UNIVERSIDADE FEDERAL DE PELOTAS

Programa de Pós-Graduação em Biotecnologia

Tese

Síntese e avaliação do potencial biológico de 1,2,3-triazóis derivados da zidovudina e ésteres graxos

Carolina Baptista Gomes

Pelotas, 2020

Carolina Baptista Gomes

Síntese e avaliação do potencial biológico de 1,2,3-triazóis derivados da zidovudina e ésteres graxos

Tese apresentada ao Programa de Pós-Graduação em Biotecnologia da Universidade Federal de Pelotas, como requisito parcial à obtenção do título de Doutor em Ciências (área do Conhecimento: Biotecnologia).

Orientador: Prof. Dr. Diego da Silva Alves
Coorientador(a): Lucielli Savegnago

Pelotas, 2020

Universidade Federal de Pelotas / Sistema de Bibliotecas

Catalogação na Publicação

G633s Gomes, Carolina Baptista

Síntese e avaliação do potencial biológico de 1,2,3-triazóis derivados da zidovudina e ésteres graxos / Carolina Baptista Gomes ; Diego da Silva Alves, orientador ; Lucielli Savegnago, coorientadora. — Pelotas, 2020.

119 f.

Tese (Doutorado) — Programa de Pós-Graduação em Biotecnologia, Centro de Desenvolvimento Tecnológico, Universidade Federal de Pelotas, 2020.

1. Triazol. 2. Esteres graxos. 3. Zidovudina. 4. Atividade antioxidante. 5. Atividade citotóxica. I. Alves, Diego da Silva, orient. II. Savegnago, Lucielli, coorient. III. Título.

CDD : 616.99262

Elaborada por Ubirajara Buddin Cruz CRB: 10/901

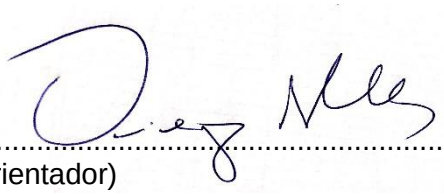
Carolina Baptista Gomes

Síntese e avaliação do potencial biológico de 1,2,3-triazóis derivados da zidovudina e ésteres graxos

Tese aprovada, como requisito parcial, para obtenção do grau de Doutor em Ciências (área do Conhecimento: Biotecnologia), Programa de Pós-Graduação em Biotecnologia, Centro de Desenvolvimento Tecnológico, Universidade Federal de Pelotas.

Data da Defesa: 18/02/2020

Banca examinadora:

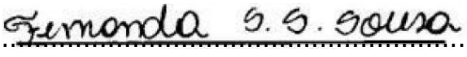


.....

Prof. Dr Diego Alves (Orientador)
Doutor em Química pela Universidade Federal de Santa Maria.

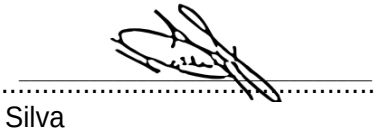
.....

Prof. Dr. Benhur de Godoi
Doutor em Química pela Universidade Federal de Santa Maria.



.....

Prof.ª Dr. Fernanda S. Sabedra Sousa
Doutora em Bioquímica e Bioprospecção pela Universidade Federal de Pelotas.



.....

Prof. Dr. Marcio Santos Silva
Doutor em Química pela Universidade de São Paulo.

Para minha filha com carinho e gratidão.

Dedico.

Agradecimentos

Primeiramente agradeço a Deus, pois foi através da fé e resignação que hoje chegamos a este momento de conclusão da tese. O termo “nós” estará sempre presente à medida que não é possível separar a vida profissional do pessoal. Andam lado a lado e este é o maravilhoso da vida. Talvez minha filha Marina hoje aos seis anos não saiba a dimensão de seus gestos, que foram capazes de abrilhantar cada dia vivido deste doutorado. Agradeço a minha filha Marina por me arrancar sorrisos e me mostrar que para uma mãe, não se tem limites, tudo está num ótimo preço.

Algumas características são essenciais para se desenvolver um bom trabalho: princípios, valores, resistência, resiliência e empatia. E eu agradeço imensamente aos meus pais Adalberto e Kátia Gomes por não apenas estarem ao meu lado, me apoiando, mas por todas estas características passadas como ensinamento de vida, pela minha construção como ser humano, refletindo no profissional. Obrigado pela confiança, carinho e palavras de apoio, sempre na hora certa. Agradeço aos meus pilares, minha família! Ao meu irmão e minha cunhada por nossos momentos de muita alegria compartilhados, nossa troca de carinho, energia e experiências.

À Universidade Federal de Pelotas fica o meu obrigado. Em especial ao Centro de Desenvolvimento Tecnológico pela acolhida ao longo desses anos e ao Programa de pós-graduação em Biotecnologia, não apenas pelo trabalho desenvolvido, mas pelo carinho como somos recebidos. Obrigado pela dedicação Daiane e Renata. O empenho e carinho dos professores Tiago, Fabiana, Luciano, Fábio e Vanessa. Aos meus colegas do PPGB Martha Ruíz, Alisson Carlos, Ângela e Denisson pela troca de conhecimento, experiência e apoio que tivemos uns com os outros a cada dia do doutorado.

