Practical applications of synthesized compounds

5.5.1 Coordination abilities

The purpose of preparing bis-triazole species was also interrogation of their potential coordination abilities to the metal centre, and consequently possible usage in various practical applications. As a result, some synthesized materials with two 1,2,3-triazole rings on quinolone framework were subjected to NMR experiment, where particular derivatives were mixed with equimolar amounts of ruthenium species $[RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})]_2$ in deuterated chloroform. While in the case of bis-triazole compounds with oxygen-containing functional groups on the first 1,2,3-triazole ring no coordination was detected to the ruthenium-cymene system, weak metal-to-ligand interactions were observed for three compounds with the phenyl segment on the position four of the first 1,2,3-triazole scaffold. Due to overlap as well as lack of several indicative cross-peaks in the spectra, especially in $^{1}H–^{15}N$ gs-HMBC, an explicit structure determination of obtained [Ru–Cym]–bis-triazole complex through the 2D NMR techniques was unsuccessful. However, the analysis of the available NMR data (Figure 24) tentatively suggested the coordination of both 1,2,3-triazole rings to the Ru–Cym unit as presented in Scheme 44. Even though, three previously mentioned compounds that exhibited some mild affinities towards ruthenium

metal centre were synthesized in our laboratory, they were not prepared as a part of my dissertation, and therefore their assignment, preparation procedure, as well as detailed spectral data are not described in this work.

Scheme 44. *Proposed structure of [Ru–Cym]–(bis-triazole) complex.*

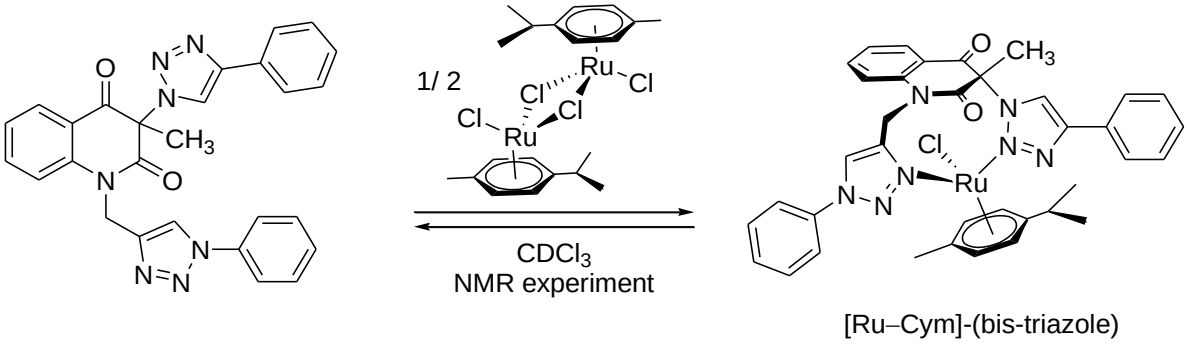
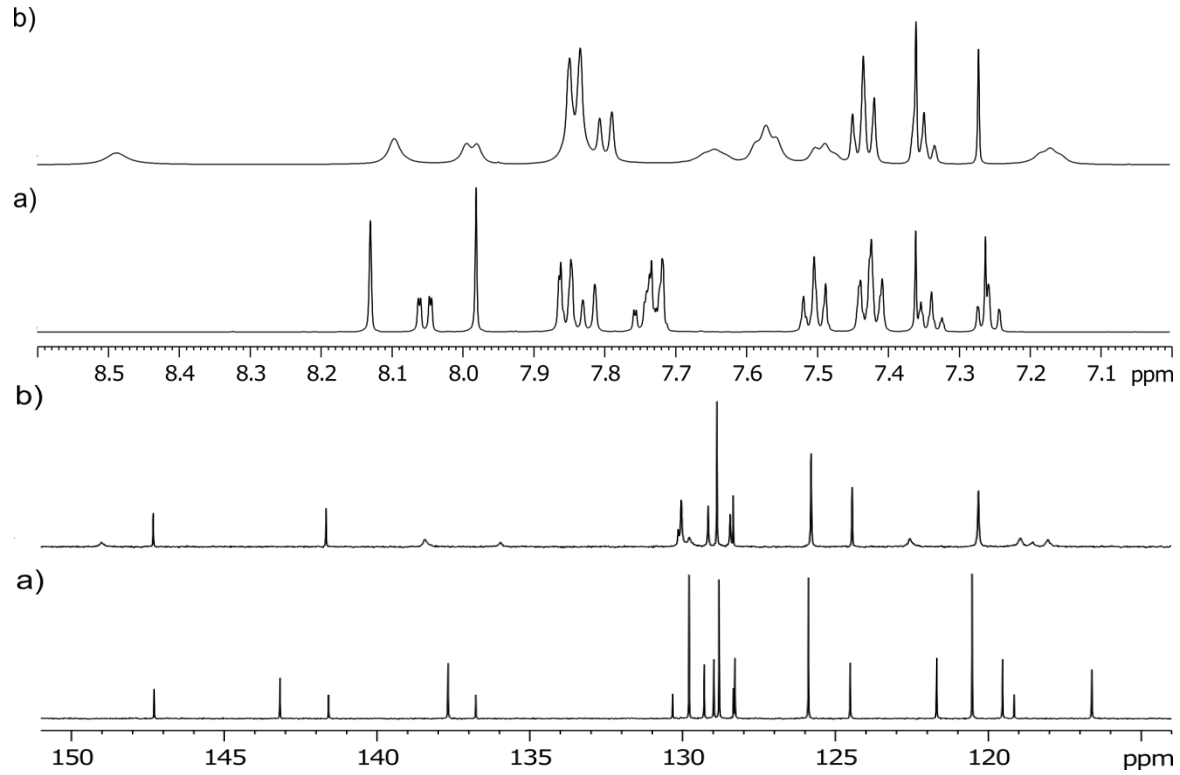


Figure 24. *Aromatic region of ^{1}H (above) and ^{13}C (bellow) NMR spectra of: a.) bis-triazole in $CDCl_3$, and b.) a mixture of bis-triazole (42 mM) and $[RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-}cymene)]_2$ (21 mM) in $CDCl_3$ immediately after dissolution.*



5.5.2 Evaluation of prepared compounds as potential photoprotective agents

Utilization of 1,2,3-triazole species as photoprotective and antiphotoaging agents has already been reported.[71] Even though, investigation of their photoprotective characteristics was mainly focused on human dermal fibroblast

cells protection, materials with similar properties might also be potentially used as additives to polymers for preservation purposes.

To evaluate possible photoprotective activities of synthesized compounds, their UV spectra were recorded. The measuring range was set to 200–400 nm. Four different solvents including ethanol, acetonitrile, chloroform and dimethyl sulfoxide were taken into consideration. In comparison with chloroform and dimethyl sulfoxide, the background of absorption spectra was considerably lower, when ethanol or acetonitrile were used. In contrast to ethanol, all studied compounds were sufficiently soluble in acetonitrile, making it suitable solvent for preparation of appropriate stock solutions.

In Table 21, UV spectral data of recorded species are collected. Relatively large deviations in attenuation coefficients for quite similar derivatives could be caused by various amounts of solvents presented in the samples. While negligible quantities of solvents are expected in crystalized compounds, the opposite could be true for amorphous, foamy solids. Nevertheless, multiple measurements of the particular specimens gave reproducible results.

Table 21. *Ultra-violet spectral data measured in acetonitrile.*

Compound	c [μM]	λ_{max} [nm]	A	10^{-3} ε [$M^{-1}cm^{-1}$]
4a	26.23	232	1.004	38.3
		346	0.074	2.8
4b	22.86	235	0.899	39.3
		348	0.066	2.9
5a	27.68	232	1.047	37.8
		347	0.081	2.9
5b	28.64	235	1.063	37.1
		348	0.078	2.7
6a	23.61	234	0,937	39.7
		343	0.072	3.1
6b	22.78	236	0.868	38.1
		343	0.062	2.7
7a	25.95	235	0.996	38.4
		343	0.080	3.1
7b	23.71	235	1.047	44.2
		342	0.071	3.0
7c	25.19	235	1.074	42.6
		271	0.312	12.4
		344	0.075	3.0
7d	24.84	237	0.882	35.5
		346	0.062	2.5
7e	23.92	237	0.992	41.5
		343	0.059	2.5

Compound	c [μM]	λ_{max} [nm]	A	10^{-3} ε [$M^{-1}cm^{-1}$]
7f	25.26	236	1.064	42.1
		271	0.231	9.1
		344	0.073	2.9
9a	22.62	203	0.764	33.8
		237	1.017	45.0
		344	0.069	3.1
10a	23.23	234	0.752	32.4
		343	0.065	2.8
11b	24.45	235	1.036	42.4
		342	0.069	2.8
11c	23.70	234	1.007	42.5
		271	0.294	12.4
		342	0.071	3.0
11d	25.28	237	0.851	33.7
		342	0.061	2.4
11e	22.09	237	0.811	36.7
		344	0.045	2.0
11f	25.14	237	1.018	40.5
		272	0.338	13.4
		343	0.062	2.5
12a	21.76	234	0,762	35.0
		341	0,059	2.7
12b	24.65	236	0.841	34.1
		343	0.060	2.4
13a	23.16	234	0.996	43.0
		342	0.064	2.8
13b	24.13	237	1.048	43.4
		346	0.062	2.6
14a	24.56	238	0.994	40.5
		346	0.068	2.8
14b	24.05	238	1.122	46.7
		347	0.065	2.7
14c	24.98	237	1.164	46.6
		271	0.311	12.5
		347	0.069	2.8
14d	24.75	239	0.983	39.7
		346	0.058	2.3
14e	25.82	239	1.170	45,3
		343	0.061	2,4
14f	26.59	239	1.196	45.0
		272	0.341	12.8
		344	0.059	2.2

Compound	c [μM]	λ_{max} [nm]	A	10^{-3} ε [$M^{-1}cm^{-1}$]
15a	26.40	236	1.226	46.4
		341	0.081	3.1
15b	27.59	238	1.260	45.7
		341	0.066	2.4
16a	26.27	232	1.073	40.8
		344	0.075	2.9
16b	25.95	235	1.037	40.0
		348	0.065	2.5
17a	25.31	235	0.927	36.6
		343	0.064	2.5
17b	27.69	235	1.325	47.9
		342	0.081	2.9
17c	24.53	234	1.016	41.4
		272	0.277	11.3
		342	0.065	2.7
17d	25.72	237	0.912	35.5
		344	0.060	2.3
17e	25.04	237	1.020	40.7
		345	0.052	2.1
17f	27.80	237	1.029	37.0
		272	0.326	11.7
		345	0.058	2.1
18a	27.44	234	1.112	40.5
		342	0.077	2.8
18b	26.56	236	1.068	40.2
		343	0.071	2.7

For the majority of tested species, two absorbance maximums and one inflection point were observed in UV spectra. In the case of bis-triazoles with 2-pyridyl segment in a molecule, the third absorbance maximum appeared in the place of the inflection point. Additional absorption of derivative **9a** most probably belongs to π-conjugated system of the phenyl ring attached to 1,2,3-triazole scaffold. For the compounds **4–18**, the most intense absorption peak (maximum at 230–240 nm) was quite narrow, covering the zone of approximately 25 nm in UV-C range. On the other hand, wide absorption band (maximum at 340–350 nm) was spread along roughly 80 nm of UV-B and UV-A regions, however its intensity was low. Finally, the eventual third absorption maximum in UV-C area, as well as absorptions of anthranilic acid derivatives **19** and **20** were found both, relatively narrow and weak. According to literature,[170] intensive and wide absorption bands in UV spectra, especially in UV-A (315–400 nm) and UV-B (280–315 nm) areas, are considered the key characteristic of efficient photoprotective agents. Consequently, measured mono- and bis-triazole

compounds could be designated as unpromising candidates for the prevention of photodamaging and photoaging processes on the surfaces of materials or tissues.

5.5.3 Antimicrobial activities

Several mono- and bis-triazole compounds were tested against Gram-positive bacteria (*Staphylococcus aureus* CCM 3953), Gram-negative bacteria (*Escherichia coli* CCM 3954 and *Pseudomonas aeruginosa* CCM 3955), yeast (*Candida albicans* CCM 8275) and fungi (*Trichoderma viride* CCM F-486 and *Aspergillus niger* CCM 8155). All microbes were obtained from Czech Collection of Microorganisms in Brno (CCM). While testing against bacteria and yeast took place on 96-well microtiter plates using Broth microdilution method, interrogation of antifungal characteristics of chosen materials was carried out in Petri plates utilizing Disc diffusion test.

a.) Broth dilution method

All tested compounds exhibited excellent solubility in DMSO, and thus were fully dissolved for the purpose of stock solutions (20 g/L, 10 g/L, 5 g/L and 1 g/L) preparation. However, after applying them into the particular wells with nutrient media, precipitation occurred in some cases. The actual concentrations in the wells were 500 mg/L, 250 mg/L, 125 mg/L and 25 mg/L. Due to drastically reduced solubility in mostly aqueous media (wells) in comparison with pure DMSO (stock solutions), the most intense precipitation was expectedly observed at the highest concentrations (500 mg/L). Consequently, non-inoculated microtiter plate was also prepared and incubated as a reference to determine either turbidity in a particular well was caused by the growth of microbes or precipitation of tested compound. Furthermore, it also served as a control that utilized accessories and nutrient media were indeed sterile before usage. In most cases, precipitation in non-inoculated microplate disappeared during 24-hour incubation at 37 °C. Based on the differences in absorbances between inoculated and non-inoculated microtiter plates, the growth of microbes was unambiguously confirmed in almost all cases. Only for one compound, the obtained results were not completely obvious. As a result, contents of the wells in question were transferred to the agar nutrient media in Petri plates. After 24 hours of incubation at 37 °C, the growth of bacteria was explicitly established also in this case.

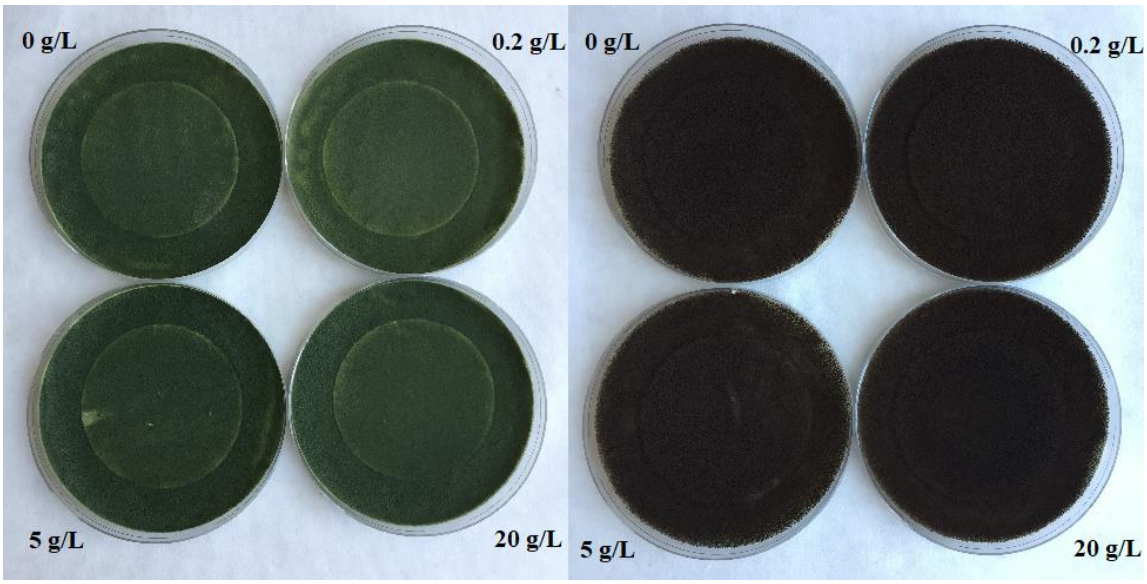
Even though, the minimum inhibitory concentration of all evaluated compounds is evidently higher than 500 mg/L, very slight suppression of microbes' growth was detected for the highest concentrations of three interrogated materials after 24 hours of incubation. While compounds **13a**, **13b** and **15a** (500 mg/L) exhibited weak repression against *Staphylococcus aureus*, similar could be said for compound **13b** (500 mg/L) against *Escherichia coli*. Although, lastly mentioned species slightly slow down the microbes' growth, they still do

not show any considerable antimicrobial activities, and thus could be designated as unpromising antimicrobial agents against all four tested strains.

b.) Disk diffusion test

A series of synthesized compounds was also tested against fungal strains *Trichoderma viride* and *Aspergillus niger*. Stock solutions of three different concentrations (20 g/L, 5 g/L and 0.2 g/L) in acetone were utilised. While majority of interrogated candidates were highly soluble in last-mentioned solvent, some of them showed poor solubility at the highest tested concentration (20 g/L). In cases, where suspension in acetone was obtained, it was firstly vigorously stirred to gain uniform distribution of present particles in liquid medium, and then immediately applied to the paper discs that served as carriers for tested materials. After 7 day of incubation, it was established that the surface of paper discs, as well as surrounding agar media were completely covered by the fungal species (Figure 25), and consequently all tested materials were characterised as totally inactive against both fungal strains.

Figure 25. *Growth of Trichoderma viride (left) and Aspergillus niger (right).*



c.) Testing against Mycobacterium strains

Ten acetates (**5a**, **5b**, **6a**, **6b**, **7a–f**), five alcohols (**4a**, **4b**, **11c**, **12a**, **12b**), ten aldehydes (**13a**, **13b**, **14a–f**, **15a**, **15b**), ten carboxylic acids (**16a**, **16b**, **17a–f**, **18a**, **18b**), as well as compounds **4c**, **8a**, **10a** and **20b** were also tested against four *Mycobacterium* strains including *Mycobacterium tuberculosis*, *Mycobacterium marinum*, *Mycobacterium kansasii* and *Mycobacterium smegmatis*. Similar to the previously described results, no worth mentioning activities against any of *Mycobacterium* species were detected for any of screened compounds.

6. EXPERIMENTAL PART

The reagents and solvents were used as obtained from the commercial sources, with the exception of MnO_2 that was prepared using slightly modified synthetic procedure.[171] Transformations were carried out on Heidolph 3001 series magnetic stirring hotplate (Germany) or in microwave synthesizer (Discover® SP, CEM Corporation, USA). Solid products were obtained by solvent evaporation on rotary evaporator (Hei-VAP Value Digital, Heidolph, Germany), while additional drying was performed on lyophilizator (Alpha 1-2 LDplus, Christ, Germany). Monitoring of transformation processes, as well as quality evaluation of all prepared materials were carried out using thin layer chromatography on pre-coated TLC sheets ALUGRAM® SIL G/UV254 for TLC, MACHEREY-NAGEL. While synthesized mono-triazole species were mostly crystallised from suitable solvents, purification of bis-triazole materials was performed on dispersed silica-gel (Fluka Silica gel 60, particle size 0.063–0.2 mm, activity acc. Brockmann and Schodder 2–3) in the appropriate organic solvents. Column chromatography was also utilised for separation and isolation of particular products, when more than one compound was detected in the reaction mixture, or as a filter for reagent residues (Cu^0, PCC, MnO_2) removal. Melting points were determined on the microscope hot stage, Kofler, PolyTherm, manufacturer Helmut Hund GmbH, Wetzlar and are uncorrected. NMR spectra were recorded with a Bruker Avance III 500 MHz NMR instrument operating at 500 MHz (^{1}H), 126 MHz (^{13}C) and 51 MHz (^{15}N) at 300 K. Proton spectra were referenced to TMS as internal standard, in some cases to the residual signal of DMSO-*d6* (at δ 2.50 ppm) or $CHCl_3$ (at δ 7.26 ppm). Carbon chemical shifts were determined relative to the ^{13}C signal of DMSO-*d6* (39.52 ppm) or $CDCl_3$ (77.16 ppm). ^{15}N chemical shifts were extracted from ^{1}H–^{15}N gs-HMBC spectra (with 20 Hz digital resolution in the indirect dimension and the parameters adjusted for a long-range ^{1}H–^{15}N coupling constant of 5 Hz), determined with respect to external nitromethane and are corrected to external ammonia by addition of 380.5 ppm. Nitrogen chemical shifts are reported to one decimal place as measured of the spectrum, however, the data should not be considered to be more accurate than ±0.5 ppm because of the digital resolution limits of the experiment. Chemical shifts are given on the δ scale (ppm). Coupling constants (*J*) are given in Hz. Multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br (broadened). Infrared spectra were recorded on FT-IR spectrometer Alpha (Bruker Optik GmbH Ettlingen, Germany) using samples in potassium bromide discs and only the strongest/structurally most important peaks are listed. Electron impact mass spectra (EI) were recorded on a Shimadzu QP–2010 instrument at 70 eV. HRMS spectra were recorded with Agilent 6224 Accurate Mass TOF LC/MS system with electrospray ionization (ESI). Elemental analyses (C, H, N) were performed with FlashEA1112 Automatic Elemental Analyser (Thermo Fisher Scientific Inc.).

6.1 X-ray crystallography

The molecular structure of compound **17d** was determined by single-crystal X-ray diffraction methods. Diffraction data was collected at room temperature with Agilent SuperNova dual source diffractometer using an Atlas detector and equipped with mirror-monochromated MoKα radiation (λ = 0.71073 Å). The data were processed by using CrysAlis PRO (Oxford Diffraction Ltd., Yarnton, England, 2009). Structures were solved using SHELXS-97[172] and refined against F^2 on all data by full-matrix least-squares with SHELXL–2016.[173] All non-hydrogen atoms were refined anisotropically. The C3 and C21 bonded hydrogen atoms were located in a difference map and refined with the distance restraints (DFIX) with C–H = 0.98 Å and with $U_{iso}(H) = 1.2U_{eq}(C)$. All other hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The crystal structure of compound **17d** contains deuterated solvent molecules ($CDCl_3$). The D and H atoms are both treated as hydrogens but the SFAC instruction for D enables the formula weight and density to be calculated correctly. The C29 and C30 bonded deuterium atoms were located in a difference map and refined with the distance restraints (DFIX) with C–D = 0.98 Å and with $U_{iso}(D) = 1.2U_{eq}(C)$.