Ao meu orientador Diego Alves, agradeço pelo aceite em me orientar, a troca que tivemos nesses anos. Sou muito grata pela oportunidade de trabalhar ao lado de um excelente profissional e um “super pai” para seus filhos, o que o torna diferenciado. Agradeço também a colaboração dos professores Lucielli e Márcio.

Aos colegas de laboratório que se tornaram amigos e porque não dizer “filhos científicos”: Thomáz, Vitória, Ariana, Bruna, Eduardo Carvalho e Carol Landim. Se hoje chego a este momento, vocês fizeram parte dessa história com muito carinho e reciprocidade. A minha querida Mariana Bach que me ensinou conceitos fundamentais de orgânica e me fez entender que o nosso lugar é onde estamos, escolhido por Deus.

A amiga e colega da química Luiza Helena que fez toda diferença nesse doutorado com sua parceria em disciplinas, congressos e vida pessoal.

Agradeço a Renata Balaguez pelos ensinamentos de orgânica e a disponibilidade sempre que necessária de Edmilson e Liane.

Ao LASOL, de modo geral, agradeço por fazer parte da equipe. Com certeza depois dessa experiência saio mais forte para o mercado de trabalho. Em especial as professoras Raquel e Daniela, foram fundamentais junto com as “meninas da Raquel” e o “pessoal do Eder”. Vocês são nota 10.

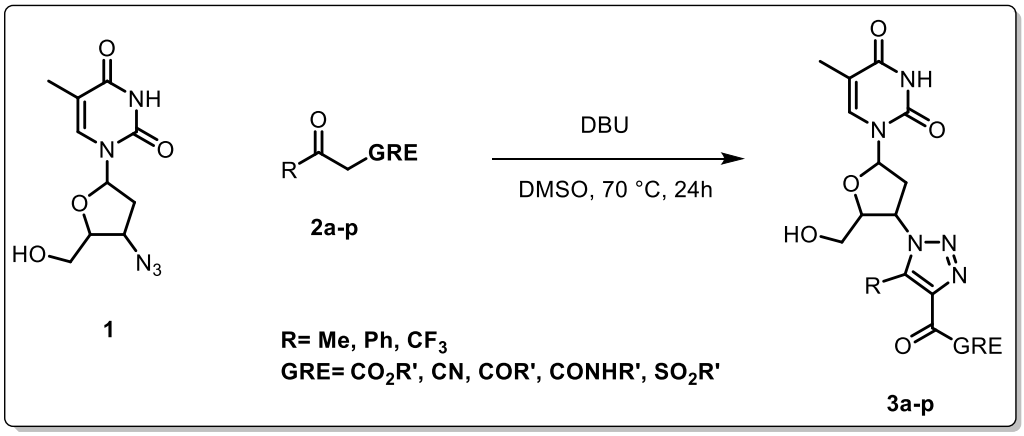
“Quanto custa um sonho? Alguma coisa ele sempre custa. Muitas vezes muitas coisas ele custa, outras vezes outros sonhos ele custa. Não importam os percalços, os sacrifícios, os espinhosos enredos. Não importa. Uma vez vivido, o sonho está sempre num ótimo preço!”

Elisa Lucinda

Resumo

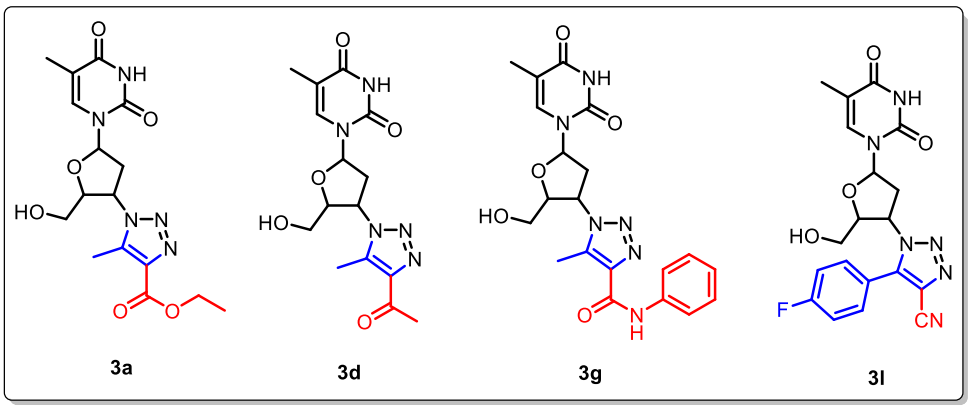
GOMES, Carolina. **Síntese e avaliação do potencial biológico de 1,2,3-triazóis derivados da zidovudina e ésteres graxos.** 2020. 119f. Tese (Doutorado) - Programa de Pós-Graduação em Biotecnologia. Universidade Federal de Pelotas, Pelotas.

Os triazóis funcionalizados são substâncias orgânicas que apresentam um amplo potencial sintético e farmacológico. O presente trabalho está dividido em duas partes, onde foram relatados os resultados da síntese e avaliação do potencial biológico dos derivados: 1,2,3-triazoil-zidovudina e 1,2,3-triazoil-ésteres graxos. Primeiramente são abordados os resultados do estudo 1,2,3-triazoil-zidovudina. O Capítulo 1 descreve o uso de um sistema organocatalítico constituído por zidovudina (0,3 mmol) **1**, cetonas α-substituídas (0,36 mmol) **2a-p**, 1,8-diazabiciclo[5,4,0]-undec-7-eno (10 mol%) como organocatalisador e dimetilsulfóxido como solvente da reação à 70 °C por 24 h. Foram obtidos dezesseis moléculas derivadas de 1*H*-1,2,3-triazol-zidovudina **3a-p** (**Esquema 1**) com moderados a excelentes rendimentos (59%-91%) e também foi avaliado o potencial farmacológico destas moléculas frente a atividade antioxidante.



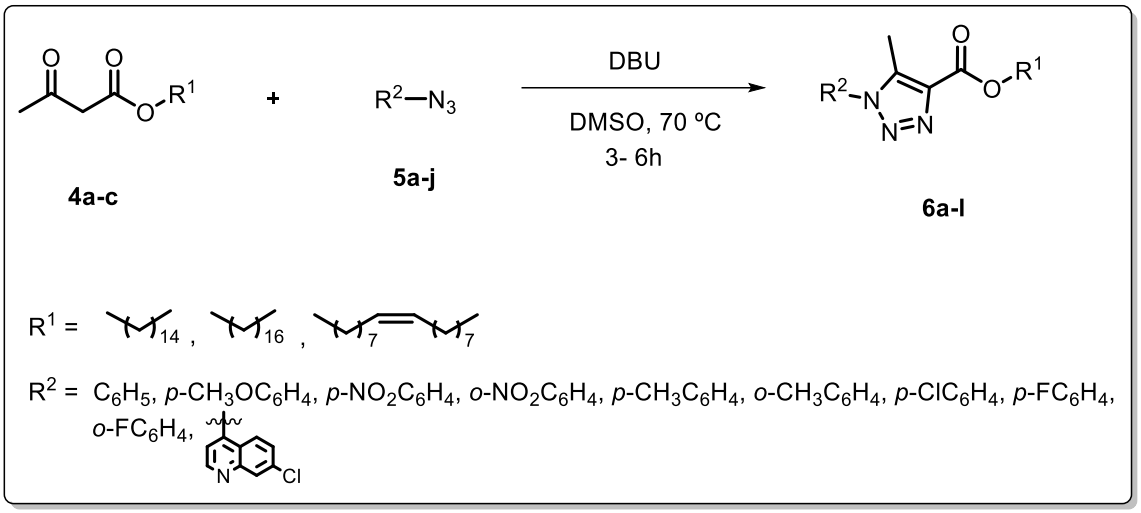
Esquema 1

Para investigar a capacidade antioxidante das moléculas foram realizados os experimentos *in vitro* de Ensaio de espécies reativas e Remoção de espécies reativas ao ácido tiobarbitúrico, sendo as moléculas avaliadas que apresentaram atividade antioxidante em menores concentrações: **3a**, **3d**, **3g** e **3l** (**Esquema 2**)**.**



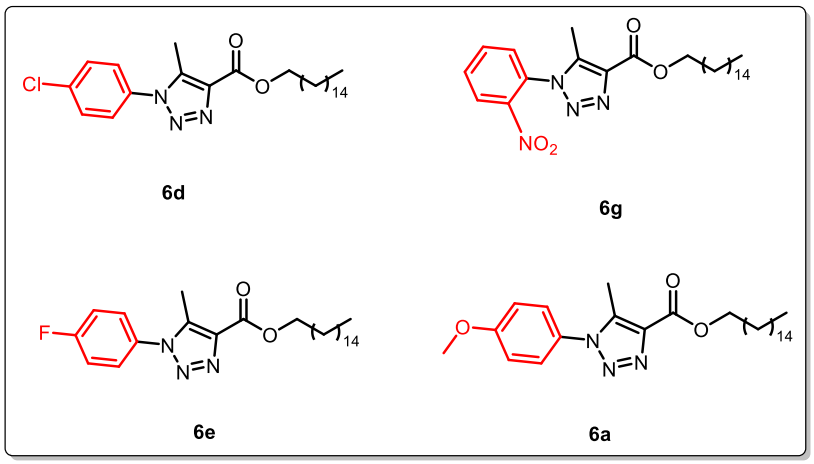
Esquema 2

Logo, foram abordados os resultados do estudo 1,2,3-triazoil-ésteres graxos. O Capítulo 2 descreve o uso de 1,8-diazabiciclo[5,4,0]-undec-7-eno (5 mol%) como organocatalisador para cicloadição 1,3-dipolar de ésteres graxos (0,2 mmol) **4a-c** com aril azidas (0,3 mmol) **5a-j**. Através da organocatálise mediada via enolato, as reações foram conduzidas à 70 °C por 3-6 horas, utilizando dimetilsulfóxido como solvente. Nessas condições reacionais, doze 1*H*-1,2,3-triazóis derivados de ésteres graxos **6a-l** (**Esquema 3**) foram obtidos com rendimentos de moderados a excelentes, variando de 35% a 99%.