6.2 UV spectra measurements

Tested compounds were weighted using microbalance (MX5, Mettler Toledo, Switzerland), dissolved in acetonitrile, quantitatively transferred to 25 mL volumetric flasks and diluted to the mark. That way prepared approximately 25 μM stock solutions were then poured into quarz glass cuvette (b=10.00 mm, Hellma, Germany) and placed into UV-VIS spectrophotometer (Unicam UV 500, Thermo Spectronic, United Kingdom), which was operated by Vision32 (Thermo Spectronic, United Kingdom) software. The UV spectra were recorded in the range 200–400 nm. From the menu selection, automatic peak picking was chosen, while deuterium lamp was automatically exchanged for the tungsten light source at λ=325 nm. Molar attenuation coefficients (ε) were calculated using Beer-Lambert law.

6.3 General procedure for the synthesis of compounds 1a and 1b

Compounds were synthesized using slightly modified literature procedure.[161] A mixture of aniline (23.3 g; 250 mmol) and suitably substituted diethyl malonate (275 mmol) was heated on a metal bath at 150–300 °C. Measuring the quantity of distilled ethanol, the reaction progress was monitored. Within the time period of 9 hours the transformation was completed, as up to 2 moles of ethanol were condensed as a by-product. To a still hot reaction mixture, toluene (200 mL) was added and the precipitated (**1a**) or solidified (**1b**) product

was filtered through the sintered glass filter. The solid residue was then washed with warm fresh toluene (7 x 150 mL) to remove all unreacted diethyl malonate from the product, which was then dried at 50 °C for the time period of 12 hours. The obtained solid was further dissolved in aqueous sodium hydroxide (1M, 700 mL), stirred in the presence of activated charcoal, filtered, and subsequently precipitated by acidification, using concentrated hydrochloric acid. That way obtained 4-hydroxyquinolin-2(1*H*)-one was collected by filtration and washed with distilled water (9 x 100 mL), provided neutral colourless product that was dried at 50 °C for 48 hours and further crystallized from the appropriate solvent.

4-Hydroxy-3-methylquinolin-2(1*H*)-one (1a). Colourless crystals (yield: 59%), m.p. 271–273 °C (ethanol), m.p.[161] 274–275 °C (ethanol); R_f = 0.32 (10% ethanol in chloroform); IR (cm^{-1}): ν 1647, 1608, 1561, 1476, 1401, 1366, 1285, 1273, 1240, 1157, 747, 671, 657.

4-Hydroxy-3-phenylquinolin-2(1*H*)-one (1b). Colourless crystals (yield: 83%), m.p. 335–339 °C (acetic acid), m.p.[161] 334–338 °C (acetic acid); R_f = 0.29 (5% ethanol in chloroform); IR (cm^{-1}): ν 1645, 1610, 1589, 1500, 1406, 1365, 1290, 1244, 1226, 1157, 1112, 756, 697, 557.

6.4 General procedure for the synthesis of compounds 2a and 2b

Compounds were synthesized using slightly modified literature procedure.[162] To a vigorously stirred, slightly heated (40–50 °C) white suspension of appropriate 4-hydroxyquinolin-2(1*H*)-one **1** (400 mmol) in 1,4-dioxane (1200 mL), sulfuryl chloride (1000 mmol) was added dropwise during 30 minutes. Afterwards, obtained reaction mixture was stirred for additional 30 minutes, and subsequently poured into ice-cooled water (10 L). Precipitated solid was filtered through the sintered glass filter, a few times washed with distilled water and dried at 50 °C for 24 hours. That way obtained crude product was crystallized from benzene.

3-Chloro-3-methylquinoline-2,4(1*H*,3*H*)-dione (2a). Yellow crystals (yield: 91%), m.p. 178–181 °C (benzene), m.p.[162] 172 °C (acetic acid–water); R_f = 0.52 (30% ethyl acetate in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.99 (s, 3H), 7.06 (d, 1H, J = 8.0 Hz), 7.22 (dd, 1H, J = 7.6, 7.6 Hz), 7.59–7.66 (m, 1H), 8.02 (d, 1H, J = 7.7 Hz), 9.41 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.2, 62.8, 116.7, 118.1, 124.5, 129.1, 136.8, 139.6, 169.2, 188.4; IR (cm^{-1}): ν 3203, 3072, 3004, 2940, 1709, 1674, 1614, 1600, 1486, 1439, 1379, 1239, 770, 440; MS (EI) *m/z* (%): 212 (4, $[M + 3]^+$), 211 (33, $[M (^{37}Cl)]^+$), 210 (17, $[M + 1]^+$), 209 (100, $[M (^{35}Cl)]^+$), 208 (18), 175 (15), 174 (36), 146 (68), 128 (17), 120 (18), 119 (59), 92 (32), 91 (15); HRMS (ESI+): *m/z* calcd for $C_{10}H_9ClNO_2^+$ $[M + H]^+$ 210.0316,

found 210.0313. Anal. Calcd for $C_{10}H_8ClNO_2$ (209.63): C, 57.30; H, 3.85; N, 6.68%. Found: C, 57.18; H, 3.83; N, 6.61%.

3-Chloro-3-phenylquinoline-2,4(1*H*,3*H*)-dione (2b). Pale yellow crystals (yield: 93%), m.p. 182–185 °C (benzene), m.p.[163] 178–180 °C (ethanol); R_f = 0.57 (30% ethyl acetate in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, 1H, J = 8.0 Hz, H-8), 7.18 (ddd, 1H, J = 7.8, 7.4, 0.7 Hz, H-6), 7.33–7.39 (m, 3H, H-3^C, H-4^C, H-5^C), 7.51–7.54 (m, 2H, H-2^C, H-6^C), 7.55 (ddd, 1H, J = 7.3, 6.5, 1.5 Hz, H-7), 7.97 (dd, 1H, J = 7.8, 1.2 Hz, H-5), 9.82 (s, 1H, H-1); ^{13}C NMR (126 MHz, $CDCl_3$) δ 74.9 (C-3), 116.9 (C-8), 118.7 (C-4a), 124.7 (C-6), 127.4 (C-2^C, C-6^C), 129.1 (C-5), 129.2 (C-3^C, C-5^C), 129.8 (C-4^C), 134.6 (C-1^C), 137.0 (C-7), 139.4 (C-8a), 168.8 (C-2), 187.9 (C-4); IR (cm^{-1}): ν 3201, 3138, 3082, 2992, 2926, 1716, 1680, 1613, 1595, 1485, 1365, 755, 743, 690; MS (EI) *m/z* (%): 273 (7, [M (^{37}Cl)]$^+$), 271 (21, [M (^{35}Cl)]$^+$), 238 (12), 237 (80), 236 (100), 218 (10), 120 (63), 119 (19), 92 (34), 89 (10), 77 (12), 76 (10), 65 (14), 63 (10); HRMS (ESI+): *m/z* calcd for $C_{15}H_{11}ClNO_2^+$ [M + H]$^+$ 272.0473, found 272.0480. Anal. Calcd for $C_{15}H_{10}ClNO_2$ (271.70): C, 66.31; H, 3.71; N, 5.16%. Found: C, 66.07; H, 3.62; N, 5.29%.

6.5 General procedure for the synthesis of compounds 3a and 3b

Compounds were synthesized using slightly modified literature procedure.[162] To a stirred solution of the appropriate 3-chloroquinoline-2,4(1*H*,3*H*)-dione **2** (40 mmol) in DMF (200 mL), sodium azide (3.90 g, 60 mmol) was added in small portions during 10 minutes. The reaction mixture was stirred in darkness for additional 2 hours and then poured into ice-cooled water (1.5 L). The precipitated solid was filtered, washed with water and dried at 50 °C in darkness for 48 hours. The obtained TLC and ^{1}H NMR pure product was then crystallized from benzene.

3-Azido-3-methylquinoline-2,4(1*H*,3*H*)-dione (3a). Colourless needles (yield: 95%), m.p. 158–161 °C (benzene); R_f = 0.30 (30% ethyl acetate in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.86 (s, 3H, CH_3), 7.11 (d, 1H, J = 8.0 Hz, H-8), 7.22 (dd, 1H, J = 7.4, 7.4 Hz, H-6), 7.60–7.67 (m, 1H, H-7), 7.98 (d, 1H, J = 7.3 Hz, H-5), 9.86 (s, 1H, H-1); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.6 (CH_3), 70.0 (C-3), 116.9 (C-8), 118.0 (C-4a), 124.6 (C-6), 128.6 (C-5), 137.2 (C-7), 140.0 (C-8a), 171.6 (C-2), 191.7 (C-4); IR (cm^{-1}): ν 3202, 3078, 3005, 2936, 2108, 1708, 1682, 1614, 1598, 1485, 1392, 1284, 1156, 755, 612; MS (EI) *m/z* (%): 217 (0.24, [M + 1]$^+$), 216 (2, [M]$^+$), 147 (15), 120 (11), 119 (100), 92 (35), 91 (11), 64 (12); HRMS (ESI+): *m/z* calcd for $C_{10}H_9N_4O_2^+$ [M + H]$^+$ 217.0720, found 217.0724. Anal. Calcd for $C_{10}H_8N_4O_2$ (216.20): C, 55.55; H, 3.73; N, 25.91%. Found: C, 55.44; H, 3.72; N, 25.98%.

3-Azido-3-phenylquinoline-2,4(1*H*,3*H*)-dione (3b). Colourless needles (yield: 97%), m.p. 186–189 °C (benzene), m.p.[43] 173–181 °C (benzene); R_f = 0.33 (38% ethyl acetate in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (d, 1H, J = 8.1 Hz, H-8), 7.16 (dd, 1H, J = 7.6, 7.6 Hz, H-6), 7.38–7.43 (m, 3H, H-3^C, H-4^C, H-5^C), 7.48–7.53 (m, 2H, H-2^C, H-6^C), 7.54 (ddd, 1H, J = 7.7, 7.7, 1.6 Hz, H-7), 7.93 (dd, 1H, J = 7.8, 1.6 Hz, H-5), 9.30 (s, 1H, H-1); ^{13}C NMR (126 MHz, $CDCl_3$) δ 78.0 (C-3), 116.7 (C-8), 119.5 (C-4a), 124.6 (C-6), 127.3 (C-2^C, C-6^C), 128.6 (C-5), 129.8 (C-3^C, C-5^C), 130.4 (C-4^C), 132.6 (C-1^C), 136.9 (C-7), 139.4 (C-8a), 170.2 (C-2), 189.9 (C-4); ^{15}N NMR (51 MHz, $CDCl_3$) δ 133.4 (N-1); IR (cm^{-1}): ν 3244, 2105, 1718, 1705, 1685, 1611, 1484, 1356, 1256, 877, 773, 744, 702, 611, 525; MS (EI) *m/z* (%): 250 (7, $[M - N_2]^+$), 236 (8, $[M - N_3]^+$), 147 (28), 120 (14), 119 (100), 104 (15), 92 (32), 77 (10), 76 (10), 64 (14); HRMS (ESI+): *m/z* calcd for $C_{15}H_{11}N_2O_2^+$ $[M - N_2 + H]^+$ 251.0815, found 251.0818. HRMS (ESI−): *m/z* calcd for $C_{15}H_9N_4O_2^-$ $[M - H]^-$ 277.0731, found 277.0732; calcd for $C_{15}H_9N_2O_2^-$ $[M - N_2 - H]^-$ 249.0670, found 249.0671. Anal. Calcd for $C_{15}H_{10}N_4O_2$ (278.27): C, 64.74; H, 3.62; N, 20.13%. Found: C, 64.54; H, 3.56; N, 20.38%.

6.6 Synthesis of compounds 4a–c

6.6.1 General procedure for the synthesis of compounds 4a and 4b

A solution of propargyl alcohol (706 mg, 12.6 mmol) in DMF (4 mL) was added dropwise to a vigorously stirred mixture of suitable 3-azidoquinoline-2,4(1*H*,3*H*)-dione **3** (12 mmol), $CuSO_4 \cdot 5H_2O$ (300 mg, 1.2 mmol), granular copper (1.53 g, 24 mmol) and DMF (24 mL). The reaction mixture was stirred in darkness for 30 minutes. Afterwards, $(NH_4)_2CO_3$ (3.5 g, 36 mmol) and water (12 mL) were added to the resulting brown-black suspension and the stirring was continued for 10 minutes. The reaction mixture was then subjected to silica-gel (15 g) column (⌀ = 1 cm) chromatography, while 10% ethanol in chloroform was utilised as a mobile phase. Combined fractions containing yellow eluate were washed with saturated aqueous NH_4Cl (5 × 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure to afford pure product, which was crystallized from ethanol.

3-(4-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)-3-methylquinoline-2,4(1*H*,3*H*)-dione (4a). Colourless crystals (yield: 99%), m.p. 188–189 °C (ethanol); R_f = 0.35 (30% ethyl acetate in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.08 (s, 3H, CH_3), 4.55 (d, 2H, J = 5.6 Hz, CH_2), 5.28 (t, 1H, J = 5.6 Hz, OH), 7.18–7.25 (m, 2H, H-6, H-8), 7.69–7.76 (m, 1H, H-7), 7.83 (dd, 1H, J = 8.1, 1.4 Hz, H-5), 8.26 (s, 1H, H-5^A), 11.39 (s, 1H, H-1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.1 (CH_3), 55.0 (CH_2), 71.9 (C-3), 116.9 (C-8), 117.5 (C-4a), 123.3 (C-6), 123.7 (C-5^A), 127.6 (C-5), 137.1 (C-7), 141.6 (C-8a), 147.4 (C-4^A), 168.7 (C-2), 190.8

(C-4); IR (cm^{-1}): *v* 3148, 2992, 2919, 1729, 1682, 1613, 1486, 1378, 1345, 1235, 1189, 1009, 751, 667, 590; MS (EI) *m/z* (%): 273 (2, $[M + 1]^+$), 272 (13, $[M]^+$), 185 (68), 175 (89), 174 (45), 146 (100), 128 (58), 120 (70), 119 (75), 92 (66), 91 (39), 77 (39), 65 (37), 55 (39), 42 (79); HRMS (ESI+): *m/z* calcd for $C_{13}H_{13}N_4O_3^+$ $[M + H]^+$ 273.0982, found 273.0981. Anal. Calcd for $C_{13}H_{12}N_4O_3$ (272.26): C, 57.35; H, 4.44; N, 20.58%. Found: C, 57.20; H, 4.42; N, 20.83%.

3-(4-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)-3-phenylquinoline-2,4(1*H*,3*H*)-dione dimethylformamide solvate (4b·DMF). Colourless crystals (yield: 98%), m.p. 139–143 °C (ethanol), m.p.[43] 116–135 °C (benzene); R_f = 0.27 (10% ethanol in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.53 (d, 2H, J = 5.7 Hz, CH_2), 5.22 (t, 1H, J = 5.7 Hz, OH), 7.09 (d, 1H, J = 8.1 Hz, H-8), 7.13–7.18 (m, 1H, H-6), 7.36–7.42 (m, 2H, H-2^C, H-6^C), 7.47–7.53 (m, 3H, H-3^C, H-4^C, H-5^C), 7.59–7.65 (m, 1H, H-7), 7.77 (s, 1H, H-5^A), 7.83 (dd, 1H, J = 7.8, 1.3 Hz, H-5), 11.60 (s, 1H, H-1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 55.0 (CH_2), 79.7 (C-3), 116.7 (C-8), 119.2 (C-4a), 123.4 (C-6), 124.8 (C-5^A), 127.5 (C-5), 128.8 (C-2^C, C-6^C), 129.6 (C-3^C, C-5 ^{C}), 130.2 (C-1^C), 130.5 (C-4^C), 136.9 (C-7), 140.6 (C-8a), 146.8 (C-4^A), 166.8 (C-2), 189.0 (C-4); IR (cm^{-1}): *v* 3392, 3136, 2926, 1724, 1692, 1654, 1613, 1485, 1438, 1353, 857, 769, 752, 665, 603; MS (EI) *m/z* (%): 335 (0.8, $[M + 1]^+$), 334 (4, $[M]^+$), 305 (37), 275 (18), 249 (30), 247 (27), 237 (50), 236 (100), 218 (35), 208 (18), 180 (20), 120 (33), 104 (23), 92 (23), 77 (34); HRMS (ESI+): *m/z* calcd for $C_{18}H_{15}N_4O_3^+$ $[M + H]^+$ 335.1139, found 335.1138. Anal. Calcd for $C_{21}H_{21}N_5O_4$ (407.42): C, 61.91; H, 5.20; N, 17.19%. Found: C, 61.89; H, 5.24; N, 17.28%.

6.6.2 3-Methyl-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)quinoline-2,4(1*H*,3*H*)-dione (4c)

To a solution of azide **3a** (162 mg, 0.75 mmol) and phenylacetylene (153 mg, 1.5 mmol) in dichloromethane (8 mL), a solution of L-ascorbic acid (106 mg, 0.6 mmol) in distilled water (4 mL), and a solution of $CuSO_4 \cdot 5H_2O$ (15 mg, 0.06 mmol) in distilled water (4 mL) were added. The two-phase reaction mixture was vigorously stirred in darkness at room temperature for 48 hours. The reaction mixture was extracted with chloroform (5 × 30 mL). Combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. That way obtained residue was dissolved in chloroform (5 mL) and subjected to silica gel (30 g) column (ø = 2 cm) chromatography using 38% ethyl acetate in hexane as eluent, affording compound **4c** as colourless crystals (199 mg, 83%), m.p. 217–219 °C (ethanol); R_f = 0.35 (30% ethyl acetate in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.15 (s, 3H, CH_3), 7.22–7.27 (m, 2H, H-6, H-8), 7.33–7.39 (m, 1H, H-4^B), 7.45–7.50 (m, 2H, H-3^B, H-5^B), 7.73–7.79 (m, 1H, H-7), 7.83–7.90 (m, 3H, H-5, H-2^B, H-6^B), 8.89 (s, 1H, H-5^A), 11.48 (s, 1H, H-1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.1 (CH_3), 72.2 (C-3), 117.0 (C-8), 117.4

(C-4a), 122.4 (C-5^A), 123.5 (C-6), 125.1 (C-2^B, C-6^B), 127.7 (C-5), 128.0 (C-4^B), 129.0 (C-3^B, C-5^B), 130.6 (C-1^B), 137.3 (C-7), 141.6 (C-8a), 145.8 (C-4^A), 168.5 (C-2), 190.7 (C-4); IR (cm^{-1}): *v* 3142, 2923, 1719, 1683, 1612, 1485, 1428, 1384, 1350, 1242, 1022, 808, 761, 695, 594; MS (EI) *m/z* (%): 319 (2, $[M + 1]^+$), 318 (8, $[M]^+$), 117 (14), 116 (100), 102 (12), 89 (14); HRMS (ESI+): *m/z* calcd for $C_{18}H_{15}N_4O_2^+$ $[M + H]^+$ 319.1190, found 319.1188. Anal. Calcd for $C_{18}H_{14}N_4O_2$ (318.33): C, 67.91; H, 4.43; N, 17.60%. Found: C, 67.80; H, 4.47; N, 17.89%.

6.7 General procedure for the synthesis of compounds 5a and 5b

Acetic anhydride (12 mL, 12.9 g, 126 mmol) was added to a light yellow solution of compound **4a** or **4b** (6 mmol) in pyridine (18 mL) under stirring during 2 minutes. The reaction mixture was stirred for 1 hour, followed by evaporation of volatiles under reduced pressure. The remaining pyridine was removed by co-distillation with ethanol (6 × 40 mL). The residue was triturated with water (300 mL) to form gummy (**5a**) or sand-like (**5b**) material that was then collected by filtration on a sintered glass filter, washed with water to neutral and dried to give acetates **5a** or **5b**. The crude product was recrystallized from ethyl acetate (**5a**) or ethanol (**5b**).

(1-(3-Methyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-1,2,3-triazol-4-yl)methyl acetate (5a). Pale yellow crystals (yield: 84%), m.p. 145–148 °C (ethyl acetate); R_f = 0.33 (5% ethanol in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.06 (s, 3H, $COCH_3$), 2.09 (s, 3H, C-3–CH_3), 5.16 (s, 2H, CH_2), 7.19–7.26 (m, 2H, H-6, H-8), 7.70–7.77 (m, 1H, H-7), 7.83 (dd, 1H, *J* = 8.0, 1.4 Hz, H-5), 8.45 (s, 1H, H-5^A), 11.40 (s, 1H, H-1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 20.6 ($COCH_3$), 23.2 (C-3–CH_3), 57.1 (CH_2), 72.4 (C-3), 116.9 (C-8), 117.5 (C-4a), 123.3 (C-6), 125.8 (C-5^A), 127.6 (C-5), 137.1 (C-7), 141.4 (C-4^A), 141.6 (C-8a), 168.6 (C-2), 170.1 ($COCH_3$), 190.7 (C-4); ^{15}N NMR (51 MHz, DMSO-d_6) δ 133.5 (N-1), 248.7 (N-1^A), 354.1 (N-3^A), 362.9 (N-2^A); IR (cm^{-1}): *v* 3467, 3249, 3148, 2920, 1722, 1685, 1613, 1485, 1439, 1384, 1355, 1239, 1028, 759, 666; MS (EI) *m/z* (%): 315 (2, $[M + 1]^+$), 314 (11, $[M]^+$), 244 (22), 201 (22), 175 (71), 174 (31), 146 (43), 128 (26), 120 (25), 119 (27), 92 (24), 55 (20), 43 (100), 42 (26); HRMS (ESI+): *m/z* calcd for $C_{15}H_{15}N_4O_4^+$ $[M + H]^+$ 315.1088, found 315.1087. Anal. Calcd for $C_{15}H_{14}N_4O_4$ (314.30): C, 57.32; H, 4.49; N, 17.83%. Found: C, 57.32; H, 4.59; N, 17.58%.