Esquema 3

Todos os compostos da classe dos triazóis acetoacetato palmítico foram avaliados quanto à atividade citotóxica contra células humanas de câncer de bexiga pelo ensaio *in vitro* de redução do sal de tetrazólio e os compostos **6a**, **6d**, **6e** e **6g** foram identificados como os mais promissores. Destacaram-se por apresentarem a menor concentração inibitória de IC_{50} (**Esquema 4**): 8,72 *μ*M (**6d**), 12,74 *μ*M (**6g**), 18,65 *μ*M (**6e**) e 22,50 *μ*M (**6a**).



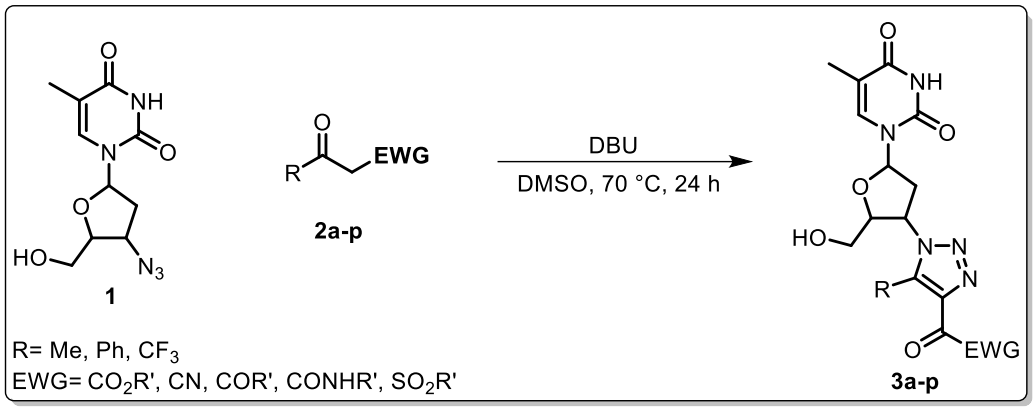
Esquema 4

Palavras-chave: triazol, organocatálise, AZT, atividade antioxidante, ésteres graxos, atividade citotóxica, câncer de bexiga.

Abstract

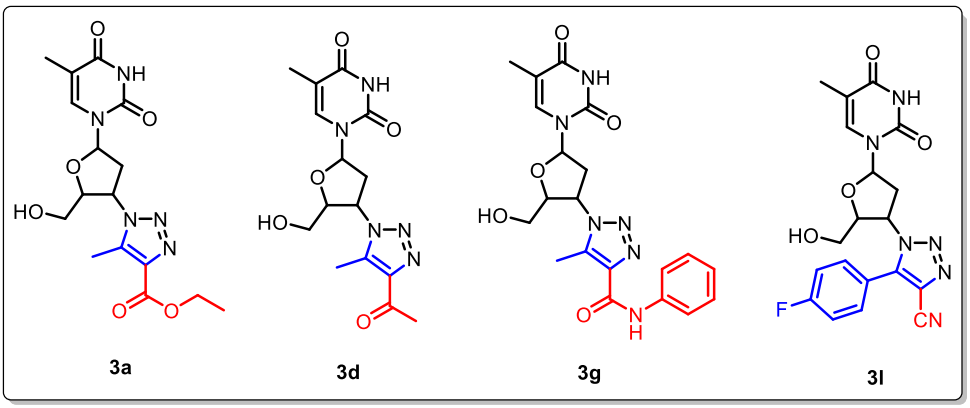
GOMES, Carolina. **Synthesis and evaluation of the biological potential of 1,2,3-triazoles derived from zidovudine and fatty esters.** 2020. 119f. Tese (Doutorado) - Programa de Pós-Graduação em Biotecnologia. Universidade Federal de Pelotas, Pelotas.

Functionalized triazoles are organic substances that have a wide synthetic and pharmacological potential. The present work is divided into two parts, where the results of the synthesis and evaluation of the biological potential of the derivatives were reported: 1,2,3-triazoyl-zidovudine and 1,2,3-triazoyl-fatty esters. Firstly, the results of the 1,2,3-triazoyl-zidovudine study were addressed. The Chapter 1 describes the use of an organocatalytic system consisting of zidovudine (0.3 mmol) **1**, α-substituted ketones, (0.36 mmol) **2a-p**, 1,8-diazabicyclo[5.4.0]undec-7-ene (10 mol%) as an organocatalyst and dimethylsulfoxide as a solvent at 70 °C for 24 h. Sixteen 1*H*-1,2,3-triazole-zidovudine **3a-p** were obtained (**Scheme A**) with excellent yields (59%-91%).