(1-(2,4-Dioxo-3-phenyl-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-1,2,3-triazol-4-yl)methyl acetate (5b). Colourless crystals (yield: 85%), m.p. 130–134 °C (ethanol); R_f = 0.40 (5% ethanol in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.04 (s, 3H, CH_3), 5.13 (s, 2H, CH_2), 7.09 (d, 1H, *J* = 8.1 Hz, H-8), 7.13–7.18 (m, 1H, H-6), 7.35–7.42 (m, 2H, H-2^C, H-6^C), 7.46–7.54 (m, 3H, H-3^C, H-4^C, H-5^C), 7.59–7.65 (m, 1H, H-7), 7.83 (dd, 1H, *J* = 7.8, 1.3 Hz), 8.07 (s, 1H, H-5^A),

11.62 (s, 1H, H-1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 20.7 (CH_3), 57.1 (CH_2), 79.9 (C-3), 116.7 (C-8), 119.3 (C-4a), 123.4 (C-6), 127.0 (C-5^A), 127.5 (C-5), 128.8 (C-2^C, C-6^C), 129.6 (C-3^C, C-5^C), 130.0 (C-1^C), 130.6 (C-4^C), 136.9 (C-7), 140.5 (C-8a), 140.8 (C-4^A), 166.8 (C-2), 170.1 ($COCH_3$), 188.8 (C-4); IR (cm^{-1}): *v* 3501, 3155, 2920, 1722, 1707, 1686, 1614, 1594, 1484, 1358, 1252, 1229, 1063, 857, 759; MS (EI) *m*/*z* (%): 377 (1, [M + 1]+), 376 (6, [M]+), 306 (16), 289 (18), 288 (54), 263 (15), 237 (50), 236 (100), 218 (34), 180 (14), 141 (14), 120 (24), 92 (14), 77 (19), 43 (16); HRMS (ESI+): *m/z* calcd for $C_{20}H_{17}N_4O_4^+$ $[M + H]^+$ 377.1244, found 377.1241.

6.8 General procedure for the synthesis of compounds 6a and 6b

The mixture of the appropriate compound **5a** or **5b** (8.00 mmol), potassium carbonate (3.32 g, 24 mmol), and DMF (40 mL) was stirred for 40 minutes. During that time, the original yellow colour of the suspension changed to orange. Afterwards, under continued stirring, an 80% solution of propargyl bromide in toluene (1.78 g, 12 mmol) diluted with DMF (20 mL) was added dropwise during one minute, and stirring was continued for additional 90 minutes. After the reaction was completed, the reaction mixture was poured into ice-cooled water and precipitated white solid was collected by filtration through the sintered glass filter, giving the first portion of crude product. Yellow filtrate was then extracted with ethyl acetate (7 × 40 mL). The organic phases were combined, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The residues of DMF were removed by subsequent co-distillations with toluene (6 × 40 mL), providing the second part of crude product. Both portions of solid product were joined together and crystalized from ethyl acetate.

(1-(3-Methyl-2,4-dioxo-1-(prop-2-yn-1-yl)-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-1,2,3-triazol-4-yl)methyl acetate (6a). Colourless crystals (yield: 81%), m.p. 159–161 °C (ethyl acetate); R_f = 0.29 (30% ethyl acetate in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.06 (s, 3H, $COCH_3$), 2.10 (s, 3H, C-3–CH_3), 3.37 (dd, 1H, *J* = 2.4, 2.4 Hz, C≡CH), 4.84 (dd, 1H, *J* = 18.1, 2.4 Hz, N-1–CHα), 4.95 (dd, 1H, *J* = 18.1, 2.4 Hz, N-1–CHβ), 5.17 (s, 2H, OCH_2), 7.37 (dd, 1H, *J* = 7.5, 7.5 Hz, H-6), 7.58 (d, 1H, *J* = 8.4 Hz, H-8), 7.87–7.93 (m, 1H, H-7), 7.96 (dd, 1H, *J* = 7.7, 1.5 Hz, H-5), 8.46 (s, 1H, H-5^A); ^{13}C NMR (126 MHz, DMSO-d_6) δ 20.6 (CO*C*H_3), 23.4 (C-3–CH_3), 32.6 (N-1–CH_2), 57.1 (OCH_2), 72.8 (C-3), 75.3 (C≡*C*H), 78.2 (*C*≡CH), 116.6 (C-8), 119.2 (C-4a), 124.0 (C-6), 126.0 (C-5^A), 128.0 (C-5), 137.1 (C-7), 140.7 (C-8a), 141.5 (C-4^A), 167.8 (C-2), 170.1 (*C*OCH_3), 189.63 (C-4); ^{15}N NMR (51 MHz, DMSO-d_6) δ 134.4 (N1), 247.9 (N-1^A), 354.0 (N-3^A), 363.4 (N-2^A); IR (cm^{-1}): *v* 3256, 3152, 2122, 1721, 1687, 1604, 1471, 1383, 1306, 1246, 1194, 1053, 1008, 756; MS (EI) *m/z* (%): 353 (3, $[M + 1]^+$), 352 (12, $[M]^+$), 213 (69), 212 (34), 184 (19), 156 (32), 146 (17), 130 (19), 129 (21), 128 (22), 77 (17), 57 (16), 55 (23), 43 (100), 42 (17);

HRMS (ESI+): *m/z* calcd for $C_{18}H_{17}N_4O_4^+$ ($[M+H]^+$): 353.1244, found 353.1246. Anal. Calcd for $C_{18}H_{16}N_4O_4$ (352.34): C, 61.36; H, 4.58; N, 15.90%. Found: C, 61.27; H, 4.64; N, 15.87%.

(1-(2,4-Dioxo-3-phenyl-1-(prop-2-yn-1-yl)-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-1,2,3-triazol-4-yl)methyl acetate (6b). Colourless crystals (yield: 63%), m.p. 210–214 °C (ethyl acetate); R_f = 0.66 (5% ethanol in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.05 (s, 3H, $COCH_3$), 3.41 (dd, 1H, J = 2.4, 2.3 Hz, C≡CH), 4.80 (dd, 1H, J = 18.0, 2.3 Hz, N-1–CHα), 5.09–5.20 (m, 3H, N-1–CHβ, OCH_2), 7.24–7.32 (m, 3H, H-6, H-2^C, H-6^C), 7.41–7.51 (m, 4H, H-8, H-3^C, H-4^C, H-5^C), 7.73–7.79 (m, 1H, H-7), 7.92 (dd, 1H, J = 7.7, 1.5 Hz, H-5), 8.15 (s, 1H, H-5^A); ^{13}C NMR (126 MHz, DMSO-d_6) δ 20.6 ($CO\mathit{C}H_3$), 33.1 (N-1–CH_2), 57.1 (OCH_2), 75.5 (C≡*C*H), 77.9 (*C*≡CH), 80.0 (C-3), 116.3 (C-8), 120.9 (C-4a), 124.2 (C-6), 127.1 (C-5^A), 127.8 (C-5), 128.6 (C-2^C, C-6^C), 129.5 (C-3^C, C-5^C), 129.9 (C-1^C), 130.7 (C-4^C), 136.7 (C-7), 140.0 (C-8a), 140.9 (C-4^A), 165.8 (C-2), 170.1 (*C*OCH_3), 187.7 (C-4); IR (cm^{-1}): ν 3227, 3152, 2116, 1736, 1715, 1683, 1602, 1467, 1379, 1303, 1251, 1036, 764, 747, 694; MS (EI) *m/z* (%): 415 (2, $[M + 1]^+$), 414 (7, $[M]^+$), 313 (26), 275 (72), 274 (63), 246 (28), 235 (31), 218 (29), 217 (30), 156 (26), 130 (29), 105 (22), 104 (29), 103 (22), 43 (100); HRMS (ESI+): *m/z* calcd for $C_{23}H_{19}N_4O_4^+$ $[M + H]^+$ 415.1401, found 415.1403. Anal. Calcd for $C_{23}H_{18}N_4O_4$: C, 66.66; H, 4.38; N, 13.52%. Found: C, 66.45; H, 4.39; N, 13.35%.

6.9 Synthesis of organic azides

6.9.1 Azidomethylbenzene (A)

Compound **A** was synthesized using slightly modified literature procedure.[174] To benzyl bromide (17.1 g, 100 mmol), 2 litres of diluted acetone (Me_2CO:H_2O 4:1 *V*/*V*) were added. Afterwards, sodium azide (9.76 g, 150 mmol) was added and obtained reaction mixture was stirred in darkness for the time period of 24 hours. Obtained mixture was then extracted with diethyl ether (5 x 70 mL) and chloroform (6 x 70 mL). The organic phases were joined, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to provide colourless viscous oil (yield: 75%), R_f = 0.59 (chloroform); IR (cm^{-1}): ν 2495, 2096, 1954, 1810, 1605, 1496, 1454, 1255, 1078, 1029, 876, 737, 699.

6.9.2 Azidobenzene (B)

Compound **B** was synthesized using slightly modified literature procedure.[175] To the ice-cooled aniline (9.1 mL, 9.3 g, 100 mmol), 63 mL of diluted hydrochloride acid (HCl : H_2O 1:1 *V*/*V*) was added. To that way obtained white suspension, $NaNO_2$ (7.04 g, 102 mmol) in distilled water (63 mL) was added during 13 minutes, resulting in formation of clear yellow solution that was

stirred for additional 30 minutes. Afterwards, addition of sodium azide (6.63g, 102 mmol) throughout the time period of 17 minutes took place. Resulting emulsion was further stirred in darkness for 100 minutes on ice-cooled bath, neutralised with $NaHCO_3$ (20.8 g, 248 mmol) and extracted with diethyl ether (6 x 50 mL). Combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to gain reddish-brown oil (yield: 81%), R_f = 0.66 (3% ethyl acetate in chloroform); IR (cm^{-1}): *v* 2418, 2257, 2129, 2095, 1938, 1594, 1492, 1296, 1129, 749, 687, 670, 533, 491.

6.9.3 Tetrazolo[1,5-*a*]pyridine (C)

Compound **C** was synthesized using slightly modified literature procedure.[176] To the solution of 2-chloropyridine (9.65, 85 mmol) in ethanol (170 mL), 10% HCl (*w*/*w*, 43 mL) and dissolved NaN_3 (11.05g 170 mmol) in distilled water (50 mL) were added. Reaction mixture was stirred in darkness at 90 °C for the time period of 45 hours. That way obtained colourless solution was neutralised using 15% (*w*/*w*) NaOH, subsequently concentrated on rotary evaporator, and finally extracted with chloroform (7 x 60 mL). Combined organic phases were dried over anhydrous Na_2SO_4, filtered and transferred to rotary evaporator, where volatiles were removed under vacuum. Resulted yellowish crude product was crystallised from slightly acidified ethanol to gain colourless crystals (yield: 62%), m.p. 161–163 °C (slightly acidified ethanol), m.p.[177] 158–160 °C; R_f = 0.34 (3% ethanol in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.45 (ddd, 1H, *J* = 6.8, 6.8, 1.1 Hz), 7.87 (ddd, 1H, *J* = 9.0, 6.8, 1.0 Hz), 8.23 (ddd, 1H, *J* = 9.0, 1.1, 1.0 Hz), 9.33 (ddd, 1H, *J* = 6.8, 1.1, 1.0 Hz); IR (cm^{-1}): *v* 3105, 3034, 1631, 1492, 1434, 1366, 1235, 1140, 1094, 1015, 989, 769, 753, 433; HRMS (ESI+): *m/z* calcd for $C_5H_5N_4^+$ $[M + H]^+$ 121.0509, found 121.0508.

6.10 Synthesis of compounds 7a–f

6.10.1 General procedure for the synthesis of compounds 7a, 7b, 7d and 7e

A solution of (azidomethyl)benzene (**A**, 220 mg, 1.65 mmol) or azidobenzene (**B**, 197 mg, 1.65 mmol) in DMF (4 mL) was added to a vigorously stirred mixture of the appropriate *N*-propargylquinoline-2,4(1*H*,3*H*)-dione **6** (1.5 mmol), $CuSO_4 \cdot 5H_2O$ (38 mg, 0.15 mmol) and granular copper (191 mg, 3.0 mmol) in DMF (5 mL). The reaction mixture was stirred in darkness at room temperature up to 4 hours. The colour of the mixture became brown-black. Then, $(NH_4)_2CO_3$ (432 mg, 4.5 mmol) and distilled water (2 mL) were added to the reaction mixture and the stirring was continued for additional 10 minutes. The reaction mixture was then poured into a narrow silica-gel (15 g) column (ø = 1 cm). The organic portion was eluted with 10% ethanol in chloroform (approximately 150 mL). The yellow eluate was washed with saturated aqueous

NH_4Cl (50 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent was removed by rotary evaporation *in vacuo*. The residues of DMF were removed by subsequent co-distillations with toluene (7 × 40 mL). The crude product thus prepared was purified on silica-gel (40 g) chromatography column (ø = 2cm), using gradually 2.5%, 3.3%, 5%, and finally 10% ethanol in chloroform, while compound **7d** was further crystalized from ethanol.

(1-(1-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-3-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-1,2,3-triazol-4-yl)methyl acetate (7a). Colourless powder (yield: 96%), m.p. 69–82 °C; R_f = 0.42 (30% ethyl acetate in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$), δ 2.09 (s, 3H, $COCH_3$), 2.12 (s, 3H, C-3–CH_3), 5.25 (s, 2H, OCH_2), 5.33 (s, 2H, N-1-CH_2), 5.45 (d, 1H, *J* = 14.8 Hz, N-1^D–CH*α*), 5.51 (d, 1H, *J* = 14.8 Hz, N-1^D–CH*β*), 7.23–7.26 (m, 3H, H-6, H-2^E, H-6^E), 7.32–7.38 (m, 3H, H-3^E, H-4^E, H-5^E), 7.55 (s, 1H, H-5^D), 7.73 (ddd, 1H, *J* = 8.7, 7.1, 1.6 Hz, H-7), 7.78 (s, 1H, H-5^A), 7.82 (d, 1H, *J* = 8.4 Hz, H-8), 8.02 (dd, 1H, *J* = 7.7, 1.6 Hz, H-5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.1 (CO*C*H_3), 23.5 (C-3–*C*H_3), 39.5 (N-1–CH_2), 54.5 (N-1^D–CH_2), 57.7 (OCH_2), 71.6 (C-3), 116.9 (C-8), 119.2 (C-4a), 123.5 (C-5^D), 124.2 (C-5^A), 124.6 (C-6), 128.3 (C-2^E, C-6^E), 129.0 (C-4^E), 129.3 (C-3^E, C-5^E), 129.3 (C-5), 134.4 (C-1^E), 137.8 (C-7), 141.7 (C-8a), 142.3 (C-4^A), 142.9 (C-4^D), 168.2 (C-2), 171.1 (*C*OCH$_3$), 189.4 (C-4); ^{15}N NMR (51 MHz, $CDCl_3$) δ 138.7 (N-1), 248.4 (N-1^A), 250.4 (N-1^D), 350.0 (N-3^D), 355.2 (N-3^A), 361.6 (N-2^A), 362.6 (N-2^D); IR (cm^{-1}): *ν* 3143, 2930, 1739, 1717, 1679, 1602, 1470, 1384, 1243, 1186, 1050, 1028, 765, 721, 664; MS (EI) *m/z* (%): 486 (0.3, $[M + 1]^+$), 485 (1, $[M]^+$), 144 (18), 91 (100), 43 (24); HRMS (ESI+): *m/z* calcd for $C_{25}H_{24}N_7O_4^+$ $[M + H]^+$ 486.1884, found 486.1884.

(1-(3-Methyl-2,4-dioxo-1-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-1,2,3-triazol-4-yl)methyl acetate (7b). Colourless powder (yield: 92%), m.p. 78–97 °C; R_f = 0.25 (30% ethyl acetate in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.10 (s, 3H, $COCH_3$), 2.20 (s, 3H, C-3–CH_3), 5.27 (s, 2H, OCH_2), 5.42 (d, 1H, *J* = 15.8 Hz, N-1–CH*α*), 5.52 (d, 1H, *J* = 15.8 Hz, N-1–CH*β*), 7.27–7.30 (m, 1H, H-6), 7.41-7.47 (m, 1H, H-4^E), 7.49–7.55 (m, 2H, H-3^E, H-5^E), 7.69-7.74 (m, 2H, H-2^E, H-6^E), 7.76 (ddd, 1H, *J* = 8.1, 7.7, 1.6 Hz, H-7), 7.85 (d, 1H, *J* = 7.3 Hz, H-8), 7.86 (s, 1H, H-5^A), 8.05 (dd, 1H, *J* = 7.8, 1.5 Hz, H-5), 8.10 (s, 1H, H-5^D); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.0 (CO*C*H_3), 23.4 (C-3–*C*H_3), 39.5 (N-1-CH_2), 57.7 (OCH_2), 71.5 (C-3), 116.8 (C-8), 119.2 (C-4a), 120.6 (C-2^E, C-6^E), 121.7 (C-5^D), 124.1 (C-5^A), 124.7 (C-6), 129.1 (C-4^E), 129.4 (C-5), 129.9 (C-3^E, C-5^E), 136.9 (C-1^E), 137.8 (C-7), 141.7 (C-8a), 142.3 (C-4^A), 143.2 (C-4^D), 168.3 (C-2), 171.1 (*C*OCH$_3$), 189.4 (C-4); ^{15}N NMR (51 MHz, $CDCl_3$) δ 138.7 (N-1), 248.8 (N-1^A), 256.3 (N-1^D), 351.9 (N-3^D), 355.5 (N-3^A); IR (cm^{-1}): *ν* 3145, 2926, 1740, 1717, 1681, 1601, 1470, 1384, 1242, 1184, 1046, 761, 691, 664; MS (EI) *m/z* (%): 472 (0.9, $[M + 1]^+$), 471

(3, $[M]^+$), 303 (20), 302 (17), 131 (13), 130 (100), 129 (14), 77 (44), 43 (25); HRMS (ESI+): *m/z* calcd for $C_{24}H_{22}N_7O_4^+$ $[M + H]^+$ 472.1728, found 472.1726.

(1-(1-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-2,4-dioxo-3-phenyl-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-1,2,3-triazol-4-yl)methyl acetate (7d). Colourless crystals (yield: 97%), m.p. 188–194 °C (ethanol); R_f = 0.41 (30% ethyl acetate in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.04 (s, 3H, CH_3), 5.17 (s, 2H, OCH_2), 5.21 (d, 1H, *J* = 15.6 Hz, N-1–CHα), 5.43 (d, 1H, *J* = 14.8 Hz, N-1^D–CHα), 5.51 (d, 1H, *J* = 15.6 Hz, N-1–CHβ), 5.55 (d, 1H, *J* = 14.8 Hz, N-1^D–CHβ), 7.08 (s, 1H, H-5^A), 7.18 (ddd, 1H, *J* = 7.5, 7.5, 0.8 Hz, H-6), 7.23–7.29 (m, 4H, H-3^C, H-5^C, H-2^E, H-6^E), 7.29–7.33 (m, 2H, H-2^C, H-6^C), 7.34–7.39 (m, 3H, H-3^E, H-4^E, H-5^E), 7.38-7.44 (m, 1H, H-4^C), 7.58 (s, 1H, H-5^D), 7.63 (ddd, 1H, *J* = 8.4, 7.4, 1.7 Hz, H-7), 7.75 (d, 1H, *J* = 8.3 Hz, H-8), 7.99 (dd, 1H, *J* = 7.7, 1.7 Hz, H-5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.0 (CH_3), 39.9 (N-1–CH_2), 54.5 (N-1^D–CH_2), 57.6 (OCH_2), 79.6 (C-3), 116.8 (C-8), 120.9 (C-4a), 123.5 (C-5^D), 124.6 (C-6), 126.4 (C-5^A), 128.3 (C-2^E, C-6^E), 128.7 (C-2^C, C-6^C), 129.0 (C-5), 129.1 (C-4^E), 129.4 (C-3^E, C-5^E), 129.7 (C-1^C), 130.0 (C-3^C, C-5^C), 131.3 (C-4^C), 134.5 (C-1^E), 137.2 (C-7), 140.9 (C-4^A), 141.1 (C-8a), 142.9 (C-4^D), 166.6 (C-2), 171.0 (*C*OCH$_3$), 187.9 (C-4); ^{15}N NMR (51 MHz, $CDCl_3$) δ 140.4 (N-1), 249.8 (N-1^A), 250.4 (N-1^D), 350.5 (N-3^D), 356.9 (N-3^A), 362.9 (N-2^D), 365.1 (N-2^A); IR (cm^{-1}): *v* 3142, 2927, 1740, 1717, 1679, 1602, 1469, 1377, 1244, 768, 749, 714, 697; MS (EI) *m/z* (%): 548 (0.1, $[M + 1]^+$), 547 (0.3, $[M]^+$), 347 (13), 289 (13), 144 (14), 105 (10), 104 (13), 91 (100), 43 (29); HRMS (ESI+): *m/z* calcd for $C_{30}H_{26}N_7O_4^+$ $[M + H]^+$ 548.2041, found 548.2032.

(1-(2,4-Dioxo-3-phenyl-1-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-1,2,3-triazol-4-yl)methyl acetate (7e). Colourless powder (yield: 93%), m.p. 93–105 °C; R_f = 0.42 (30% ethyl acetate in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05 (s, 3H, CH_3), 5.19 (s, 2H, OCH_2), 5.42 (d, 1H, *J* = 15.7 Hz, N-1–CHα), 5.55 (d, 1H, *J* = 15.7 Hz, N-1–CHβ), 7.14 (s, 1H, H-5^A), 7.20 (ddd, 1H, *J* = 7.6, 7.6, 0.8 Hz, H-6), 7.38-7.49 (m, 6H, H-2^C, H-3^C, H-4^C, H-5^C, H-6^C, H-4^E), 7.49–7.55 (m, 2H, H-3^E, H-5^E), 7.66 (ddd, 1H, *J* = 8.5, 7.3, 1.7 Hz, H-7), 7.68–7.72 (m, 2H, H-2^E, H-6^E), 7.76 (d, 1H, *J* = 8.4 Hz, H-8), 8.03 (dd, 1H, *J* = 7.8, 1.5 Hz, H-5), 8.05 (s, 1H, H-5^D); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.0 (CH_3), 39.8 (N-1-CH_2), 57.6 (OCH_2), 79.6 (C-3), 116.7 (C-8), 120.7 (C-2^E, C-6^E), 120.9 (C-4a), 121.8 (C-5^D), 124.7 (C-6), 126.4 (C-5^A), 128.9 (C-2^C, C-6^C), 129.1 (C-5), 129.2 (C-4^E), 129.9 (C-1^C), 130.0 (C-3^E, C-5^E), 130.2 (C-3^C, C-5^C), 131.4 (C-4^C), 136.9 (C-1^E), 137.4 (C-7), 140.9 (C-4^A), 140.9 (C-8a), 143.2 (C-4^D), 166.9 (C-2), 171.0 (*C*OCH$_3$), 187.9 (C-4); ^{15}N NMR (51 MHz, $CDCl_3$) δ 140.4 (N-1), 249.9 (N-1^A), 256.3 (N-1^D), 352.9 (N-3^D), 357.2 (N-3^A); IR (cm^{-1}): *v* 3146, 2962, 1741, 1718, 1681, 1600, 1468, 1376, 1243, 1043, 762, 693, 665, 608; MS (EI) *m/z* (%): 534 (0.2, $[M + 1]^+$), 533 (0.6, $[M]^+$), 366 (12), 365 (11), 262 (12), 131 (11), 130 (100), 129 (19), 128 (12), 104 (14), 103 (16),

99 (18), 77 (62), 44 (17), 43 (52); HRMS (ESI+): *m/z* calcd for $C_{29}H_{24}N_7O_4^+$ $[M + H]^+$ 534.1884, found 534.1882.