Scheme 1

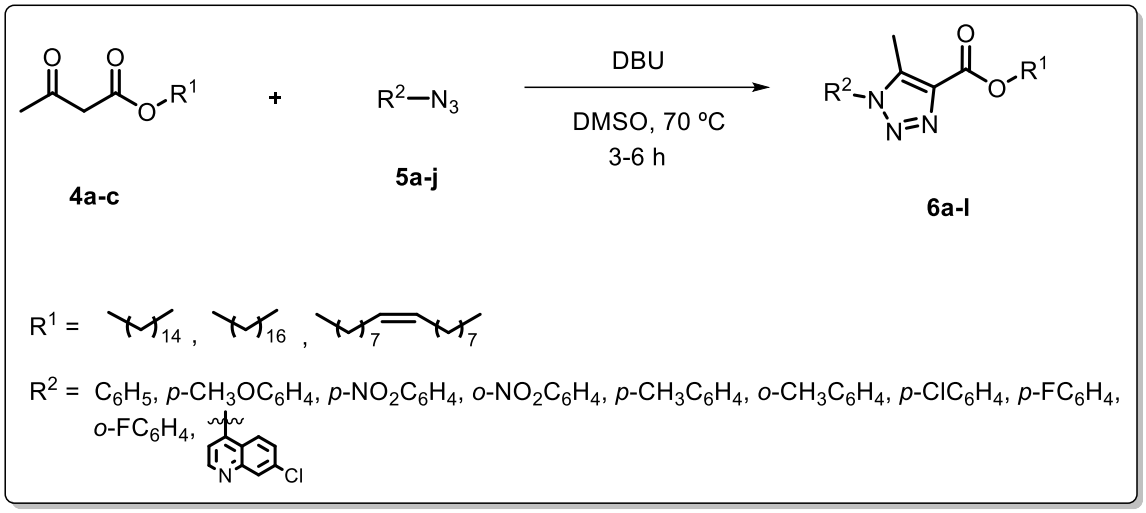
In order to investigate the antioxidant capacity of the molecules, the *in vitro* experiments of reactive species assay and removal of species reactive to thiobarbituric acid were carried out, which the molecules that showed antioxidant activity in lower concentrations were **3a**, **3k**, **3f** and **3h** (**Scheme 2**).



Scheme 2

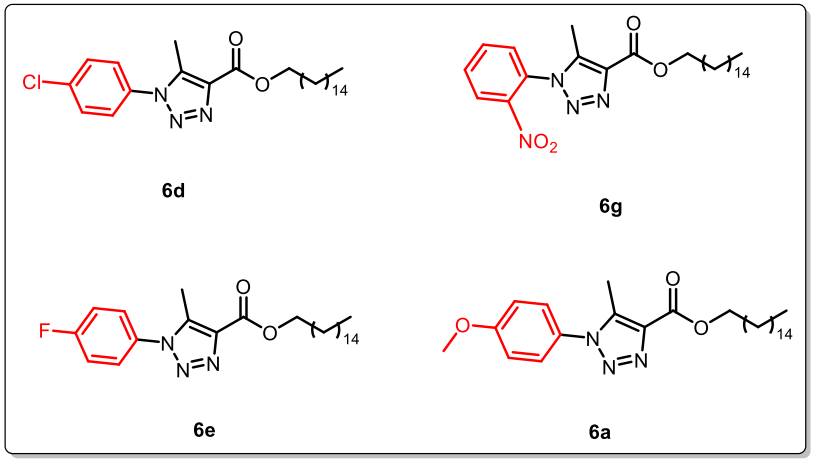
Therefore, the results of the study 1,2,3-triazoyl-fatty esters were addressed. The Chapter 2 describes the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (5 mol%) as an

organocatalyst for 1,3-dipolar cycloaddition of fatty esters (0.2 mmol) **4a-c** with aryl azides (0.3 mmol) **5a-j**. Through enolate-mediated organocatalysis, the reactions were conducted at 70 °C for 3-6 hours, using dimethylsulfoxide as solvent. In these reaction conditions, twelve 1*H*-1,2,3-triazoles derived from **6a-l** fatty esters (**Scheme 3**) were obtained with moderate to excellent yields, ranging from 35% to 99%.



Scheme 3

All compounds of the palmitic acetoacetate triazole class were evaluated for cytotoxic activity against human bladder cancer cells by the *in vitro* tetrazolium salt reduction assay and compounds **6a**, **6d**, **6e** and **6g** were identified as the most promising. They stood out for presenting the lowest IC_{50} inhibitory concentration (**Scheme 4**): 8.72 μM (**6d**), 12.74 μM (**6g**), 18.65 μM (**6e**) and 22.50 μM (**6a**).



Scheme 4

Keywords: triazole, organocatalysis, AZT, antioxidant activity, fatty esters, cytotoxic activity, bladder cancer.

Lista de Figuras

Lista de Abreviaturas

CuAAC = Cicloadição Alquino-Azida catalisada por Cobre

DBU = 1,8-diazabiciclo[5,4,0]-undec-7-eno

DMSO = dimetilsulfóxido

AZT = zidovudina

AIDS = síndrome da imunodeficiência adquirida

HIV = Vírus da Imunodeficiência Humana

UNAIDS = The Joint United Nations Programme on HIV/AIDS

SAR = Structure- Activity Relationship

EAG = Ésteres de ácidos graxos

GDE = Grupo doador de elétrons

GRE = Grupo retirador de elétrons

NaASc = Ascorbato de sódio

Sumário

1 INTRODUÇÃO GERAL

Heterociclos representam uma das unidades estruturais mais encontradas em compostos bioativos naturais e sintéticos (DEBIA *et al*., 2018), pois desempenham um papel muito importante no desenvolvimento de novas drogas terapêuticas, uma vez que apresentam grupos farmacofóricos, ou seja, a parte da substância responsável por sua atividade biológica (SONEGO *et al*., 2019).

Algumas das novas estratégias para a síntese de moléculas complexas e biologicamente ativas envolvem o núcleo 1,2,3-triazol, que são heterociclos de 5 membros compostos por três átomos de nitrogênio e dois átomos de carbono (SALMAN *et al*., 2019). Uma das vantagens no uso dessa classe de moléculas é o fato de serem considerados suportes versáteis, pois atuam como conectores entre duas substâncias ativas: uma estratégia denominada hibridação molecular (SONEGO *et al*., 2019) para a síntese de uma ampla variedade de produtos, ou seja, não são apenas ligantes (ZHANG *et al.*, 2017).

O núcleo 1,2,3-triazol apresenta a capacidade de se associar a alvos biológicos por meio de interações químicas como ligações de hidrogênio e interações dipolo-dipolo (BODNÁR *et al*., 2016; MACAN *et al*., 2019; SALMAN *et al*., 2019; THI *et al*., 2016). Além disso, a porção 1,2,3-triazol é resistente à degradação metabólica, o que representa uma elevada estabilização aromática (KOSIOVA *et al*., 2007).

Na literatura, ao longo dos anos, foram descritos compostos que contém o núcleo triazólico e que possuem atividades farmacológicas como anti-inflamatória **7** (DAYAKAR *et al*., 2017; WILHELM *et al*., 2014), antiviral **8** (VERNEKAR *et al*., 2015; WANG *et al*., 2011; WANG Q. *et al*., 2010), antifúngica **9** (AHER *et al*., 2009; CHAVAN *et al*., 2017; ZHOU *et al*. 2016), antibacteriana **10** (DEMARAY *et al*., 2008; KLIMESOVA *et al*., 2004; MAO *et al*., 2017; THATIPAMULA *et al*., 2015; WANG X. *et al*., 2010) e anticâncer **11** (BEGNINI *et al*., 2017; CUI *et al*. 2018; ZHANG *et al*., 2016). Alguns desses compostos, cujos núcleos triazólicos encontram-se destacados, estão demostrados na **Figura 1**.

As atividades descritas para os 1,2,3-triazóis funcionalizados estão diretamente associadas às posições de seus substituintes: 1,4- e 1,5-dissubstituídos ou 1,4,5-trissubstituídos (RAMACHARY *et al*., 2016). Os estudos que buscam o entendimento a respeito dessas especificidades são chamados de estudos de relação estrutura-atividade (SAR = *Structure-Activity Relationship*). Como consequência, no decorrer dos anos, dados e informações foram produzidos, identificando posições e grupos funcionais ativos e inativos para aplicação em diferentes atividades biológicas.

Por esse motivo, o desenvolvimento de métodos catalíticos eficientes para a síntese regiosseletiva de 1,2,3-triazóis substituídos ainda desperta grande interesse entre químicos orgânicos sintéticos (LIN *et al*., 2010; VERNEKAR *et al*., 2015; WANG X. *et al*., 2010).