6.10.2 General procedure for the synthesis of compounds 7c and 7f

A mixture of the appropriate *N*-propargylquinoline-2,4(1*H*,3*H*)-dione **6** (1.5 mmol), tetrazolo[1,5-*a*]pyridine (**C**, 189 mg, 1.58 mmol), $CuSO_4 \cdot 5H_2O$ (38 mg, 0.15 mmol), granular copper (191 mg, 3.0 mmol) and DMF (9 mL) was heated in darkness to 95–105 °C (oil bath) for up to 1 hour, whereas the colour of the mixture changed from brown-black to dark green. The mixture was then allowed to cool to room temperature. Subsequently, $(NH_4)_2CO_3$ (432 mg, 4.5 mmol) and water (2 mL) were added and after stirring for 15 minutes, the mixture was poured into a narrow silica-gel (15 g) column (ø = 1 cm). The organic portion was eluted from the column with 10% ethanol in chloroform. The yellow eluate was washed with saturated aqueous NH_4Cl (50 mL), dried over anhydrous sodium sulfate, filtered, and the solvent was removed by rotary evaporation *in vacuo*. The residues of DMF were removed by subsequent co-distillations with toluene (7 × 40 mL). The crude product thus obtained was purified on silica-gel (40 g) chromatography column (ø = 1 cm), using ethanol or ethyl acetate in chloroform as an eluent.

(1-(3-Methyl-2,4-dioxo-1-((1-(pyridin-2-yl)-1*H*-1,2,3-triazol-4-yl)methyl)-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-1,2,3-triazol-4-yl)methyl acetate (7c). Colourless powder (yield: 85%), m.p. 69–82 °C; R_f = 0.29 (30% ethyl acetate in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.06 (s, 3H, $COCH_3$), 2.18 (s, 3H, C3–CH_3), 5.17 (d, 1H, *J* = 12.7 Hz, O–CHα), 5.20 (d, 1H, *J* = 12.7 Hz, O–CHβ), 5.41 (d, 1H, *J* = 16.5 Hz, N-1–CHα), 5.53 (d, 1H, *J* = 16.5 Hz, N-1–CHβ), 7.31 (dd, 1H, *J* = 7.4, 7.4 Hz, H-6), 7.54 (dd, 1H, *J* = 8.8, 4.5 Hz, H-5^E), 7.59 (d, 1H, *J* = 8.5 Hz, H-8), 7.77–7.83 (m, 1H, H-7), 7.96 (dd, 1H, *J* = 7.7 Hz, *J* = 1.6 Hz, H-5), 8.08–8.14 (m, 2H, H-3^E, H-4^E), 8.47 (s, 1H, H-5^A), 8.55–8.59 (m, 1H, H-6^E), 8.82 (s, 1H, H-5^D); ^{13}C NMR (126 MHz, DMSO-d_6) δ 20.6 (CO*C*H_3), 23.5 (C3–*C*H_3), 38.7 (N-1–CH_2), 57.2 (OCH_2), 73.3 (C-3), 113.7 (C-3^E), 116.5 (C-8), 119.4 (C-4a), 120.6 (C-5^D), 123.8 (C-6), 124.4 (C-5^E), 126.1 (C-5^A), 127.9 (C-5), 137.0 (C-7), 140.2 (C-4^E), 141.3 (C-8a), 141.6 (C-4^A), 143.2 (C-4^D), 148.3 (C-2^E), 148.9 (C-6^E), 168.6 (C-2), 170.1 (*C*OCH_3), 189.9 (C-4); ^{15}N NMR (51 MHz, DMSO-d_6) δ 135.3 (N1), 247.6 (N-1^A), 260.0 (N-1^D), 284.7 (N-1^E), 353.4 (N-3^A), 356.5 (N-3^D), 361.9 (N-2^D), 363.7 (N-2^A); IR (cm^{-1}): ν 3152, 1741, 1718 1681, 1600, 1471, 1384, 1314, 1242, 1183, 1038, 782, 756, 663; MS (EI) *m/z* (%): 473 (0.7, $[M + 1]^+$), 472 (2, $[M]^+$), 304 (27), 303 (26), 302 (17), 132 (13), 131 (100), 79 (22), 78 (100), 43 (21); HRMS (ESI+): *m/z* calcd for $C_{23}H_{21}N_8O_4^+$ $[M + H]^+$ 473.1680, found 473.1684. Anal. Calcd for $C_{23}H_{20}N_8O_4 \cdot ½H_2O$ (472.46): C, 57.38; H, 4.40; N, 23.27%. Found: C, 57.39; H, 4.36; N, 23.47%.

(1-(2,4-Dioxo-3-phenyl-1-((1-(pyridin-2-yl)-1*H*-1,2,3-triazol-4-yl)methyl)-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-1,2,3-triazol-4-yl)methyl acetate (7f). Colourless powder (yield: 85%), m.p. 93–102 °C; R_f = 0.18 (30% ethyl acetate in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05 (s, 3H, $COCH_3$), 5.19 (s, 2H, OCH_2), 5.30 (d, 1H, J = 15.8 Hz, N-1–CHα), 5.71 (d, 1H, J = 15.8 Hz, N-1–CHβ), 7.13 (s, 1H, H-5^A), 7.19 (dd, 1H, J = 7.5, 7.5 Hz, H-6), 7.36 (dd, 1H, J = 7.3, 4.9 Hz, H-5^E), 7.38–7.42 (m, 2H, H-3^C, H-5^C), 7.42-7.48 (m, 3H, H-2^C, H-4^C, H-6^C), 7.63 (ddd, 1H, J = 8.3, 7.4, 1.6 Hz, H-7), 7.70 (d, 1H, J = 8.4 Hz, H-8), 7.88-7.95 (m, 1H, H-4^E), 8.02 (dd, 1H, J = 7.8, 1.5 Hz, H-5), 8.15 (d, 1H, J = 8.2 Hz, H-3^E), 8.47-8.53 (m, 1H, H-6^E), 8.63 (s, 1H, H-5^D); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.0 (CO*C*H$_3$), 39.9 (N-1–CH_2), 57.6 (OCH_2), 79.7 (C-3), 113.9 (C-3^E), 116.6 (C-8), 121.0 (C-4a), 121.0 (C-5^D), 124.0 (C-5^E), 124.6 (C-6), 126.4 (C-5^A), 128.9 (C-2^C, C-6^C), 129.1 (C-5), 129.7 (C-1^C), 130.2 (C-3^C, C-5^C), 131.3 (C-4^C), 137.2 (C-7), 139.3 (C-4^E), 140.9 (C-4^A), 141.2 (C-8a), 143.0 (C-4^D), 148.9 (C-6^E), 149.0 (C-2^E), 166.6 (C-2), 171.0 (*C*OCH$_3$), 187.9 (C-4); ^{15}N NMR (51 MHz, $CDCl_3$) δ 138.9 (N-1), 249.7 (N-1^A), 261.2 (N-1^D), 285.1 (N-1^E), 355.8 (N-3^D), 357.1 (N-3^A); IR (cm^{-1}): ν 3155, 2926, 1741, 1718, 1682, 1599, 1470, 1375, 1313, 1243, 1034, 779, 697, 665; MS (EI) *m/z* (%): 535 (0.4, $[M + 1]^+$), 534 (0.7, $[M]^+$), 132 (14), 131 (100), 79 (19), 78 (93), 44 (11), 43 (31); HRMS (ESI+): *m/z* calcd for $C_{28}H_{23}N_8O_4^+$ $[M + H]^+$ 535.1837, found 535.1846.

6.10.3 Microwave-assisted synthesis of compounds 7c and 7f

A mixture of appropriate *N*-propargylquinoline-2,4(1*H*,3*H*)-dione **6** (0.5 mmol), tetrazolo[1,5-*a*]pyridine (**C**, 63 mg, 0.53 mmol), $CuSO_4 \cdot 5H_2O$ (13 mg, 0.05 mmol) and granular copper (64 mg, 1.0 mmol) in DMF (4 mL) was placed into microwave reactor and stirred at 90 °C (P = 150 W) for the time period of 15 minutes. The colour of the mixture changed from brown-black to dark green. The mixture was then cooled down to laboratory temperature. Afterwards, $(NH_4)_2CO_3$ (144 mg, 1.5 mmol) and water (1 mL) were added and stirring was continued for additional 15 minutes. The mixture was then poured into a narrow silica-gel (15 g) column (ø = 1 cm). The organic portion was eluted from the column using 10% ethanol in chloroform. The yellow eluate was washed with saturated aqueous NH_4Cl (25 mL), dried over anhydrous sodium sulphate, filtered and evaporated to dryness. The residues of DMF were removed by subsequent co-distillations with toluene (5 × 20 mL). The crude product thus obtained was purified on silica-gel (40 g) chromatography column (ø = 2 cm), using ethyl acetate in chloroform as an eluent.

6.10.4 Additional procedures for the synthesis of compound 7a

a.) Employing t-BuOH / water / $CuSO_4 \cdot 5H_2O$ / L-ascorbic acid conditions.

To a mixture of *N*-propargyl derivative **6a** (264 mg, 0.75 mmol) and benzyl azide **A** (105 mg, 0.79 mmol), a solution of L-ascorbic acid (13 mg, 0.074 mmol) and $CuSO_4 \cdot 5H_2O$ (2 mg, 0.008 mmol) in water (3.5 mL), and *t*-BuOH (3.5 mL) were added. The reaction mixture was stirred in darkness at room temperature. After 8.5 and 22 hours of stirring, additional portions of L-ascorbic acid / $CuSO_4 \cdot 5H_2O$ / water / *t*-BuOH (40 mg, 0.23 mmol / 6 mg, 0.02 mmol / 1 mL / 1 mL and 53 mg, 0.3 mmol / 7.5 mg, 0.03 mmol / 1 mL / 1 mL, respectively) were added. Although, after stirring for additional 23 hours (total reaction time: 45 hours), TLC analysis indicated the presence of azide **A** and acetylene **6a** starting compounds, the heterogeneous reaction mixture (a sticky sediment was formed) was diluted with water and extracted with chloroform (5 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was dissolved in chloroform (5 mL) and subjected to silica-gel (35 g) column (ø = 2 cm) chromatography using 33% ethyl acetate in petroleum ether as eluent, affording regenerated starting acetylene **6a** (114 mg, 43%) and product **7a** (165 mg, 45%).

b.) Employing t-BuOH / water / CH_3CN / $CuSO_4 \cdot 5H_2O$ / Na-ascorbate conditions.

To a mixture of *N*-propargyl derivative **6a** (264 mg, 0.75 mmol), benzyl azide **A** (105 mg, 0.79 mmol) and *t*-BuOH (3.5 mL), a solution of sodium ascorbate (30 mg, 0.15 mmol) in water (2.5 mL), and a solution of $CuSO_4 \cdot 5H_2O$ (4 mg, 0.02 mmol) in water (1 mL) were added. The reaction mixture was stirred in darkness at room temperature for 9 h. Then a solution of sodium ascorbate (89 mg, 0.45 mmol) in water (1 mL), and a solution of $CuSO_4 \cdot 5H_2O$ (11 mg, 0.044 mmol) in water (1 mL) and *t*-BuOH (2 mL) were added. The reaction mixture was stirred for additional 20 h. The resulting sticky sediment that formed in the course of the reaction was dissolved by addition of acetonitrile (3 mL) to the reaction mixture. The reaction mixture was stirred for additional 19 h (total reaction time 48 hours). Although the azide **A** and acetylene **6a** coupling partners were still present in the mixture, as judged by TLC analysis, the reaction was stopped by the addition of water (50 mL) and extracted with chloroform (4 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was dissolved in chloroform and subjected to silica-gel (35 g) column (ø = 2 cm) chromatography using 67% ethyl acetate in petroleum ether as eluent, affording regenerated starting acetylene **6a** (48 mg, 18%) and desired product **7a** (295 mg, 81%).

c.) Employing CH_2Cl_2 / water / $CuSO_4 \cdot 5H_2O$ / Na-ascorbate conditions.

To a solution of *N*-propargyl derivative **6a** (132 mg, 0.375 mmol) and benzyl azide **A** (52.4 mg, 0.394 mmol) in dichloromethane (6.5 mL) a solution of sodium ascorbate (59.5 mg, 0.3 mmol) in water (5.5 mL), and a solution of $CuSO_4 \cdot 5H_2O$ (7.5 mg, 0.03 mmol) in water (1 mL) were added. The two-phase liquid reaction mixture was stirred in darkness at room temperature for the time period of 4 hours, until the compound **6a** reacted completely according to TLC analysis. The reaction mixture was then diluted with water (50 mL) and extracted with chloroform (4 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was dissolved in chloroform (5 mL) and subjected to silica-gel (30 g) column (ø = 2 cm) chromatography, using 67% ethyl acetate in petroleum ether as eluent, affording product **7a** (155 mg, 85%).

6.11 3-Azido-3-methyl-1-(prop-2-yn-1-yl)quinoline-2,4(1*H*,3*H*)-dione (8a)

A mixture of the azide **3a** (649 mg, 3.0 mmol) and potassium carbonate (1.24 g, 9 mmol) in DMF (15 mL) was stirred at room temperature in darkness for the time period of 40 minutes. Propargyl bromide (80% solution in toluene, 669 mg, 4.5 mmol) diluted with DMF (7 mL) was added dropwise under vigorous stirring during one minute. The reaction mixture was then stirred for 6 hours, during which time it turned yellow, diluted with cold water (200 mL) and extracted with chloroform (5 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. Trace amounts of DMF were removed by five subsequent co-distillations with toluene (30 mL) at 50 °C. The residual yellow oil was dissolved in chloroform (5 mL) and chromatographed on silica-gel (35 g) column (ø = 2 cm), using chloroform as an eluent, affording product **8a** (717 mg, 94%, dried *in vacuo* to constant weight); off-white oil, R_f = 0.57 (chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.79 (s, 3H), 2.29 (dd, 1H, J = 2.5, 2.5 Hz), 4.67 (dd, 1H, J = 17.8, 2.5 Hz), 4.98 (dd, 1H, J = 17.8, 2.5 Hz), 7.26 (ddd, 1H, J = 7.7, 7.4, 0.8 Hz), 7.35 (d, 1H, J = 8.3 Hz), 7.71 (ddd, 1H, J = 8.3, 7.4, 1.7 Hz), 8.02 (dd, 1H, J = 7.7, 1.7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.6, 32.7, 70.7, 73.4, 77.1, 115.8, 119.6, 124.4, 129.0, 136.9, 140.8, 169.1, 191.1; IR (cm^{-1}): ν 3241, 2980, 2138, 2107, 1711, 1678, 1603, 1471, 1383, 1366, 1305, 1285, 1260, 1218, 762; UV λ_{max} [nm] (10^{-3} ε [$M^{-1}cm^{-1}$]): 233 (33.1), 341 (2.7); HRMS (ESI+): *m/z* calcd for $C_{13}H_{11}N_4O_2^+$ $[M + H]^+$ 255.0877, found 255.0877; calcd for $C_{13}H_{11}N_2O_2^+$ $[M - N_2 + H]^+$ 227.0815, found 227.0814.

6.12 3-Methyl-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-1-(prop-2-yn-1-yl)quinoline-2,4(1*H*,3*H*)-dione (9a)

A mixture of compound **8a** (286 mg, 1.13 mmol), phenylacetylene (230 mg, 2.25 mmol), $CuSO_4 \cdot 5H_2O$ (28 mg, 0.11 mmol) and granular copper (143 mg, 2.25 mmol) in DMF (5 mL) was stirred in darkness at room temperature for 60 minutes. To the resulting brown-green suspension, $(NH_4)_2CO_3$ (324 mg, 3.38 mmol) and water (3 mL) were added and stirring was continued for 10 minutes. The resulting mixture was diluted with 10% ethanol in chloroform (10 mL). The organic layer was separated and the aqueous layer was extracted with chloroform (3 × 10 mL). The combined organic layers were passed through a narrow silica-gel (13 g) column (ø = 1 cm) that was subsequently washed with 10% ethanol in chloroform (210 mL), applying overpressure to the top of the column. The yellow eluate was washed with saturated aqueous NH_4Cl (1 × 50 mL) and distilled water (1 × 50 mL), dried (Na_2SO_4), filtered, and evaporated to dryness. Trace amounts of DMF were removed by five subsequent co-distillations *in vacuo* at 50 °C with toluene (40 mL). The residue was chromatographed on a silica-gel (30 g) column (ø = 2 cm) using 38% ethyl acetate in hexane. The resulting white solid (88 mg) was crystallized from benzene affording compound **9a** (66 mg, 16%); colourless crystals, m.p. 187–189 °C (benzene); R_f = 0.63 (30% ethyl acetate in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.16 (s, 3H, CH_3), 3.39 (dd, 1H, J = 2.3, 2.3 Hz, C≡CH), 4.90 (dd, 1H, J = 18.1, 2.3 Hz, N-1–CHα), 4.97 (dd, 1H, J = 18.1, 2.3 Hz, N-1–CHβ), 7.34–7.42 (m, 2H, H-6, H-4^B), 7.48 (dd, 2H, J = 7.7, 7.7 Hz, H-3^B, H-5^B), 7.61 (d, 1H, J = 8.4 Hz, H-8), 7.84–7.89 (m, 2H, H-2^B, H-6^B), 7.89–7.95 (m, 1H, H-7), 8.00 (dd, J = 7.7, 1.5 Hz, H-5), 8.89 (s, 1H, H-5^A); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.3 (CH_3), 32.7 (N-1–CH_2), 72.6 (C-3), 75.4 (C≡*C*H), 78.2 (*C*≡CH), 116.7 (C-8), 119.0 (C-4a), 122.5 (C-5^A), 124.2 (C-6), 125.1 (C-2^B, C-6^B), 128.1 (C-4^B), 128.2 (C-5), 129.0 (C-3^B, C-5^B), 130.5 (C-1^B), 137.3 (C-7), 140.8 (C-8a), 145.9 (C-4^A), 167.7 (C-2), 189.7 (C-4); IR (cm^{-1}): ν 3261, 3173, 2122, 1713, 1678, 1601, 1469, 1427, 1381, 1368, 1353, 1306, 1189, 769, 754; MS (EI) *m/z* (%): 357 (2, $[M + 1]^+$), 356 (8, $[M]^+$), 259 (10), 128 (11), 117 (16), 116 (100), 102 (17), 90 (11), 89 (16), 77 (10), 76 (10); HRMS (ESI+): *m/z* calcd for $C_{21}H_{17}N_4O_2^+$ $[M + H]^+$ 357.1346, found 357.1342. Anal. Calcd for $C_{21}H_{16}N_4O_2$ (356.38): C, 70.77; H, 4.53; N, 15.72%. Found: C, 70.81; H, 4.58; N, 15.82%.

6.13 3-Azido-1-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-3-methylquinoline-2,4(1*H*,3*H*)-dione (10a)

A mixture of acetylene **8a** (254 mg, 1.0 mmol), (azidomethyl)benzene (**A**) (266 mg, 2.0 mmol), $CuSO_4 \cdot 5H_2O$ (25 mg, 0.1 mmol) and granular copper (127 mg, 2.0 mmol) in DMF (10 mL) was stirred at room temperature for 21 hours. Then $(NH_4)_2CO_3$ (288 mg, 3.0 mmol) and water (3 mL) were added and

the stirring was continued for 10 minutes. The resulting mixture was poured into a narrow silica-gel (13 g) column (ø = 1 cm). The organic portion was eluted with 10% ethanol in chloroform (190 mL). The yellow eluate was washed with saturated aqueous NH_4Cl (50 mL) and distilled water (50 mL), dried (Na_2SO_4), filtered, and evaporated to dryness. Trace amounts of DMF were removed by six subsequent co-distillations *in vacuo* at 50 °C with toluene (30 mL). The residue was dissolved in chloroform (5 mL) and chromatographed on silica-gel (35 g) column (ø = 2 cm) using gradually 38% and 50% ethyl acetate in petroleum ether as mobile phase, affording compound **10a** (164 mg, 42%); white solid, m.p. 42–47 °C; R_f = 0.21 (38% ethyl acetate in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.73 (s, 3H), 5.20 (d, 1H, *J* = 15.6 Hz), 5.31 (d, 1H, *J* = 15.6 Hz), 5.45 (d, 1H, *J* = 14.8 Hz), 5.49 (d, 1H, *J* = 14.8 Hz), 7.16–7.28 (m, 3H), 7.32–7.39 (m, 3H), 7.54 (s, 1H), 7.67 (ddd, 1H, *J* = 8.3, 7.4, 1.6 Hz), 7.77 (d, 1H, *J* = 8.4 Hz), 7.96 (dd, 1H, *J* = 7.7, 1.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.6, 39.1, 54.5, 70.6, 116.6, 119.5, 123.5, 124.3, 128.3, 128.8, 129.0, 129.3, 134.3, 137.1, 141.4, 143.0, 169.8, 191.3; IR (cm^{-1}): *ν* 3137, 3033, 2980, 2106, 1713, 1676, 1602, 1489, 1469, 1379, 1336, 1279, 1223, 765, 724; HRMS (ESI+): *m*/*z* calcd for $C_{20}H_{18}N_7O_2^+$ $[M + H]^+$ 388,1516, found 388.1514. Anal. Calcd for $C_{20}H_{17}N_7O_2$ (387.39): C, 62.01; H, 4.42; N, 25.31%. Found: C, 61.74; H, 4.77; N, 25.15%.