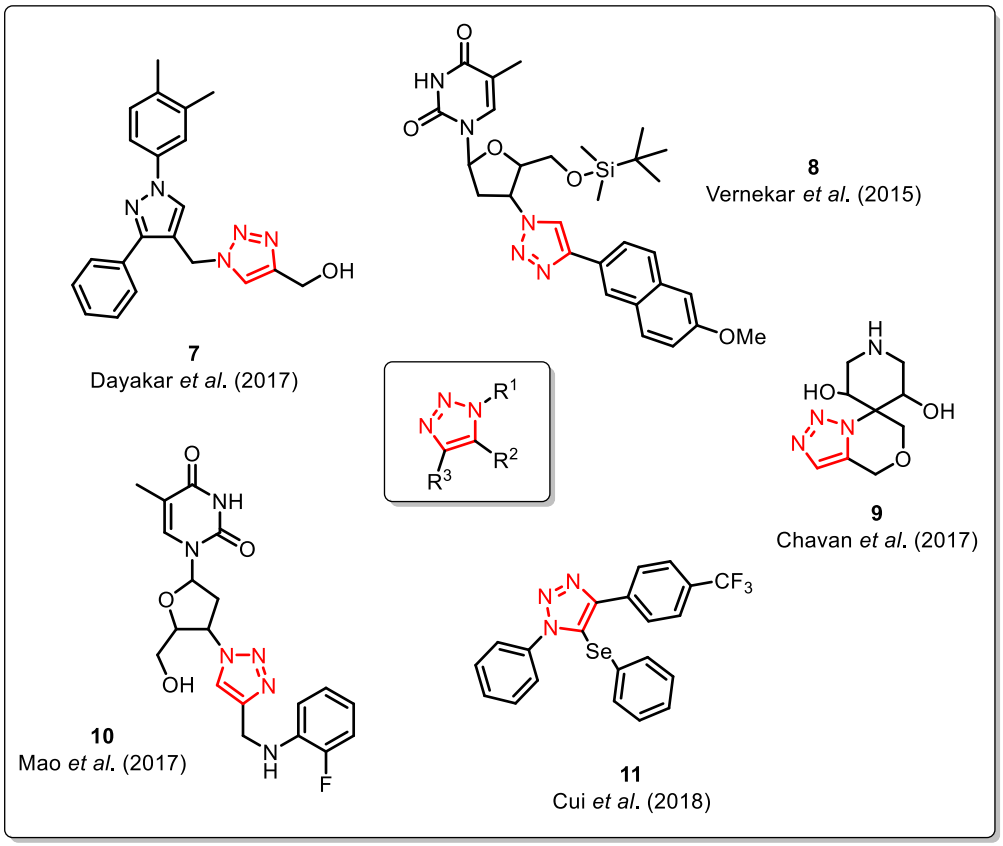


Figura 1. Compostos que contém o núcleo triazol.

De uma forma geral, no que diz respeito aos núcleos nitrogenados, uma das alternativas para obter compostos biologicamente ativos é a inserção de derivados de nucleosídeos. Isso pode ser visto, por exemplo, nos compostos **8** e **10** da **Figura 1**, em que o núcleo 1,2,3-triazol está ligado a um derivado da

zidovudina (AZT), apresentando as atividades antiviral e antibacteriana, respectivamente. O AZT foi o primeiro análogo de nucleosídeo aplicado na terapia anti-HIV e ainda hoje é utilizado (SOLYEV *et al*., 2014; THI *et al*., 2016; TIAN *et al*., 2018). A estrutura do AZT **13** é análoga da base nitrogenada timidina **12** e estas estruturas estão demostradas na **Figura 2**. O grupo azida do AZT pode atuar como sítio 1,3-dipolo em reações, o que o torna suscetível à cicloadições com dipolarófilos. Essas reações serão abordadas no **Capítulo 1** desse trabalho.

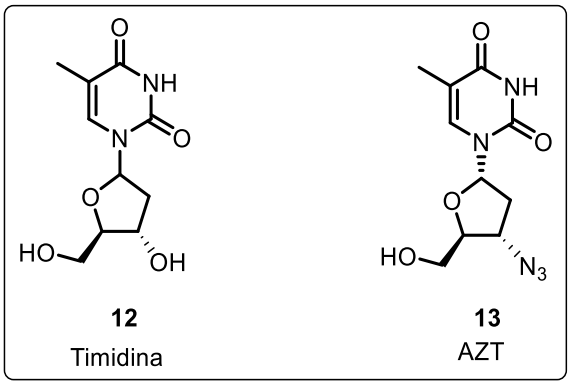


Figura 2. Estruturas da timidina e do AZT.

Outra classe de compostos orgânicos que tem merecido grande destaque na literatura são os derivados de ésteres graxos que, além da porção éster, apresentam uma longa cadeia alifática (GHIANO *et al*., 2017; SALMAN *et al*., 2019) que possibilita gerar compostos funcionalizados. Esta cadeia pode conter saturações ou insaturações e variar de 4 a 28 átomos de carbono (VENEPALLY *et al.*, 2017), como pode ser observado em Brinkerhoff e colaboradores (2019), nos compostos acetoacetatos graxos **14** e β-ceto-ésteres graxos **15** (**Figura 3**). Os compostos **14** serão utilizados como substratos no estudo desenvolvido no **Capítulo 2**.

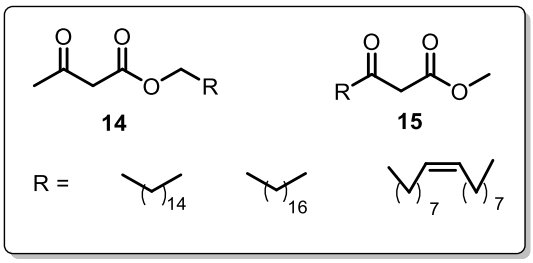


Figura 3. Compostos derivados de ésteres graxos.