6.14 General procedure for preparation of alcohols 11a–f, 12a and 12b

A solution of an appropriate acetate **6** or **7** (1 mmol) in acidified ethanol (20 mL, 37% HCl:EtOH 1:100 *V*/*V*) was stirred at the reflux temperature (T = 90–100 °C) for the time period up to 4 hours. Obtained pale yellow solution was then allowed to cool to laboratory temperature, and subsequently neutralised with saturated aqueous $NaHCO_3$. Resulting suspension was concentrated by rotary evaporation *in vacuo*, diluted with deionised water and extracted with chloroform (3–6 x 50 mL). Organic phases were joined together, washed with deionised water (1 x 50 mL), dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residual oily or solid product was then purified by chromatography on silica-gel (40 g) column (ø = 2 cm) using 5% ethanol or 30% ethyl acetate in chloroform as an eluent, or crystalized from ethyl acetate.

1-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-3-(4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)-3-methylquinoline-2,4(1*H*,3*H*)-dione (11a). Colourless powder (yield: 86%), m.p. 69–98 °C; R_f = 0.24 (5% ethanol in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$), *δ* 2.11 (s, 3H, CH_3), 2.59 (s, 1H, OH), 4.80 (s, 2H, OCH_2), 5.29 (d, 1H, *J* = 15.8 Hz, N-1–CH*α*), 5.33 (d, 1H, *J* = 15.8 Hz, N-1–CH*β*), 5.44 (d, 1H, *J* = 14.8 Hz, N-1^D–CH*α*), 5.50 (d, 1H, *J* = 14.8 Hz, N-1^D–CH*β*), 7.19-7.28 (m, 3H, H-2^E, H-6^E, H-6), 7.29-7.38 (m, 3H, H-3^E, H-4^E, H-5^E), 7.56 (s, 1H, H-5^D), 7.67-7.74 (m, 2H, H-7, H-5^A), 7.79 (d, 1H, *J* = 8.4 Hz, H-8), 7.99 (dd, 1H, *J* = 7.8,

1.6 Hz, H-5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.5 (CH_3), 39.5 (N-1–CH_2), 54.5 (N-1^D–CH_2), 56.9 (OCH_2), 71.7 (C-3), 116.9 (C-8), 119.2 (C-4a), 122.1 (C-5^A), 123.5 (C-5^D), 124.6 (C-6), 128.2 (C-2^E, C-6^E), 129.0 (C-5), 129.3 (C-4^E), 129.3 (C-3^E, C-5^E), 134.4 (C-1^E), 137.7 (C-7), 141.7 (C-8a), 142.9 (C-4^D), 147.3 (C-4^A), 168.3 (C-2), 189.6 (C-4); ^{15}N NMR (51 MHz, $CDCl_3$) δ 138.6 (N-1), 247.1 (N-1^A), 250.4 (N-1^D), 349.3 (N-3^D), 350.4 (N-3^A), 361.6 (N-2^D), 362.1 (N-2^A); IR (cm^{-1}): ν 3413, 3141, 1714, 1678, 1602, 1470, 1384, 1185, 1051, 793, 762, 722, 664; HRMS (ESI+): *m/z* calcd for $C_{23}H_{22}N_7O_3^+$ $[M + H]^+$ 444.1779, found 444.1773.

3-(4-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)-3-methyl-1-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)quinoline-2,4(1*H*,3*H*)-dione (**11b**). Colourless powder (yield: 98%), m.p. 96–115 °C; R_f = 0.41 (10% ethanol in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.17 (s, 3H, CH_3), 2.65 (s, 1H, OH), 4.82 (s, 2H, OCH_2), 5.37 (d, 1H, *J* = 15.8 Hz, N-1–CHα), 5.48 (d, 1H, *J* = 15.8 Hz, N-1–CHβ), 7.22-7.27 (m, 1H, H-6), 7.39-7.44 (m, 1H, H-4^E), 7.46-7.52 (m, 2H, H-3^E, H-5^E), 7.68-7.75 (m, 3H, H-2^E, H-6^E, H-7), 7.76 (s, 1H, H-5^A), 7.82 (d, 1H, *J* = 8.4 Hz, H-8), 8.01 (dd, 1H, *J* = 7.8, 1.6 Hz, H-5), 8.09 (s, 1H, H-5^D); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.4 (CH_3), 39.5 (N-1–CH_2), 56.9 (OCH_2), 71.6 (C-3), 116.8 (C-8), 119.2 (C-4a), 120.6 (C-2^E, C-6^E), 121.8 (C-5^D), 122.1 (C-5^A), 124.6 (C-6), 129.1 (C-4^E), 129.4 (C-5), 129.9 (C-3^E, C-5^E), 136.9 (C-1^E), 137.8 (C-7), 141.7 (C-8a), 143.2 (C-4^D), 147.3 (C-4^A), 168.4 (C-2), 189.5 (C-4); ^{15}N NMR (51 MHz, $CDCl_3$) δ 138.5 (N-1), 247.4 (N-1^A), 256.2 (N-1^D), 350.8 (N-3^A), 351.6 (N-3^D); IR (cm^{-1}): ν 3400, 3143, 1715, 1678, 1601, 1470, 1384, 1303, 1233, 1183, 1047, 760, 690, 663; HRMS (ESI+): *m/z* calcd for $C_{22}H_{20}N_7O_3^+$ $[M + H]^+$ 430.1622, found 430.1614.

3-(4-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)-3-methyl-1-((1-(pyridin-2-yl)-1*H*-1,2,3-triazol-4-yl)methyl)quinoline-2,4(1*H*,3*H*)-dione (**11c**). Colourless powder (yield: 80%), m.p. 66–89 °C; R_f = 0.32 (10% ethanol in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.19 (s, 3H, CH_3), 2.32 (s, 1H, OH), 4.83 (s, 2H, OCH_2), 5.36 (d, 1H, *J* = 15.9 Hz, N-1–CHα), 5.52 (d, 1H, *J* = 15.9 Hz, N-1–CHβ), 7.23 (ddd, 1H, *J* = 7.7, 7.3, 1.0 Hz, H-6), 7.30-7.37 (m, 1H, H-5^E), 7.71 (ddd, 1H, *J* = 8.5, 7.2, 1.6 Hz, H-7), 7.75-7.78 (m, 2H, H-5^A, H-8), 7.87-7.92 (m, 1H, H-4^E), 8.01 (dd, 1H, *J* = 7.7, 1.6 Hz, H-5), 8.10-8.15 (m, 1H, H-3^E), 8.45-8.49 (m, 1H, H-6^E), 8.58 (s, 1H, H-5^D); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.7 (CH_3), 39.4 (N-1–CH_2), 56.9 (OCH_2), 72.0 (C-3), 113.9 (C-3^E), 116.6 (C-8), 119.3 (C-4a), 120.9 (C-5^D), 122.3 (C-5^A), 124.0 (C-5^E), 124.6 (C-6), 129.3 (C-5), 137.6 (C-7), 139.3 (C-4^E), 141.6 (C-8a), 143.0 (C-4^D), 147.4 (C-4^A), 148.8 (C-6^E), 149.0 (C-2^E), 168.3 (C-2), 189.6 (C-4); ^{15}N NMR (51 MHz, $CDCl_3$) δ 137.7 (N-1), 246.7 (N-1^A), 259.9 (N-1^D), 283.6 (N-1^E), 350.3 (N-3^A), 355.0 (N-3^D); IR (cm^{-1}): ν 3379, 3132, 1715, 1679, 1600, 1471, 1384, 1298, 1234, 1183, 1040, 782, 755,

658; HRMS (ESI+): *m/z* calcd for $C_{21}H_{19}N_8O_3^+$ $[M + H]^+$ 431.1575, found 431.1579.

1-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-3-(4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)-3-phenylquinoline-2,4(1*H*,3*H*)-dione (**11d**). Colourless powder (yield: 89%), m.p. 93–121 °C; R_f = 0.23 (5% ethanol in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.34 (t, 1H, J = 5.6 Hz, OH), 4.75 (d, 2H, J = 4.6 Hz, OCH_2), 5.20 (d, 1H, J = 15.6 Hz, N-1^D–CHα), 5.43 (d, 1H, J = 14.8 Hz, N-1–CHα), 5.49 (d, 1H, J = 15.6 Hz, N-1^D–CHβ), 5.54 (d, 1H, J = 14.8 Hz, N-1–CHβ), 7.03 (s, 1H, H-5^A), 7.17 (ddd, 1H, J = 7.9, 7.2, 0.8 Hz, H-6), 7.23-7.28 (m, 4H, H-2^E, H-3^E, H-5^E, H-6^E), 7.29-7.32 (m, 2H, H-2^C, H-6^C), 7.34–7.42 (m, 4H, H-3^C, H-4^C, H-5^C, H-4^E), 7.59 (s, 1H, H-5^D), 7.62 (ddd, 1H, J = 7.9, 7.9, 1.6 Hz, H-7), 7.74 (d, 1H, J = 8.4 Hz, H-8), 7.98 (dd, 1H, J = 7.7, 1.6 Hz, H-5); ^{13}C NMR (126 MHz, $CDCl_3$) δ ^{13}C NMR (126 MHz, $CDCl_3$) δ 39.9 (N-1^D–CH_2), 54.5 (N-1–CH_2), 56.9 (OCH_2), 79.6 (C-3), 116.8 (C-8), 120.9 (C-4a), 123.6 (C-5^D), 124.5 (C-5^A), 124.5 (C-6), 128.3 (C-2^E, C-6^E), 128.8 (C-2^C, C-6^C), 129.0 (C-5), 129.0 (C-4^C), 129.3 (C-3^C, C-5^C), 129.9 (C-1^E), 130.0 (C-3^E, C-5^E), 131.2 (C-4^E), 134.5 (C-1^C), 137.2 (C-7), 141.1 (C-8a), 142.9 (C-4^D), 145.8 (C-4^A), 166.6 (C-2), 188.0 (C-4); ^{15}N NMR (51 MHz, $CDCl_3$) δ 140.4 (N-1), 248.9 (N-1^A), 250.6 (N-1^D), 350.0 (N-3^D), 352.8 (N-3^A), 362.8 (N-2^D), 364.9 (N-2^A); IR (cm^{-1}): ν 3391, 3141, 1715, 1678, 1601, 1469, 1450, 1376, 1049, 1032, 871, 761, 665, 608; HRMS (ESI+): *m/z* calcd for $C_{28}H_{24}N_7O_3^+$ $[M + H]^+$ 506.1935, found 506.1937.

3-(4-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)-3-phenyl-1-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)quinoline-2,4(1*H*,3*H*)-dione (**11e**). Colourless powder (yield: 97%), m.p. 118–131 °C; R_f = 0.35 (5% ethanol in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 1H, OH), 4.78 (s, 2H, OCH_2), 5.41 (d, 1H, J = 15.7 Hz, N-1–CHα), 5.53 (d, 1H, J = 15.7 Hz, N-1–CHβ), 7.09 (s, 1H, H-5^A), 7.20 (ddd, 1H, J = 7.9, 7.2, 0.7 Hz, H-6), 7.38-7.48 (m, 6H, H-2^C, H-3^C, H-4^C, H-5^C, H-6^C, H-4^E), 7.49-7.55 (m, 2H, H-3^E, H-5^E), 7.65 (ddd, 1H, J = 8.7, 7.1, 1.7 Hz, H-7), 7.68-7.72 (m, 2H, H-2^E, H-6^E), 7.75 (d, 1H, J = 8.4 Hz, H-8), 8.02 (dd, 1H, J = 7.8, 1.5 Hz, H-5), 8.07 (s, 1H, H-5^D); ^{13}C NMR (126 MHz, $CDCl_3$) δ 39.8 (N-1–CH_2), 56.9 (OCH_2), 79.6 (C-3), 116.7 (C-8), 120.7 (C-2^E, C-6^E), 120.9 (C-4a), 121.8 (C-5^D), 124.6 (C-5^A), 124.6 (C-6), 128.9 (C-2^C, C-6^C), 129.1 (C-5), 129.2 (C-4^E), 130.0 (C-1^C), 130.0 (C-3^E, C-5^E), 130.1 (C-3^C, C-5^C), 131.3 (C-4^C), 136.9 (C-1^E), 137.3 (C-7), 140.9 (C-8a), 143.2 (C-4^D), 145.8 (C-4^A), 166.9 (C-2), 188.0 (C-4); ^{15}N NMR (51 MHz, $CDCl_3$) δ 139.5 (N-1), 249.0 (N-1^A), 256.2 (N-1^D), 352.6 (N-3^D), 353.0 (N-3^A); IR (cm^{-1}): ν 3401, 3144, 1716, 1679, 1600, 1501, 1468, 1449, 1377, 1044, 871, 760, 692; HRMS (ESI+): *m/z* calcd for $C_{27}H_{22}N_7O_3^+$ $[M + H]^+$ 492.1779, found 492.1768.

3-(4-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)-3-phenyl-1-((1-(pyridin-2-yl)-1*H*-1,2,3-triazol-4-yl)methyl)quinoline-2,4(1*H*,3*H*)-dione (**11f**). Colourless powder (yield: 87%), m.p. 185–194 °C; R_f = 0.37 (5% ethanol in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.38 (s, 1H, OH), 4.77 (s, 2H, OCH_2), 5.28 (d, 1H, J = 15.8 Hz, N-1–CHα), 5.69 (d, 1H, J = 15.8 Hz, N-1–CHβ), 7.09 (s, 1H, H-5^A), 7.17 (ddd, 1H, J = 7.7, 7.3, 1.0 Hz, H-6), 7.32-7.48 (m, 6H, H-5^E, H-2^C, H-3^C, H-4^C, H-5^C, H-6^C), 7.61 (ddd, 1H, J = 8.4, 7.2, 1.7 Hz, H-7), 7.68 (d, 1H, J = 8.3 Hz, H-8), 7.86-7.94 (m, 1H, H-4^E), 8.01 (dd, 1H, J = 7.8, 1.5 Hz, H-5), 8.11-8.16 (m, 1H, H-3^E), 8.47-8.51 (m, 1H, H-6^E), 8.61 (s, 1H, H-5^D); ^{13}C NMR (126 MHz, $CDCl_3$) δ 39.9 (N-1–CH_2), 56.9 (OCH_2), 79.7 (C-3), 113.9 (C-3^E), 116.6 (C-8), 121.0 (C-4a), 121.0 (C-5^D), 124.0 (C-5^E), 124.5 (C-6), 124.5 (C-5^A), 128.9 (C-2^C, C-6^C), 129.0 (C-5), 130.0 (C-1^C), 130.1 (C-3^C, C-5^C), 131.2 (C-4^C), 137.1 (C-7), 139.3 (C-4^E), 141.2 (C-8a), 143.0 (C-4^D), 145.9 (C-4^A), 148.9 (C-6^E), 149.0 (C-2^E), 166.7 (C-2), 188.0 (C-4); IR (cm–1): ν 3401, 3156, 1716, 1680, 1599, 1469, 1375, 1313, 1034, 999, 779, 760, 695, 683; HRMS (ESI+): m/z calcd for $C_{26}H_{21}N_8O_3^+$ [M + H]+ 493.1731, found 493.1732.

3-(4-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)-3-methyl-1-(prop-2-ynyl)quinoline-2,4(1*H*,3*H*)-dione (**12a**). Colourless crystals (yield: 83%), m.p. 182–188 °C (ethyl acetate); R_f = 0.31 (10% ethanol in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.08 (s, 3H), 3.35-3.38 (m, 1H), 4.56 (d, 2H, J = 5.7 Hz), 4.84 (dd, 1H, J = 18.1, 2.4 Hz), 4.95 (dd, 1H, J = 18.1, 2.4 Hz), 5.29 (t, 1H, J = 5.7 Hz), 7.36 (ddd, 1H, J = 7.6, 7.4, 0.9 Hz), 7.57 (d, 1H, J = 8.4 Hz), 7.89 (ddd, 1H, J = 8.4, 7.4, 1.7 Hz), 7.96 (dd, 1H, J = 7.8, 1.6 Hz), 8.26 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.3, 32.6, 55.1, 72.4, 75.3, 78.3, 116.6, 119.2, 123.9, 124.1, 128.1, 137.1, 140.8, 147.5, 167.9, 189.8; IR (cm^{-1}): ν 3270, 3134, 2126, 1709, 1677, 1600, 1465, 1385, 1301, 1180, 1022, 1011, 791, 762; HRMS (ESI+): *m/z* calcd for $C_{16}H_{15}N_4O_3^+$ [M + H]$^+$ 311.1139, found 311.1138.

3-(4-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)-3-phenyl-1-(prop-2-ynyl)quinoline-2,4(1*H*,3*H*)-dione (**12b**). Colourless crystals (yield: 87%), m.p. 141–148 °C (ethyl acetate); R_f = 0.21 (5% ethanol in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.34 (t, 1H, J = 2.5 Hz), 2.35-2.41 (m, 1H), 4.48 (dd, 1H, J = 17.8, 2.4 Hz), 4.71-4.79 (m, 2H), 5.33 (dd, 1H, J = 17.8, 2.4 Hz), 7.05 (s, 1H), 7.22 (ddd, 1H, J = 7.6, 7.5, 0.9 Hz), 7.33 (d, 1H, J = 8.3 Hz), 7.41-7.50 (m, 5H), 7.65 (ddd, 1H, J = 8.3, 7.4, 1.7 Hz), 8.03 (dd, 1H, J = 7.8, 1.6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 33.6, 56.8, 73.6, 79.7, 115.8, 120.9, 124.6, 128.9, 129.2, 129.7, 130.1, 131.3, 136.9, 140.5, 145.8, 165.7, 187.5; IR (cm^{-1}): ν 3273, 3158, 2125, 1715, 1682, 1602, 1468, 1374, 1302, 1175, 1044, 871, 761; HRMS (ESI+): *m/z* calcd for $C_{21}H_{17}N_4O_3^+$ [M + H]$^+$ 373.1295, found 373.1291.

6.15 Preparation of aldehydes 13a, 13b, 14a–f, 15a and 15b

6.15.1 General procedure for preparation of aldehydes 13a, 13b, 14a–f, 15a and 15b using PCC

To a vigorously stirred solution (or suspension) of suitable alcohol (1 mmol) in dichloromethane (15 mL), PCC (259 mg, 1.2 mmol) was added. Obtained reaction mixture was then stirred at the reflux temperature (40 °C) for up to one hour. The original orange colour of mixture changed to almost black. Resulting solution with the sticky sediment was poured into a narrow silica-gel (13 g) column (ø = 1 cm). The organic portion was eluted with 5% ethanol in chloroform (250–350 mL). Dark yellow eluate was evaporated *in vacuo* and obtained residue was chromatographed on a silica-gel (35 g) column (ø = 2 cm), using 50% or 67% ethyl acetate in petroleum ether. In case of mono-triazole species, crude products were further crystalized from ethyl acetate or benzene.

1-(1,2,3,4-Tetrahydro-3-methyl-2,4-dioxoquinolin-3-yl)-1*H*-1,2,3-triazole-4-carbaldehyde (**13a**). Colourless crystals (yield: 31%), m.p. 267–271 °C (ethyl acetate); R_f = 0.54 (10% ethanol in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.16 (s, 3H, CH_3), 7.23 (d, 1H, J = 7.7 Hz, H-8), 7.21–7.27 (m, 1H, H-6), 7.75 (ddd, 1H, J = 7.8, 7.7, 1.5 Hz, H-7), 7.85 (dd, 1H, J = 7.8, 1.7 Hz, H-5), 9.18 (s, 1H, H-5^A), 10.08 (s, 1H, CHO), 11.50 (s, 1H, H-1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.4 (CH_3), 73.6 (C-3), 117.0 (C-8), 117.6 (C-4a), 123.5 (C-6), 127.6 (C-5), 129.6 (C-5^A), 137.2 (C-7), 141.4 (C-8a), 146.6 (C-4^A), 168.3 (C-2), 185.1 (CHO), 190.3 (C-4); ^{15}N NMR (51 MHz, DMSO-d_6) δ 133.4 (N-1), 252.0 (N-1^A), 358.6 (N-3^A), 367.9 (N-2^A); IR (cm^{-1}): ν 3308, 3140, 2851, 1716, 1680, 1614, 1531, 1484, 1378, 1345, 1231, 1211, 816, 757, 667; HRMS (ESI+): *m/z* calcd for $C_{13}H_{11}N_4O_3^+$ $[M + H]^+$ 271.0826, found 271.0833.

1-(1,2,3,4-Tetrahydro-2,4-dioxo-3-phenylquinolin-3-yl)-1*H*-1,2,3-triazole-4-carbaldehyde (**13b**). Colourless crystals (yield: 44%), m.p. 188–191 °C (ethyl acetate); R_f = 0.36 (5% ethanol in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.09 (d, 1H, J = 8.0 Hz, H-8), 7.17 (ddd, 1H, J = 7.6, 7.6, 1.0 Hz, H-6), 7.34–7.41 (m, 2H, H-2^C, H-6^C), 7.47–7.54 (m, 3H, H-3^C, H-4^C, H-5^C), 7.63 (ddd, 1H, J = 8.2, 7.3, 1.6 Hz, H-7), 7.85 (dd, 1H, J = 7.8, 1.4 Hz, H-5), 8.93 (s, 1H, H-5^A), 10.05 (s, 1H, CHO), 11.68 (s, 1H, H-1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 80.7 (C-3), 116.7 (C-8), 119.5 (C-4a), 123.5 (C-6), 127.5 (C-5), 128.9 (C-2^C, C-6^C), 129.7 (C-3^C, C-5^C), 129.7 (C-1^C), 130.7 (C-4^C), 130.7 (C-5^A), 136.8 (C-7), 140.4 (C-8a), 146.2 (C-4^A), 166.6 (C-2), 185.1 (CHO), 188.4 (C-4); ^{15}N NMR (51 MHz, DMSO-d_6) δ 134.8 (N-1), 249.8 (N-1^A), 351.6 (N-3^A), 356.4 (N-2^A); IR (cm^{-1}): ν 3253, 2914, 2860, 1723, 1689, 1615, 1595, 1486, 1355, 1208, 1045, 857, 780, 752, 697; HRMS (ESI+): *m/z* calcd for $C_{18}H_{13}N_4O_3^+$ $[M + H]^+$ 333.0982, found 333.0988.

1-(1-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-1,2,3,4-tetrahydro-3-methyl-2,4-dioxoquinolin-3-yl)-1*H*-1,2,3-triazole-4-carbaldehyde (**14a**). Colourless powder (yield: 41%), m.p. 63–87 °C; R_f = 0.48 (5 % ethanol in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$), δ 2.16 (s, 3H, CH_3), 5.28 (d, 1H, J = 15.7 Hz, N-1–CHα), 5.37 (d, 1H, J = 15.7 Hz, N-1–CHβ), 5.45 (d, 1H, J = 14.8 Hz, N-1^D–CHα), 5.50 (d, 1H, J = 14.8 Hz, N-1^D–CHβ), 7.21-7.26 (m, 2H, H-2^E, H-6^E), 7.27 (ddd, 1H, J = 7.6, 7.5, 0.9 Hz, H-6), 7.31-7.38 (m, 3H, H-3^E, H-4^E, H-5^E), 7.53 (s, 1H, H-5^D), 7.75 (ddd, 1H, J = 8.4, 7.4, 1.7 Hz, H-7), 7.86 (d, 1H, J = 8.4 Hz, H-8), 8.02 (dd, 1H, J = 7.8, 1.6 Hz, H-5), 8.30 (s, 1H, H-5^A), 10.15 (s, 1H, CHO); ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.8 (CH_3), 39.5 (N-1–CH_2), 54.5 (N-1^D–CH_2), 72.6 (C-3), 117.0 (C-8), 119.0 (C-4a), 123.4 (C-5^D), 124.8 (C-6),126.3 (C-5^A), 128.2 (C-2^E, C-6^E), 129.0 (C-4^E), 129.3 (C-3^E, C-5^E), 129.3 (C-5), 134.3 (C-1^E), 138.0 (C-7), 141.5 (C-8a), 142.7 (C-4^D), 147.0 (C-4^A), 167.7 (C-2), 185.0 (CHO), 188.9 (C-4); ^{15}N NMR (51 MHz, $CDCl_3$) δ 138.4 (N-1), 250.6 (N-1^D), 251.7 (N-1^A), 350.0 (N-3^D), 361.8 (N-2^A), 362.6 (N-2^D); IR (cm^{-1}): ν 3137, 2929, 2852, 1681, 1601, 1470, 1385, 1211, 1186, 1048, 799, 763, 721, 686, 663; HRMS (ESI+): *m/z* calcd for $C_{23}H_{20}N_7O_3^+$ $[M + H]^+$ 442.1622, found 442.1620.

1-(1,2,3,4-Tetrahydro-3-methyl-2,4-dioxo-1-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)quinolin-3-yl)-1*H*-1,2,3-triazole-4-carbaldehyde (**14b**). Colourless powder (yield: 40%), m.p. 71–93 °C; R_f = 0.40 (5% ethanol in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.22 (s, 3H, CH_3), 5.45 (s, 2H, N-1–CH_2), 7.29 (ddd, 1H, J = 7.6, 7.5, 0.9 Hz, H-6), 7.41–7.46 (m, 1H, H-4^E), 7.48–7.53 (m, 2H, H-3^E, H-5^E), 7.68–7.72 (m, 2H, H-2^E, H-6^E), 7.78 (ddd, 1H, J = 8.4, 7.4, 1.7 Hz, H-7), 7.90 (d, 1H, J = 8.4 Hz, H-8), 8.04 (dd, 1H, J = 7.9, 1.6 Hz, H-5), 8.05 (s, 1H, H-5^D), 8.36 (s, 1H, H-5^A), 10.17 (s, 1H, CHO) ^{13}C NMR (126 MHz, $CDCl_3$) δ 23.8 (CH_3), 39.5 (N-1–CH_2), 72.5 (C-3), 117.0 (C-8), 119.0 (C-4a), 120.6 (C-2^E, C-6^E), 121.8 (C-5^D), 124.9 (C-6), 126.2 (C-5^A), 129.2 (C-4^E), 129.4 (C-5), 130.0 (C-3^E, C-5^E), 136.8 (C-1^E), 138.1 (C-7), 141.5 (C-8a), 143.0 (C-4^D), 147.0 (C-4^A), 167.8 (C-2), 185.0 (CHO), 188.8 (C-4); ^{15}N NMR (51 MHz, $CDCl_3$) δ 138.5 (N-1), 251.6 (N-1^A), 256.2 (N-1^D), 352.0 (N-3^D), 362.2 (N-2^A); IR (cm^{-1}): ν 3138, 2928, 2853, 1682, 1601, 1470, 1385, 1212, 1185, 1046, 760, 690, 663; HRMS (ESI+): *m/z* calcd for $C_{22}H_{18}N_7O_3^+$ $[M + H]^+$ 428.1466, found 428.1461.

1-(1,2,3,4-Tetrahydro-3-methyl-2,4-dioxo-1-((1-(pyridin-2-yl)-1*H*-1,2,3-triazol-4-yl)methyl)quinolin-3-yl)-1*H*-1,2,3-triazole-4-carbaldehyde (**14c**). Colourless powder (yield: 48%), m.p. 47–65 °C; R_f = 0.34 (5% ethanol in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (s, 3H, CH_3), 5.35 (d, 1H, J = 15.9 Hz, N-1–CHα), 5.58 (d, 1H, J = 15.9 Hz, N-1–CHβ), 7.24-7.31 (m, 1H, H-6), 7.32-7.38 (m, 1H, H-5^E), 7.76 (ddd, 1H, J = 8.4, 7.3, 1.7 Hz, H-7), 7.83 (d, 1H, J = 8.4 Hz, H-8), 7.88-7.93 (m, 1H, H-4^E), 8.04 (dd, 1H, J = 7.8, 1.6 Hz, H-5), 8.11-8.16 (m, 1H, H-3^E), 8.35 (s, 1H, H-5^A), 8.46-8.49 (m, 1H, H-6^E), 8.59

(s, 1H, H-5^{D}), 10.18 (s, 1H, CHO); ^{13}C NMR (126 MHz, $CDCl_3$) δ 24.0 (CH_3), 39.4 (N-1–CH_2), 72.9 (C-3), 113.9 (C-3^{E}), 116.8 (C-8), 119.1 (C-4a), 120.8 (C-5^{D}), 124.1 (C-5^{E}), 124.8 (C-6), 126.4 (C-5^{A}), 129.4 (C-5), 137.9 (C-7), 139.3 (C-4^{E}), 141.6 (C-8a), 142.8 (C-4^{D}), 147.1 (C-4^{A}), 148.8 (C-6^{E}), 148.9 (C-2^{E}), 167.7 (C-2), 185.1 (CHO), 189.0 (C-4); ^{15}N NMR (51 MHz, $CDCl_3$) δ 137.8 (N-1), 251.1 (N-1^{A}), 261.0 (N-1^{D}), 283.9 (N-1^{E}), 355.3 (N-3^{D}), 361.8 (N-2^{A}); IR (cm^{-1}): ν 3138, 2929, 2854, 1683, 1600, 1471, 1385, 1211, 1184, 1038, 999, 781, 760, 663; HRMS (ESI+): *m/z* calcd for $C_{21}H_{17}N_8O_3^+$ $[M + H]^+$ 429.1418, found 429.1431.

1-(1-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-1,2,3,4-tetrahydro-2,4-dioxo-3-phenylquinolin-3-yl)-1*H*-1,2,3-triazole-4-carbaldehyde (**14d**). Colourless powder (yield: 41%), m.p. 87–113 °C; R_f = 0.58 (5% ethanol in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.20 (d, 1H, *J* = 15.6 Hz, N-1–CHα), 5.44 (d, 1H, *J* = 14.8 Hz, N-1^{D}–CHα), 5.53 (d, 1H, *J* = 15.6 Hz, N-1–CHβ), 5.56 (d, 1H, *J* = 14.8 Hz, N-1^{D}–CHβ), 7.20 (ddd, 1H, *J* = 7.6, 7.5, 0.8 Hz, H-6), 7.26-7.28 (m, 4H, H-3^{C}, H-5^{C}, H-3^{E}, H-5^{E}), 7.28-7.30 (m, 2H, H-2^{C}, H-6^{C}), 7.37-7.40 (m, 3H, H-2^{E}, H-6^{E}, H-4^{C}), 7.41-7.47 (m, 1H, H-4^{E}), 7.58 (s, 1H, H-5^{D}), 7.58 (s, 1H, H-5^{A}), 7.65 (ddd, 1H, *J* = 8.4, 7.4, 1.7 Hz, H-7), 7.78 (d, 1H, *J* = 8.4 Hz, H-8), 8.00 (dd, 1H, *J* = 7.7, 1.6 Hz, H-5), 10.13 (s, 1H, CHO); ^{13}C NMR (126 MHz, $CDCl_3$) δ 40.0 (N-1–CH_2), 54.5 (N-1^{D}–CH_2), 80.1 (C-3), 117.0 (C-8), 120.7 (C-4a), 123.5 (C-5^{D}), 124.8 (C-6), 128.3 (C-3^{C}, C-5^{C}), 128.4 (C-5^{A}), 128.6 (C-3^{E}, C-5^{E}), 129.0 (C-5), 129.0 (C-1^{C}), 129.1 (C-4^{C}), 129.4 (C-2^{E}, C-6^{E}), 130.4 (C-2^{C}, C-6^{C}), 131.7 (C-4^{E}), 134.4 (C-1^{E}), 137.5 (C-7), 141.0 (C-8a), 142.7 (C-4^{D}), 145.8 (C-4^{A}), 165.9 (C-2), 185.2 (CHO), 187.3 (C-4); ^{15}N NMR (51 MHz, $CDCl_3$) δ 140.0 (N-1), 250.6 (N-1^{D}), 253.7 (N-1^{A}), 350.8 (N-3^{D}), 362.5 (N-2^{D}); IR (cm^{-1}): ν 3138, 2850, 1701, 1680, 1601, 1469, 1376, 1044, 871, 772, 748, 724, 696; HRMS (ESI+): *m/z* calcd for $C_{28}H_{22}N_7O_3^+$ $[M + H]^+$ 504.1779, found 504.1782.

1-(1,2,3,4-Tetrahydro-2,4-dioxo-3-phenyl-1-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)quinolin-3-yl)-1*H*-1,2,3-triazole-4-carbaldehyde (**14e**). Colourless powder (yield: 45%), m.p. 91–122 °C; R_f = 0.62 (5% ethanol in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.41 (d, 1H, *J* = 15.7 Hz, N-1–CHα), 5.58 (d, 1H, *J* = 15.7 Hz, N-1–CHβ), 7.23 (ddd, 1H, *J* = 7.6, 7.5, 0.9 Hz, H-6), 7.41-7.43 (m, 2H, H-2^{C}, H-6^{C}), 7.43-7.45 (m, 2H, H-3^{C}, H-5^{C}), 7.45-7.48 (m, 1H, H-4^{E}), 7.48-7.51 (m, 1H, H-4^{C}), 7.51-7.55 (m, 2H, H-3^{E}, H-5^{E}), 7.64 (s, 1H, H-5^{A}), 7.68 (ddd, 1H, *J* = 9.5, 7.4, 1.7 Hz, H-7), 7.69-7.72 (m, 2H, H-2^{E}, H-6^{E}), 7.79 (d, 1H, *J* = 8.4 Hz, H-8), 8.04 (dd, 1H, *J* = 7.8, 1.6 Hz, H-5), 8.06 (s, 1H, H-5^{D}), 10.15 (s, 1H, CHO); ^{13}C NMR (126 MHz, $CDCl_3$) δ 39.8 (N-1–CH_2), 80.1 (C-3), 116.8 (C-8), 120.7 (C-2^{E}, C-6^{E}), 120.7 (C-4a), 121.8 (C-5^{D}), 124.8 (C-6), 128.4 (C-5^{A}), 128.8 (C-2^{C}, C-6^{C}), 129.1 (C-1^{C}), 129.2 (C-4^{E}), 129.3 (C-5), 130.0 (C-3^{E}, C-5^{E}), 130.5 (C-3^{C}, C-5^{C}), 131.8 (C-4^{C}), 136.8 (C-1^{E}), 137.6 (C-7), 140.9 (C-8a), 143.0 (C-4^{D}), 145.8 (C-4^{A}), 166.2 (C-2), 185.1 (CHO), 187.2 (C-4); ^{15}N NMR (51 MHz,

$CDCl_3$) δ 139.3 (N-1), 254.3 (N-1^A), 256.1 (N-1^D), 256.1 (N-2^D), 352.7 (N-3^D), 363.4 (N-2^A), IR (cm^{-1}): ν 3141, 2848, 1701, 1682, 1600, 1468, 1376, 1306, 1042, 872, 772, 691, 665; HRMS (ESI+): *m/z* calcd for $C_{27}H_{20}N_7O_3^+$ $[M + H]^+$ 490.1622, found 490.1616.

1-(1,2,3,4-Tetrahydro-2,4-dioxo-3-phenyl-1-((1-(pyridin-2-yl)-1*H*-1,2,3-triazol-4-yl)methyl)quinolin-3-yl)-1*H*-1,2,3-triazole-4-carbaldehyde (**14f**). Colourless powder (yield: 41%), m.p. 88–114 °C; R_f = 0.44 (5% ethanol in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.31 (d, 1H, *J* = 15.8 Hz, N-1–CHα), 5.72 (d, 1H, *J* = 15.8 Hz, N-1–CHβ), 7.21 (ddd, 1H, *J* = 7.5, 7.5, 0.9 Hz, H-6), 7.35-7.39 (m, 1H, H-5^E), 7.40-7.51 (m, 5H, H-2^C, H-3^C, H-4^C, H-5^C, H-6^C), 7.62-7.68 (m, 2H, H-5^A, H-7), 7.72 (d, 1H, *J* = 8.4 Hz, H-8), 7.89-7.95 (m, 1H, H-4^E), 8.04 (dd, 1H, *J* = 7.8, 1.5 Hz, H-5), 8.13-8.17 (m, 1H, H-3^E), 8.48-8.52 (m, 1H, H-6^E), 8.63 (s, 1H, H-5^D), 10.15 (s, 1H, CHO); ^{13}C NMR (126 MHz, $CDCl_3$) δ 39.9 (N-1–CH_2), 80.2 (C-3), 113.9 (C-3^E), 116.7 (C-8), 120.8 (C-4a), 120.9 (C-5^D), 124.1 (C-5^E), 124.8 (C-6), 128.4 (C-5^A), 128.8 (C-2^C, C-6^C), 129.0 (C-1^C), 129.1 (C-5), 130.5 (C-3^C, C-5^C), 131.7 (C-4^C), 137.4 (C-7), 139.3 (C-4^E), 141.1 (C-8a), 142.8 (C-4^D), 145.8 (C-4^A), 148.9 (C-6^E), 149.0 (C-2^E), 165.9 (C-2), 185.2 (CHO), 187.3 (C-4); ^{15}N NMR (51 MHz, $CDCl_3$) δ 139.2 (N-1), 254.0 (N-1^A), 260.2 (N-1^D), 284.4 (N-1^E), 355.5 (N-3^D), 363.1 (N-2^A); IR (cm^{-1}): ν 3153, 2852, 1700, 1681, 1599, 1470, 1375, 1313, 1035, 999, 776, 750, 696; HRMS (ESI+): *m/z* calcd for $C_{26}H_{19}N_8O_3^+$ $[M + H]^+$ 491.1575, found 491.1578.

1-(1,2,3,4-Tetrahydro-3-methyl-2,4-dioxo-1-(prop-2-ynyl)quinolin-3-yl)-1*H*-1,2,3-triazole-4-carbaldehyde (**15a**). Colourless crystals (yield: 41%), m.p. 189–194 °C (benzene); R_f = 0.40 (5% ethanol in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.23 (s, 3H), 3.32-3.37 (m, 1H), 4.66 (dd, 1H, *J* = 17.9, 1.6 Hz), 5.11 (dd, 1H, *J* = 17.9, 1.6 Hz), 7.30-7.37 (m, 1H), 7.47 (d, 1H, *J* = 8.4 Hz), 7.81 (ddd, 1H, *J* = 8.4, 7.3, 1.5 Hz), 8.09 (d, 1H, *J* = 7.7 Hz), 8.31 (s, 1H), 10.18 (s, 1H);^{13}C NMR (126 MHz, $CDCl_3$) δ 23.9, 33.2, 72.8, 73.9, 76.7, 116.3, 119.2, 124.9, 126.3, 129.6, 137.7, 140.9, 147.1, 166.9, 185.1, 188.7; IR (cm^{-1}): ν 3282, 3150, 2125, 1704, 1673, 1601, 1528, 1470, 1444, 1381, 1306, 1206, 798, 761; HRMS (ESI+): *m/z* calcd for $C_{16}H_{13}N_4O_3^+$ $[M + H]^+$ 309.0982, found 309.0979.

1-(1,2,3,4-Tetrahydro-2,4-dioxo-3-phenyl-1-(prop-2-ynyl)quinolin-3-yl)-1*H*-1,2,3-triazole-4-carbaldehyde (**15b**). Colourless crystals (yield: 38%), m.p. 176–182 °C (benzene); R_f = 0.68 (5% ethanol in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33-2.37 (m, 1H), 4.52 (dd, 1H, *J* = 17.8, 1.4 Hz), 5.34 (dd, 1H, *J* = 17.8, 1.4 Hz), 7.22-7.28 (m, 1H), 7.33-7.38 (m, 1H), 7.44-7.55 (m, 5H), 7.61 (s, 1H), 7.64-7.71 (m, 1H), 8.05 (d, 1H, *J* = 7.7 Hz), 10.13 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 33.7, 73.8, 76.6, 80.2, 116.0, 120.8, 124.8, 128.5, 128.8, 129.0, 129.2, 130.5, 131.8, 137.2, 140.4, 145.8, 165.1, 185.2, 186.9; IR (cm^{-1}): ν 3237, 3151, 2124, 1716, 1682, 1603, 1469, 1373, 1301, 1200, 1170,

1042, 774, 692; HRMS (ESI+): *m/z* calcd for $C_{21}H_{15}N_4O_3^+$ $[M + H]^+$ 371.1139, found 371.1130.

6.15.2 Manganese dioxide[171]

To a solution of $MnSO_4 \cdot H_2O$ (50.70 g, 0.3 mol) in distilled water (400 mL) preheated to 70 °C, solution of $KMnO_4$ (31.61 g, 0.2 mol) in distilled water (300 mL) also preheated to 70 °C was added. Obtained reaction mixture was stirred at 90 °C for the time period of 30 minutes, and was subsequently filtered under reduced pressure using Büchner flask and funnel. MnO_2 filter cake was then dispersed in distilled water (300 mL), treated with 15% NaOH (*w*/*w*), filtered, and intensively washed with hot distilled water (70 °C), methanol and diethyl ether, respectively. Resulted dark brown solid was then dried to constant mass at 95 °C to gain activated manganese dioxide (35.7 g, 82%).

6.15.3 General procedure for preparation of aldehydes 13a, 13b, 14b, 15a and 15b using MnO_2[178]

To a vigorously stirred solution of suitable alcohol (1 mmol) in acetone (10 mL), MnO_2 (869 mg; 10 mmol) was added. Obtained reaction mixture was then stirred at the reflux temperature (56 °C) for up to two hours. Resulting black suspension was filtered through the filter paper and the filtrate was evaporated to dryness. Resulting crude oily product was chromatographed on silica-gel (35 g) column (ø = 2 cm), using 50% ethyl acetate in petroleum ether as mobile phase. In case of mono-triazole compounds, combined fractions were further crystalized from ethyl acetate.

6.15.4 Preparation of aldehyde 13b using Swern reaction[179]

To a dry 25 mL evacuated flask, oxalyl chloride (155 μL, 1.8 mmol) and dry tetrahydrofurane (THF) were added. The flask was equipped with nitrogen gas inlet and cooled to -70 °C using dry ice–ethanol bath. Afterwards, DMSO (280 μL) was added dropwise and obtained solution was stirred for 60 minutes, keeping the temperature bellow -65 °C. Then, the solution of alcohol **4b** (500 mg, 1.5 mmol) dissolved in dry dichloromethane or acetone (11 mL) was added and stirring was continued for 90 minutes. Finally, after addition of DIPEA (1.275 mL, 7.32 mmol), the content of the flask was stirred for additional 2 hours and tempered to the laboratory temperature. The reaction mixture was diluted with distilled water (10 mL) and extracted with dichloromethane (3 x 20 mL). Combined organic phases were washed with ice-cold water (4 x 20 mL), dried over anhydrous Na_2SO_4, filtered and finally evaporated to dryness. Obtained oily crude product was purified on silica-gel (35 g) column (ø = 2 cm), using 38% ethyl acetate in petroleum ether as mobile phase. To that way gained oily joined

fractions, diethyl ether was added and it was cooled to -20 °C, resulting in formation of solid compound **13b** that was filtered out using sintered glass filter and dried at 50 °C to constant mass (yield: 33%).

6.16 General procedure for preparation of carboxylic acids 16a, 16b, 17a–f, 18a and 18b

To a vigorously stirred ice-cooled solution of appropriate alcohol (0.5 mmol) in acetone (30 mL), also ice-cooled solution of CrO_3 (1.20 g, 12 mmol) in 2M H_2SO_4 (12 mL) was added during 5 minutes, and stirring was continued still for up to 3 hours. Almost black reaction mixture was then diluted with a few millilitres of ethanol and poured into ice-cooled distilled water (250 mL). After the ice melted, the residual suspension was filtered through the sintered glass filter to obtain the first portion of crude product. The filtrate was extracted with chloroform (7 × 50 mL), washed with distilled water, dried over anhydrous Na_2SO_4, filtered and evaporated to dryness, yielding the second portion of crude product. In case of mono-triazole species, both portions of crude product were joined together and crystalized from ethyl acetate.

1-(1,2,3,4-Tetrahydro-3-methyl-2,4-dioxoquinolin-3-yl)-1*H*-1,2,3-triazole-4-carboxylic acid (**16a**). Colourless crystals (yield: 33%), m.p. 198–201 °C (ethyl acetate); R_f = 0.05-0.37 (50% ethanol in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.14 (s, 3H, CH_3), 7.22 (d, 1H, J = 7.9 Hz, H-8), 7.21–7.27 (m, 1H, H-6), 7.74 (ddd, 1H, J = 7.8, 7.7, 1.5 Hz, H-7), 7.84 (d, 1H, J = 7.6 Hz, H-5), 8.99 (s, 1H, H-5^A), 11.45 (s, 1H, H-1), 13.21 (br, 1H, COOH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.4 (CH_3), 73.4 (C-3), 117.0 (C-8), 117.7 (C-4a), 123.4 (C-6), 127.6 (C-5), 130.4 (C-5^A), 137.2 (C-7), 139.5 (C-4^A), 141.5 (C-8a), 161.7 (COOH), 168.5 (C-2), 190.5 (C-4); ^{15}N NMR (51 MHz, DMSO-d_6) δ 133.2 (N-1), 250.2 (N-1^A), 357.1 (N-3^A), 367.5 (N-2^A); IR (cm^{-1}): ν 3436, 3141, 2927, 1718, 1684, 1614, 1485, 1392, 1361, 1260, 1163, 1020, 761, 665, 597; HRMS (ESI+): *m/z* calcd for $C_{13}H_{11}N_4O_4^+$ $[M + H]^+$ 287.0775, found 287.0777.

1-(1,2,3,4-Tetrahydro-2,4-dioxo-3-phenylquinolin-3-yl)-1*H*-1,2,3-triazole-4-carboxylic acid (**16b**). Colourless crystals (yield: 71%), m.p. 205–209 °C (ethyl acetate); R_f = 0.00–0.19 (10% ethanol in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.07 (d, 1H, J = 8.0 Hz, H-8), 7.16 (ddd, 1H, J = 7.7, 7.5, 1.0 Hz, H-6), 7.32-7.40 (m, 2H, H-2^C, H-6^C), 7.45-7.53 (m, 3H, H-3^C, H-4^C, H-5^C), 7.62 (ddd, 1H, J = 8.2, 7.3, 1.6 Hz, H-7), 7.83 (dd, 1H, J = 7.8, 1.4 Hz, H-5), 8.71 (s, 1H, H-5^A), 11.63 (s, 1H, H-1), 13.06 (br, 1H, COOH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 80.6 (C-3), 116.7 (C-8), 119.6 (C-4a), 123.4 (C-6), 127.4 (C-5), 128.9 (C-2^C, C-6^C), 129.6 (C-3^C, C-5^C), 129.8 (C-1^C), 130.6 (C-4^C), 131.1 (C-5^A), 136.7 (C-7), 139.2 (C-4^A), 140.4 (C-8a), 161.7 (COOH), 166.8 (C-2), 188.6 (C-4); IR (cm^{-1}): ν 3364, 3157, 1740, 1724, 1679, 1613, 1594, 1485, 1201, 1183, 1039,

855, 778, 754; HRMS (ESI+): *m/z* calcd for $C_{18}H_{13}N_4O_4^+$ $[M + H]^+$ 349.0931, found 349.0927.

1-(1-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-1,2,3,4-tetrahydro-3-methyl-2,4-dioxoquinolin-3-yl)-1*H*-1,2,3-triazole-4-carboxylic acid (**17a**). Colourless solid (yield: 88%), m.p. 129-148 °C; R_f = 0.00-0.35 (10% ethanol in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6), δ 2.15 (s, 3H, CH_3), 5.18 (d, 1H, J = 16.2 Hz, N-1–CHα), 5.48 (d, 1H, J = 16.2 Hz, N-1–CHβ), 5.57 (s, 2H, N-1^D–CH_2), 7.24-7.28 (m, 2H, H-2^E, H-6^E), 7.28-7.38 (m, 4H, H-6, H-3^E, H-4^E, H-5^E), 7.64 (d, 1H, J = 8.5 Hz, H-8), 7.81 (ddd, 1H, J = 8.7, 7.1, 1.7 Hz, H-7), 7.93 (dd, 1H, J = 7.6, 1.2 Hz, H-5), 8.16 (s, 1H, H-5^D), 8.96 (s, 1H, H-5^A), 12.98 (br, 1H, COOH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.6 (CH_3), 38.9 (N-1–CH_2), 52.9 (N-1^D–CH_2), 74.0 (C-3), 116.7 (C-8), 119.3 (C-4a), 123.9 (C-5^D), 123.9 (C-6), 127.9 (C-2^E, C-6^E), 128.0 (C-4^E), 128.2 (C-5),128.8 (C-3^E, C-5^E), 130.6 (C-5^A), 136.0 (C-1^E), 137.1 (C-7), 139.6 (C-4^A), 141.4 (C-8a), 142.3 (C-4^D), 161.7 (COOH), 168.2 (C-2), 189.8 (C-4); ^{15}N NMR (51 MHz, DMSO-d_6) δ 136.8 (N-1), 249.3 (N-1^A), 251.2 (N-1^D), 351.1 (N-3^D), 357.4 (N-3^A), 362.4 (N-2^D), 367.7 (N-2^A); IR (cm^{-1}): ν 3468, 3140, 2945, 1716, 1679, 1602, 1470, 1385, 1278, 1222, 1045, 784, 764, 721; HRMS (ESI+): *m/z* calcd for $C_{23}H_{20}N_7O_4^+$ $[M + H]^+$ 458.1571, found 458.1579.

1-(1,2,3,4-Tetrahydro-3-methyl-2,4-dioxo-1-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)quinolin-3-yl)-1*H*-1,2,3-triazole-4-carboxylic acid (**17b**). Colourless solid (yield: 92%), m.p. 143–168 °C; R_f = 0.00-0.35 (10% ethanol in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.22 (s, 3H, CH_3), 5.27 (d, 1H, J = 16.3 Hz, N-1–CHα), 5.62 (d, 1H, J = 16.3 Hz, N-1–CHβ), 7.34 (dd, 1H, J = 7.4, 7.4 Hz, H-6), 7.45-7.52 (m, 1H, H-4^E), 7.55-7.62 (m, 2H, H-3^E, H-5^E), 7.69 (d, 1H, J = 8.4 Hz, H-8), 7.81-7.91 (m, 3H, H-7, H-2^E, H-6^E), 7.96 (d, 1H, J = 7.3 Hz, H-5), 8.74 (s, 1H, H-5^D), 8.97 (s, 1H, H-5^A), 13.02 (br, 1H, COOH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.6 (CH_3), 38.8 (N-1–CH_2), 74.1 (C-3), 116.8 (C-8), 119.4 (C-4a), 120.2 (C-2^E, C-6^E), 121.8 (C-5^D), 124.0 (C-6), 128.0 (C-5), 128.9 (C-4^E), 130.0 (C-3^E, C-5^E), 130.6 (C-5^A), 136.5 (C-1^E), 137.2 (C-7), 139.7 (C-4^A), 141.5 (C-8a), 143.3 (C-4^D), 161.7 (COOH), 168.3 (C-2), 189.9 (C-4); ^{15}N NMR (51 MHz, DMSO-d_6) δ 135.9 (N-1), 249.4 (N-1^A), 255.7 (N-1^D), 353.2 (N-3^D), 357.0 (N-3^A), 367.8 (N-2^A); IR (cm^{-1}): ν 3142, 3085, 2925, 1717, 1679, 1601, 1470, 1386, 1278, 1226, 1193, 1045, 760, 690, 663; HRMS (ESI+): *m/z* calcd for $C_{22}H_{18}N_7O_4^+$ $[M + H]^+$ 444.1415, found 444.1413.

1-(1,2,3,4-Tetrahydro-3-methyl-2,4-dioxo-1-((1-(pyridin-2-yl)-1*H*-1,2,3-triazol-4-yl)methyl)quinolin-3-yl)-1*H*-1,2,3-triazole-4-carboxylic acid (**17c**). Colourless solid (yield: 84%), m.p. 152–161 °C; R_f = 0.14 (50% ethanol in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.22 (s, 3H, CH_3), 5.29-5.68 (m, 2H, N-1–CH_2), 7.16-8.24 (m, 7H, H-6, H-5^E, H-8, H-7, H-5, H-3^E, H-4^E),

8.46-9.12 (m, 3H, H-6^{E}, H-5^{D}, H-5^{A}), 13.24 (br, 1H, COOH); δ 2.22 (s, 3H), 5.40 (d, 1H, J = 16.5 Hz), 5.55 (d, 1H, J = 16.5 Hz), 7.33 (ddd, 1H, J = 7.6, 7.4, 0.8 Hz), 7.51-7.57 (m, 1H), 7.61 (d, 1H, J = 8.5 Hz), 7.81 (ddd, 1H, J = 8.4, 7.4, 1.7 Hz), 7.96 (dd, 1H, J = 7.7, 1.6 Hz), 8.09-8.13 (m, 2H), 8.56-8.60 (m, 1H), 8.83 (s, 1H), 8.99 (s, 1H), 13.19 (br, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.6 (CH_3), 38.8 (N-1–CH_2), 74.2 (C-3), 113.7 (C-3^{E}) 116.6 (C-8), 119.4 (C-4a), 120.7 (C-5^{D}), 123.9 (C-6), 124.5 (C-5^{E}), 128.0 (C-5), 130.6 (C-5^{A}), 137.1 (C-7), 139.7 (C-4^{A}), 140.2 (C-4^{E}), 141.2 (C-8a), 143.2 (C-4^{D}), 148.4 (C-2^{E}), 149.0 (C-6^{E}), 161.7 (COOH), 168.5 (C-2), 189.8 (C-4); δ 23.6, 38.8, 74.2, 113.7, 116.6, 119.4, 120.7, 123.9, 124.5, 128.0, 130.7, 137.1, 139.7, 140.3, 141.2, 143.2, 148.4, 149.0, 161.7, 168.6, 189.8; ^{15}N NMR (51 MHz, DMSO-d_6) δ 249.2 (N-1^{A}), 260.3 (N-1^{D}), 284.1 (N-1^{E}); IR (cm^{-1}): ν 3147, 2926, 1717, 1680, 1600, 1471, 1385, 1278, 1223, 1038, 1000, 781, 755, 663; HRMS (ESI+): *m/z* calcd for $C_{21}H_{17}N_8O_4^+$ $[M + H]^+$ 445.1367, found 445.1372.

1-(1-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-1,2,3,4-tetrahydro-2,4-dioxo-3-phenylquinolin-3-yl)-1*H*-1,2,3-triazole-4-carboxylic acid (**17d**). Colourless solid (yield: 75%), m.p. 139–162 °C; R_f = 0.12-0.46 (10% ethanol in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.11 (d, 1H, J = 15.9 Hz, N-1–CHα), 5.61 (d, 1H, J = 15.9 Hz, N-1–CHβ), 5.61 (d, 2H, J = 14.8 Hz, N-1^{D}–CH_2), 7.13-7.20 (m, 2H, H-2^{C}, H-6^{C}), 7.21-7.29 (m, 3H, H-6, H-3^{C}, H-5^{C}), 7.29-7.44 (m, 6H, H-2^{E}, H-6^{E}, H-4^{E}, H-3^{E}, H-5^{E}, H-4^{C}), 7.66 (d, 1H, J = 8.2 Hz, H-8), 7.71 (dd, 1H, J = 8.0, 7.9 Hz, H-7), 7.90 (d, 1H, J = 7.4 Hz, H-5), 8.24 (s, 1H, H-5^{D}), 8.76 (s, 1H, H-5^{A}), 13.25 (br, 1H, COOH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 39.8 (N-1–CH_2), 52.8 (N-1^{D}–CH_2), 80.5 (C-3), 116.6 (C-8), 121.1 (C-4a), 124.0 (C-6), 124.3 (C-5^{D}), 127.7 (C-5), 128.0 (C-2^{E}, C-6^{E}), 128.2 (C-4^{E}), 128.7 (C-2^{C}, C-6^{C}), 128.8 (C-3^{E}, C-5^{E}), 129.3 (C-3^{C}, C-5^{C}), 129.6 (C-1^{C}), 130.5 (C-4^{C}), 131.2 (C-5^{A}), 136.0 (C-1^{E}), 136.6 (C-7), 139.3 (C-4^{A}), 140.8 (C-8a), 141.9 (C-4^{D}), 161.7 (COOH), 166.1 (C-2), 187.9 (C-4); ^{15}N NMR (51 MHz, DMSO-d_6) δ 249.8 (N-1^{A}), 250.9 (N-1^{D}), 351.6 (N-3^{D}), 356.4 (N-3^{A}), 362.7 (N-2^{D}); IR (cm^{-1}): ν 3467, 3141, 1717, 1680, 1601, 1469, 1376, 1224, 1038, 872, 760, 724, 696, 665, 610; HRMS (ESI+): *m/z* calcd for $C_{28}H_{22}N_7O_4^+$ $[M + H]^+$ 520.1728, found 520.1730.

1-(1,2,3,4-Tetrahydro-2,4-dioxo-3-phenyl-1-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)quinolin-3-yl)-1*H*-1,2,3-triazole-4-carboxylic acid (**17e**). Colourless solid (yield: 77%), m.p. 153–169 °C; R_f = 0.00-0.22 (10% ethanol in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.28 (d, 1H, J = 16.0 Hz, N-1–CHα), 5.70 (d, 1H, J = 16.0 Hz, N-1–CHβ), 7.26 (dd, 1H, J = 7.4, 7.3 Hz, H-6), 7.28-7.34 (m, 2H, H-2^{C}, H-6^{C}), 7.35-7.41 (m, 2H, H-3^{C}, H-5^{C}), 7.41-7.46 (m, 1H, H-4^{C}), 7.48-7.54 (m, 1H, H-4^{E}), 7.57-7.65 (m, 2H, H-3^{E}, H-5^{E}), 7.68 (d, 1H, J = 8.3 Hz, H-8), 7.73 (dd, 1H, J = 7.6, 7.4 Hz, H-7), 7.85-7.91 (m, 2H, H-2^{E}, H-6^{E}), 7.93 (d, 1H, J = 7.4 Hz, H-5), 8.79 (s, 1H, H-5^{A}), 8.81 (s, 1H, H-5^{D}), 13.12 (br, 1H, COOH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 39.2 (N-1–CH_2), 80.7 (C-3), 116.7

(C-8), 120.2 (C-2^{E}, C-6^{E}), 121.1 (C-4a), 122.4 (C-5^{D}), 124.1 (C-6), 127.8 (C-5), 128.9 (C-4^{E}), 129.0 (C-2^{C}, C-6^{C}), 129.4 (C-3^{C}, C-5^{C}), 129.7 (C-1^{C}), 130.0 (C-3^{E}, C-5^{E}), 130.7 (C-4^{C}), 131.3 (C-5^{A}), 136.5 (C-1^{E}), 136.8 (C-7), 139.3 (C-4^{A}), 140.7 (C-8a), 142.9 (C-4^{D}), 161.8 (COOH), 166.3 (C-2), 188.0 (C-4); ^{15}N NMR (51 MHz, DMSO-d_6) δ 139.5 (N-1), 249.8 (N-1^{A}), 255.6 (N-1^{D}), 354.2 (N-3^{D}), 357.5 (N-3^{A}), 372.6 (N-2^{A}); IR (cm^{-1}): ν 3525, 3145, 3067, 1717, 1681, 1600, 1469, 1377, 1234, 1041, 872, 759, 692, 665; HRMS (ESI+): *m/z* calcd for $C_{27}H_{20}N_7O_4^+$ $[M + H]^+$ 506.1571, found 506.1567.

1-(1,2,3,4-Tetrahydro-2,4-dioxo-3-phenyl-1-((1-(pyridin-2-yl)-1*H*-1,2,3-triazol-4-yl)methyl)quinolin-3-yl)-1*H*-1,2,3-triazole-4-carboxylic acid (**17f**). Colourless solid (yield: 69%), m.p. 116–172 °C; R_f = 0.06 (10% ethanol in chloroform), ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.43 (d, 1H, *J* = 16.2 Hz, N-1–CHα), 5.64 (d, 1H, *J* = 16.2 Hz, N-1–CHβ), 7.25 (dd, 1H, *J* = 7.4, 7.3 Hz, H-6), 7.28-7.36 (m, 2H, H-2^{C}, H-6^{C}), 7.38-7.48 (m, 3H, H-3^{C}, H-4^{C}, H-5^{C}), 7.50-7.59 (m, 2H, H-8, H-5^{E}), 7.69 (dd, 1H, *J* = 7.6, 7.5 Hz, H-7), 7.95 (d, 1H, *J* = 7.4 Hz, H-5), 8.07-8.19 (m, 2H, H-3^{E}, H-4^{E}), 8.56-8.64 (m, 1H, H-6^{E}), 8.79-8.91 (m, 2H, H-5^{D}, H-5^{A}), 13.23 (br, 1H, COOH); ^{13}C NMR (126 MHz, DMSO-d_6) δ 39.7 (N-1–CH$_2$), 80.8 (C-3), 113.7 (C-3^{E}), 116.5 (C-8), 120.9 (C-5^{D}), 121.2 (C-4a), 124.0 (C-6), 124.5 (C-5^{E}), 127.9 (C-5), 128.9 (C-2^{C}, C-6^{C}), 129.5 (C-3^{C}, C-5^{C}), 129.8 (C-1^{C}), 130.7 (C-4^{C}), 131.3 (C-5^{A}), 136.7 (C-7), 139.2 (C-4^{A}), 140.3 (C-4^{E}), 140.4 (C-8a), 143.0 (C-4^{D}), 148.3 (C-2^{E}), 149.0 (C-6^{E}), 161.8 (COOH), 166.7 (C-2), 187.9 (C-4); ^{15}N NMR (51 MHz, DMSO-d_6) δ 137.8 (N-1), 249.7 (N-1^{A}), 260.4 (N-1^{D}), 284.9 (N-1^{E}), 356.8 (N-3^{A}), 357.1 (N-3^{D}); IR (cm^{-1}): ν 3435, 3157, 2927, 1718, 1682, 1600, 1470, 1375, 1313, 1189, 1035, 779, 758, 696; HRMS (ESI+): *m/z* calcd for $C_{26}H_{19}N_8O_4^+$ $[M + H]^+$ 507.1524, found 507.1527.

1-(1,2,3,4-Tetrahydro-3-methyl-2,4-dioxo-1-(prop-2-ynyl)quinolin-3-yl)-1*H*-1,2,3-triazole-4-carboxylic acid (**18a**). Colourless crystals (yield: 55%), m.p. 187–190 °C (ethyl acetate); R_f = 0.15 (50% ethanol in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.14 (s, 3H), 3.25-3.44 (m, 1H), 4.84 (dd, 1H, *J* = 18.1, 2.4 Hz), 4.97 (dd, 1H, *J* = 18.1, 2.4 Hz), 7.38 (dd, 1H, *J* = 7.5, 7.5 Hz), 7.59 (d, 1H, *J* = 8.4 Hz), 7.91 (ddd, 1H, *J* = 8.5, 7.3, 1.5 Hz), 7.97 (dd, 1H, *J* = 7.7, 1.4 Hz), 8.99 (s, 1H), 13.23 (br, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 23.5, 32.7, 73.7, 75.4, 78.2, 116.7, 119.2, 124.2, 128.1, 130.6, 137.1, 139.6, 140.7, 161.7, 167.7, 189.5; IR (cm^{-1}): ν 3259, 3137, 2127, 1742, 1693, 1650, 1603, 1472, 1393, 1304, 1214, 1187, 1045, 781, 753; HRMS (ESI+): *m/z* calcd for $C_{16}H_{13}N_4O_4^+$ $[M + H]^+$ 325.0931, found 325.0930.

1-(1,2,3,4-Tetrahydro-2,4-dioxo-3-phenyl-1-(prop-2-ynyl)quinolin-3-yl)-1*H*-1,2,3-triazole-4-carboxylic acid (**18b**). Colourless crystals (yield: 68%), m.p. 154–161 °C (ethyl acetate); R_f = 0.23 (50% ethanol in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.40-3.44 (m, 1H), 4.80 (dd, 1H, *J* = 16.8, 3.3 Hz), 5.16

(dd, 1H, *J* = 16.8, 3.3 Hz), 7.23-7.32 (m, 3H), 7.39-7.53 (m, 4H), 7.75 (ddd, 1H, *J* = 8.4, 7.4, 1.7 Hz), 7.92 (dd, 1H, *J* = 7.7, 1.5 Hz), 8.79 (s, 1H), 13.23 (br, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 33.2, 75.5, 77.8, 80.5, 116.3, 121.0, 124.2, 127.8, 128.7, 129.5, 129.7, 130.7, 131.3, 136.7, 139.2, 139.9, 161.7, 165.7, 187.5; IR (cm^{-1}): ν 3494, 3205, 2118, 1720, 1683, 1603, 1469, 1374, 1306, 1218, 1040, 871, 764, 696; HRMS (ESI+): *m/z* calcd for $C_{21}H_{15}N_4O_4^+$ $[M + H]^+$ 387.1088, found 387.1084.

6.17 General procedure for preparation of compounds 19a, 19b, 20b and 20c

Yellow solution of an appropriate starting compound (1 mmol) and sodium methoxide (54 mg, 1 mmol) in dry methanol (11 mL) was stirred at laboratory (23 °C) or reflux (65 °C) temperature. After transformation was completed, the mixture was neutralised using 1.0 M HCl, and subsequently evaporated to dryness. Yellow oily residue was dissolved in chloroform (50 mL) and washed with distilled water (3 x 50 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. That way obtained oily or solid mixture of products was then subjected to silica-gel (35 g) column (ø = 2 cm) chromatography, using ethyl acetate in petroleum ether or ethanol in chloroform as an eluent. Particular TLC pure compounds were further crystalized from ethyl acetate.

Methyl 2-(2-(4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)propanamido) benzoate (19a). Prepared from compound **5a**. Colourless crystals (yield: 23%), m.p. 116–130 °C (ethyl acetate); R_f = 0.51 (10% ethanol in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.95 (d, 3H, *J* = 7.3 Hz, C-3–CH_3), 2.66 (s, 1H, OH), 3.88 (s, 3H, OCH_3), 4.84 (d, 2H, *J* = 5.4 Hz, CH_2), 5.53 (q, 1H, *J* = 7.3 Hz, H-3), 7.12 (ddd, 1H, *J* = 8.4, 7.0, 1.1 Hz, H-6), 7.54 (ddd, 1H, *J* = 8.7, 7.1, 1.7 Hz, H-7), 7.84 (s, 1H, H-5^A), 8.01 (dd, 1H, *J* = 8.0, 1.5 Hz, H-5), 8.62 (d, 1H, *J* = 8.5 Hz, H-8), 11.19 (s, 1H, H-1); ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.2 (C-3–CH_3), 52.8 (OCH_3), 56.8 (CH_2), 60.9 (C-3), 115.8 (C-4a), 120.6 (C-8), 121.3 (C-5^A), 123.7 (C-6), 131.1 (C-5), 134.9 (C-7), 140.4 (C-8a), 148.3 (C-4^A), 167.4 (C-2), 168.7 (C-4); ^{15}N NMR (51 MHz, $CDCl_3$) δ 123.8 (N-1), 249.3 (N-1^A), 349.0 (N-3^A), 362.6 (N-2^A); IR (cm^{-1}): *v* 3342, 3160, 1714, 1681, 1610, 1587, 1534, 1450, 1315, 1301, 1258, 1056, 759, 613; UV λ_{max} [nm] (10^{-3} ε [$M^{-1}cm^{-1}$]): 223 (31.4), 254 (14.3), 305 (5.4); HRMS (ESI+): *m/z* calcd for $C_{14}H_{17}N_4O_4^+$ $[M + H]^+$ 305.1244, found 305.1244.

Methyl 2-(2-(4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)-2-phenylacetamido) benzoate (19b). Prepared from compound **5b**. Colourless crystals (yield: 26%), m.p. 142–145 °C (ethyl acetate); R_f = 0.34 (5% ethanol in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.66 (s, 3H, CH_3), 4.52 (d, 2H, *J* = 5.7 Hz, CH_2), 5.18

(t, 1H, *J* = 5.7 Hz, OH), 6.97 (s, 1H, H-3), 7.26 (ddd, 1H, *J* = 7.7, 7.5, 1.2 Hz, H-6), 7.43–7.52 (m, 3H, H-3^{C}, H-4^{C}, H-5^{C}), 7.55–7.60 (m, 2H, H-2^{C}, H-6^{C}), 7.63 (ddd, 1H, *J* = 8.3, 7.4, 1.7 Hz, H-7), 7.87 (dd, 1H, *J* = 7.9, 1.5 Hz, H-5), 8.00 (s, 1H, H-5^{A}), 8.10 (d, 1H, *J* = 8.3 Hz, H-8), 10.87 (s, 1H, H-1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 52.3 (CH_3), 55.0 (CH_2), 66.5 (C-3), 119.8 (C-8a), 122.2 (C-8), 122.8 (C-5^{A}), 124.5 (C-6), 128.7 (C-2^{C}, C-6^{C}), 129.2 (C-3^{C}, C-5^{C}), 129.3 (C-4^{C}), 130.6 (C-5), 133.7 (C-7), 134.3 (C-1^{C}), 137.7 (C-4a), 148.1 (C-4^{A}), 165.6 (C-2), 167.0 (C-4); ^{15}N NMR (51 MHz, DMSO-d_6) δ 128.8 (N-1), 249.7 (N-1^{A}), 351.8 (N-3^{A}), 361.9 (N-2^{A}); IR (cm^{-1}): *ν* 3307, 1711, 1698, 1606, 1591, 1531, 1453, 1431, 1314, 1296, 1277, 1041, 769, 730, 700; UV λ_{max} [nm] (10^{-3} ε [M^{-1}cm^{-1}]): 224 (28.2), 255 (12.7), 305 (4.9); HRMS (ESI+): *m/z* calcd for $C_{19}H_{19}N_4O_4^+$ [M + H]$^+$ 367.1401, found 367.1400.

2-(2-(4-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)-2-phenylacetamido)benzoic acid (20b). Prepared from compound **5b**. Colourless crystals (yield: 33%), m.p. 227–230 °C (ethyl acetate); R_f = 0.04–0.35 (33% ethanol in chloroform); ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.52 (s, 2H, CH_2), 6.90 (s, 1H, H-3), 7.14 (ddd, 1H, *J* = 7.7, 7.5, 1.2 Hz, H-6), 7.41–7.48 (m, 3H, H-3^{C}, H-4^{C}, H-5^{C}), 7.52 (ddd, 1H, *J* = 8.3, 7.4, 1.7 Hz, H-7), 7.56–7.62 (m, 2H, H-2^{C}, H-6^{C}), 7.96 (dd, 1H, *J* = 7.9, 1.5 Hz, H-5), 8.02 (s, 1H, H-5^{A}), 8.44 (d, 1H, *J* = 8.2 Hz, H-8), 12.58 (s, 1H, H-1); ^{13}C NMR (126 MHz, DMSO-d_6) δ 55.0 (CH_2), 67.3 (C-3), 119.7 (C-8), 119.7 (C-4a), 123.0 (C-5^{A}), 123.2 (C-6), 128.8 (C-2^{C}, C-6^{C}), 129.1 (C-3^{C}, C-5^{C}), 129.3 (C-4^{C}), 131.1 (C-5), 132.9 (C-7), 134.5 (C-1^{C}), 139.8 (C-8a), 147.9 (C-4^{A}), 165.5 (C-2), 169.4 (C-4); ^{15}N NMR (51 MHz, DMSO-d_6) δ 128.9 (N-1), 249.9 (N-1^{A}), 351.8 (N-3^{A}), 362.3 (N-2^{A}); IR (cm^{-1}): *ν* 3361, 3150, 1703, 1672, 1606, 1589, 1537, 1509, 1453, 1416, 1273, 1046, 763, 698; UV λ_{max} [nm] (10^{-3} ε [M^{-1}cm^{-1}]): 223 (28.1), 255 (12.0), 307 (4.5); HRMS (ESI+): *m/z* calcd for $C_{18}H_{17}N_4O_4^+$ [M + H]$^+$ 353.1244, found 353.1244.

2-(2-(4-(Hydroxymethyl)-1H-1,2,3-triazol-1-yl)-2-phenyl-N-(prop-2-ynyl)acetamido)benzoic acid (20c). Prepared from compound **6b**. Colourless crystals (yield: 69%), m.p. 164–168 °C (ethyl acetate); R_f = 0.49 (50% ethanol in chloroform); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.23 (dd, 1H, *J* = 2.5, 2.4 Hz, C≡CH), 4.26 (dd, 1H, *J* = 17.4, 2.4 Hz, N-1–CH*α*), 4.59 (d, 1H, *J* = 13.8 Hz, OCH*α*), 4.69 (d, 1H, *J* = 13.8 Hz, OCH*β*), 4.85 (dd, 1H, *J* = 17.4, 2.4 Hz, N-1–CH*β*), 6.54 (s, 1H, H-3), 6.82 (d, 1H, *J* = 7.8 Hz, H-8), 7.20–7.25 (m, 2H, H-2^{C}, H-6^{C}), 7.31–7.43 (m, 4H, H-7, H-3^{C}, H-4^{C}, H-5^{C}), 7.50 (ddd, 1H, *J* = 7.7, 7.6, 1.1 Hz, H-6), 7.79 (s, 1H, H-5^{A}), 8.15 (dd, 1H, *J* = 7.7, 1.3 Hz, H-5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 39.4 (N-1–CH_2), 55.2 (OCH_2), 65.3 (C-3), 73.7 (C≡*C*H), 77.9 (*C*≡CH), 123.2 (C-5^{A}), 128.5 (C-2^{C}, C-6^{C}), 129.5 (C-3^{C}, C-5^{C}), 130.0 (C-6), 130.0 (C-4^{C}), 130.9 (C-4a), 131.3 (C-8), 132.8 (C-5), 132.8 (C-7), 133.1 (C-1^{C}), 138.4 (C-8a), 146.5 (C-4^{A}), 166.5 (C-2), 169.0 (C-4); ^{15}N NMR (51 MHz, $CDCl_3$) δ 125.6 (N-1), 250.3 (N-1^{A}), 326.6 (N-3^{A}), 360.2 (N-2^{A}); IR (cm^{-1}): *ν* 3437, 3285,

2121, 1667, 1599, 1494, 1456, 1412, 1298, 1281, 1242, 1022, 715, 700; UV λ_{max} [nm] (10^{-3} ε [$M^{-1}cm^{-1}$]): 281 (1.3); HRMS (ESI+): *m/z* calcd for $C_{21}H_{19}N_4O_4^+$ $[M + H]^+$ 391.1401, found 391.1394.

6.17.1 Additional procedure for preparation of compound 20b

To a starting compound **5b** (0.5 g, 1.33 mmol), solution of potassium hydroxide (2.244 g, 40 mmol) in distilled water (4 mL) and ethanol (30 mL) was added. Obtained mixture was stirred at laboratory temperature for the time period of 45 minutes. Afterwards, reaction mixture was neutralised with diluted HCl (1:1 *V*/*V*) and evaporated *in vacuo* to gain yellow oily crude product that was further purified on silica-gel (35 g) column (ø = 2 cm), using pure chloroform and 33% ethanol in chloroform to gain colourless solid compound (yield: 75%).

6.18 Antimicrobial susceptibility testing

6.18.1 Broth dilution method

Stock solutions (20 g/L, 10 g/L, 5 g/L and 1 g/L) were prepared by dissolving appropriate quantities of tested compounds in DMSO. Tryptone–soya peptone–glucose (TSG) broth was obtained by mixing 1.0 g of tryptone (HiMedia Laboratories Pvt. Ltd., Mumbai, India), 0.5 g of soya peptone (HiMedia Laboratories Pvt. Ltd., Mumbai, India), 0.5 g of NaCl (Lachema, a.s., Czech Republic), 0.3 g of K_2HPO_4 (Uherský Brod, Czech Republic) and 1.1 g of glucose monohydrate (Penta, Czech Republic). All ingredients were joined, dissolved in 100 mL of distilled water and sterilized by filtration through the 0.22 pore-sized filter (Millex®GS, Carrighwohill, Co. Cork, Ireland) into three 50 mL Falcon tubes (Schoeller Pharma Praha, Czech Republic). The physiological solution was prepared by dissolving 8.5 g NaCl in 1.0 L of distilled water. That way prepared saline solution was then sterilized in microwave autoclave (Microjet, The Rodwell Autoclave Company, United Kingdom) at 135 °C for the time period of 30 seconds, and cooled down to laboratory temperature before usage. Biomasses of appropriate microbe cultures were suspended into approximately 5 mL of sterile saline solution in sterile plastic tubes (Gama Group a.s., Czech Republic), corresponding density of 2nd degree of McFarland scale (0.2 mL 1% $BaCl_2$ in 9.8 mL 1% H_2SO_4). Antimicrobial testing against *Staphylococcus aureus* (CCM 3953), *Escherichia coli* (CCM 3954), *Pseudomonas aeruginosa* (CCM 3955) and *Candida albicans* (CCM 8275) was carried out on sterile plastic 96-well microtiter plates (Gama Group a.s., Czech Republic). Each microplate was inoculated with only one microbe species. Sixteen wells were utilised for interrogation of one compound against one microbe strain. Firstly, nutrient media was placed into 16 wells (185 μL into each). Afterwards, each of four stock concentrations of a particular compound was put into three wells with TSG broth

(5 μL into each), occupying all together 12 wells. In 4 unoccupied wells, DMSO (5 μL into each) was added. Finally, all 16 used wells were inoculated with microbe suspension (10 μL into each). Taking into account dilutions in the wells, actual concentrations of the screened compounds were 25, 125, 250 and 500 mg/L. Appropriate volumes of TSG broth nutrient media, stocks solutions in DMSO, as well as microbe culture suspensions were dosed using micropipettes (PZ HTL S.A., Poland) with the volume ranges of 2–20 μL and 20–200 μL. After inoculation, microtiter plates were covered with sterile plastic lids (Gama Group a.s., Czech Republic) and incubated at 37 °C for the time period of 24–48 hours. The growth of microbes was evaluated by visual check of incubated microplates or by measuring of absorbance in particular wells at the wavelength of 600 nm, using Microplate Reader Spectrophotometer (Sunrise, Tecan Trading AG, Switzerland). In some cases, the growth of microbes was additionally confirmed by inoculation of suspensions from chosen wells to the Petri plates (ø = 90 mm; Gama Group a.s., Czech Republic) with agar.

6.18.2 Disk diffusion test

Stock solutions (20 g/L, 5 g/L and 0.2 g/L) were prepared by dissolving appropriate quantities of tested compounds in acetone. Testing against fungal cultures *Trichoderma viride* (CCM F-486) and *Aspergillus niger* (CCM 8155) was carried out on chloramphenicol yeast glucose agar (HiMedia Laboratories Pvt. Ltd., Mumbai, India) in Petri plates (ø = 90 mm; Gama Group a.s., Czech Republic). The nutrient agar media was prepared by dispersing of 24 g agar powder in 600 mL of distilled water and sterilized in microwave autoclave (Microjet, The Rodwell Autoclave Company, United Kingdom) at 135 °C for the time period of 30 seconds. Still hot that way obtained solution was evenly poured into approximately 35 Petri plates and let to cool down to laboratory temperature. The physiological solution was prepared by dissolving 8.5 g NaCl (Lachema, a.s., Czech Republic) in 1.0 L of distilled water. Saline solution, as well as filter paper discs (ø = 55 mm) were sterilized in common autoclave at 121 °C for the time period of 20 minutes. Appropriate fungal culture was suspended into approximately 10 mL of sterile physiological solution in sterile plastic tube, corresponding density of 2nd degree of McFarland scale. Afterwards, 200 μL of suitable stock solution was uniformly applied on a sterile paper disc that was then placed on agar. Nutrient media, as well as paper disc in Petri plate were then inoculated with the suspension of chosen fungal culture, covered with plastic lid (Gama Group a.s., Czech Republic) and left for incubation at 25 °C for the time period of 7 days. Each of three tested concentrations of a particular compound, as well as reference value (pure acetone) were applied on two paper discs that were further placed on two separate agar Petri plates. As a result, 8 Petri plates were used for evaluation of one single compound against one fungal strain. The growth of microbes was established by visual check.

7. CONCLUSIONS

Throughout my doctoral studies, a collection of quinoline-2,4(1*H*,3*H*)-dione species with one and two 1,2,3-triazole rings was prepared. The multi-step transformation scheme started with condensation reactions between aniline and suitably substituted diethyl malonates to give appropriate 4-hydroxyquinolin-2(1*H*)-ones **1** that were further transformed into 3-chloroquinoline-2,4(1*H*,3*H*)-diones **2**, and finally into 3-azidoquinoline-2,4(1*H*,3*H*)-diones **3**.

Using copper-catalysed 1,3-dipolar cycloaddition between azides **3** and propargyl alcohol, mono-triazole alcohols **4** were formed. Compounds **4** were further acetylated to provide corresponding esters **5**. By protecting primary alcohol group, potential *O*-alkylation during the propargylation reaction was effectively avoided, and therefore only *N*-alkylation of synthesized acetates **5** took place. As a result, *N*-propargyl derivatives **6** were obtained in very good yields.

In the next step, second 1,2,3-triazole ring was introduced to the quinolone segment, as materials **6** were further combined with three organic azides, namely benzyl azide **A**, phenyl azide **B** and tetrazolo[1,5-*a*]pyridine **C**, a synthetic equivalent for 2-azidopyridine **C'**. Consequently, six different bis-triazole acetates were synthesized, employing similar reaction conditions to those for the first »click«.

Apart from Cu^0/Cu^{2+} catalytic system in DMF, more commonly used bivalent copper in the presence of L-ascorbic acid or its sodium salt in various organic solvent(s)/water systems were also studied. Due to highly hydrophobic nature of synthesized compounds, the presence of water turned reactants and products into sticky, gummy materials that stuck on the flask's wall, as well as magnetic stirring bar and thus prevented reactions from going to completion. As a result, considerably lower yields and longer transformation times were established, when water was added to the reaction mixture. Consequently, Cu^0/Cu^{2+} catalytic pair in DMF was recognised superior for 1,2,3-triazole-bearing quinoline-2,4-dione species preparation.

Beside presented »click–propargylation–click« synthetic approach, its »propargylation–click–click« modification was also briefly evaluated. While the former provided only one expected product in each reaction step, 3-azido-1-propargyl bifunctional quinolone (**8a**) self-polymerization was detected during the latter. Consequently, observed reaction yields were significantly lower than in the case of »click–propargylation–click« reaction sequence.

Due to the fact that numerous materials with 1,2,3-triazole and/or quinolone building blocks exhibit large variety of desirable physical properties and biological activities, the number of synthesized compounds was maximized, using chemical functionality as an efficient tool for various derivatives preparation. Appropriate mono- and bis-triazole esters (**5**–**7**) were firstly deacetylated, and subsequently oxidized to suitable aldehydes and carboxylic acids. In all cases, reaction conditions were firstly optimised on more accessible *N*-unsubstituted

mono-triazole species, and then successfully utilised for bis-triazoles and propargyl derivatives preparation.

Three different deprotection approaches were evaluated for preparation of alcohols **4**, **11** and **12**. While basic reaction environments resulted in quinoline-2,4-dione ring-opening, desirable products were obtained by acidic alcoholysis of appropriate acetates. In addition, last-mentioned quinolinedione framework cleavage, using sodium methoxide in dry methanol, as well as potassium hydroxide in ethanol was also taken into consideration. While mixture of anthranilic acid derivatives commonly arose during the former, only one product was expectedly isolated throughout the latter.

Comparing PCC and MnO_2 as reagents for aldehydes **13**–**15** preparation, slightly higher reaction yields were gained, when manganese dioxide was used as an oxidant. In both cases, desirable aldehydes were prepared in only moderate yields. Relatively low transformation yields, especially in the case of pyridinium chlorochromate, were most probably caused by reagents' residues that apparently encaged formed products, preventing them from being transferred into organic solvent. In addition, Swern oxidation approach was found unsuitable for 1,2,3-triazole-bearing quinoline-2,4-dione aldehydes preparation.

Hexavalent chromium CrO_3 in sulphuric(VI) acid and acetone was proved to be an efficient reagent for the oxidation of primary alcohols **4**, **11** and **12** to carboxylic acids **16**–**18** that were obtained in very good to excellent yields. Even though, quite large quantities of toxic chromium-based oxidant were added to the reaction mixtures, pure carboxylic acids were provided, as reagent residuals were effectively removed during the isolation process.

Finally, several synthesized materials were interrogated for their coordination properties to ruthenium metal centre, as well as for antimicrobial activities against ten microbial strains including *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, *Mycobacterium tuberculosis*, *Mycobacterium marinum*, *Mycobacterium kansasii*, *Mycobacterium smegmatis*, *Trichoderma viride* and *Aspergillus niger*. In addition, prepared species were also briefly screened for their potential photoprotective properties. Unfortunately, none of the tested compounds synthesized in the context of this dissertation exhibited any promising characteristics at all.

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CURRICULUM VITAE

PERSONAL INFORMATION

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EDUCATION

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2003 – 2007 High School: Diocesan Classical Gymnasium – St. Stanislav's Institution, Ljubljana, Slovenia

PAPERS IN SCIENTIFIC JOURNALS

1.) **Milićević, D**.; Kimmel, R.; Urankar, D.; Pevec, A.; Košmrlj, J.; Kafka, S. Preparation of Quinoline-2,4-dione Functionalized 1,2,3-Triazol-4-ylmethanols, 1,2,3-Triazole-4-carbaldehydes and 1,2,3-Triazole-4-carboxylic Acids.
*J. Heterocycl. Chem. (**Submitted Manuscript**)*

2.) **Milićević, D.**; Kimmel, R.; Gazvoda, M.; Urankar, D.; Kafka, S.; Košmrlj, J. Synthesis of Bis(1,2,3-Triazole) Functionalized Quinoline-2,4-Diones.
Molecules **2018**, *23*(9), 2310.

3.) De Macedo, M. B.; Kimmel, R.; Urankar, D.; Gazvoda, M.; Peixoto, A.; Cools, F.; Torfs, E.; Verschaeve, L.; Lima, E. S.; Lyčka, A.; **Milićević, D.**; Klásek, A.; Cos, P.; Kafka, S.; Košmrlj, J.; Cappoen, D. Design, synthesis and antitubercular potency of 4-hydroxyquinolin-2(1*H*)-ones. *Eur. J. Med. Chem.* **2017**, *138*, 491–500.

CONFERENCE CONTRIBUTIONS

1.) **Milićević D.**, Kimmel R., Košmrlj J., Kafka S.: New Compounds with 1,2,3-Triazole Moiety. *70th Congress of the Czech and Slovak Chemical Societies*, Zlín, 9-12 September 2018. *Czech Chemical Society Symposium Series* **2018**, *16*, 342–343. ISSN: 2336-7202 *(Presentation)*

2.) **Milićević D.**, Kimmel R., Košmrlj J., Kafka S.: Synthesis and Analysis of 3-Azidoquinoline-2,4-diones. *46th EuroCongress on Drug Synthesis and Analysis*, Bratislava, 5-8 September 2017. Planková A., Ježko P., Maráková K. (editors): *Book of Abstracts*, p. 163. ISBN: 978-80-223-4388-6 *(Poster)*

TRAINEESHIP

1.) Comenius University in Bratislava, Faculty of Pharmacy, Department of Pharmaceutical Chemistry. Supervisor: Prof. PharmDr. Josef Jampílek, Ph.D. Bratislava, August–September 2017.

PROJECTS

1.) IGA/FT/2019/010 – Synthesis and study of chemical reactivity of nitrogen heterocycles derivatives; *Principal investigator*

2.) IGA/FT/2018/007 – Study of chemical reactivity of compounds with quinoline, pyridine and 1,2,3-triazole structure in molecule; *Principal Investigator*

3.) IGA/FT/2017/005 – Synthesis and investigation of chemical transformations of quinoline and 1,2,3-triazole derivatives; (*Principal) Investigator*

4.) IGA/FT/2016/004 – Syntheses and investigation of chemical transformations of derivatives of quinoline, 1,2,3-triazole, and pyridine attached to the bornane system; *Investigator*