Quanto aos métodos de preparo, o mais amplamente explorado para construção do núcleo 1,2,3-triazol é a cicloadição 1,3-dipolar de alquinos

terminais com azidas catalisada por metais (Cu, Ru, Ag ou Ir), também conhecida como reação *Click Chemistry* (KANTARIA *et al*, 2018; ZHANG *et al*., 2017). Dentre esses metais, a reação mais aplicada para a geração de produtos com triazóis funcionalizados é a Cicloadição Azida-Alquino catalisada por Cu (CuAAC) (GONTIJO *et al.*, 2015; ISRAR *et al.*, 2018; TORNØE *et al.*, 2002).

Entretanto, metodologias que utilizam metais de transição podem restringir os estudos com atividades biológicas, tendo em vista seus efeitos adversos (BASKIN *et al*., 2007; GAETKE *et al*., 2003; GIERLICH *et al*., 2006; JOMOVA *et al*., 2011; KENNEDY *et al*., 2011; LALLANA *et al*., 2009). Nesse sentido, estudos recentes têm sido direcionados ao desenvolvimento de metodologias isentas de metais de transição para a síntese de 1,2,3-triazóis substituídos (DEBETS *et al*., 2011).

Como alternativa, a organocatálise emergiu sendo uma ferramenta eficiente para a síntese desses 1,2,3-triazóis, superando as limitações causadas por eventuais contaminantes (DUARTE *et al*., 2017), através de métodos mediados via enamina ou enolato (RAMACHARY *et al*., 2017) na ausência de metais de transição. É considerada um campo em constante crescimento da química orgânica, por desenvolver diferentes organocatalisadores para diversos tipos de reações orgânicas (ANEBOUSELVY *et al.*, 2017). Além da vantagem de evitar o risco de contaminação por metais (BARAN *et al.*, 2013), os organocatalisadores são geralmente termicamente estáveis, permitindo resultados reproduzíveis e requerendo condições simples de reação (HACK *et al.*, 2018).

2 REVISÃO BIBLIOGRÁFICA

2.1 1*H*-1,2,3-triazóis

Compostos heterocíclicos representam uma das unidades estruturais mais encontradas em compostos bioativos sintéticos (DEBIA *et al*., 2018). São compostos cíclicos com pelo menos dois elementos diferentes como membros do anel, sendo que o elemento diferente de carbono é denominado heteroátomo (MALANI *et al*., 2017; SALMAN *et al*., 2019; VENEPALLY *et al*., 2017).

Os heterociclos aromáticos de cinco membros contendo um ou mais átomos de nitrogênio, são genericamente denominados azóis, sendo o mais simples destes o pirrol **16** (**Figura 4**). Existem também os compostos heterocíclicos de cinco membros contendo outros heteroátomos como, por exemplo, enxofre ou oxigênio, adicionalmente a um átomo de nitrogênio, os quais recebem a mesma denominação azol, sendo chamados respectivamente, de tiazol **17** e oxazol **18**. Na **Figura 4** também estão alguns dos compostos mais simples da classe: pirazol **19**, imidazol **20**, 1,2,3-triazol **21**, 1,2,4-triazol **22** e o tetrazol **23** (EICHER e HAUPTMANN, 2003).

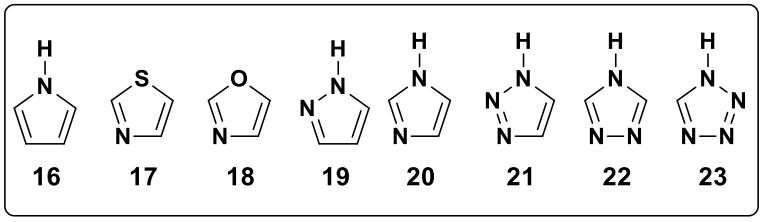


Figura 4. Heterociclos aromáticos azólicos.

Nessa linha, os 1,2,3-triazóis são uma classe de heterociclos de cinco membros que apresenta uma alta estabilidade, e cujas ligações possibilitam modificações para uma gama de aplicações (JANA *et al*., 2016; KUMAR *et al.*, 2013; SALMAN *et al*., 2019; ZHANG *et al*., 2017). Existem dois diferentes regioisômeros relacionados aos compostos triazólicos, os quais se diferenciam pela posição em que se encontram os átomos de nitrogênios, são eles o 1,2,3-triazóis e o 1,2,4-triazóis (EICHER e HAUPTMANN, 2003) (**Figura 5**).

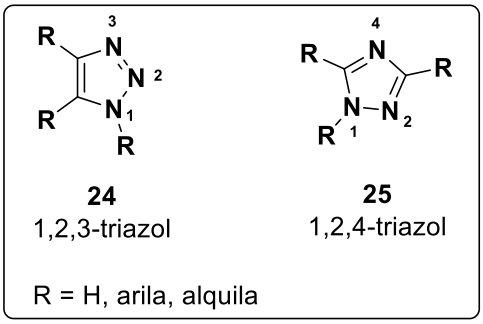


Figura 5. Regioisômeros de triazóis.

Os seus derivados possuem uma importância na química orgânica de compostos bioativos, apresentando diferentes atividades biológicas, como as atividades antifúngica e anticancerígena nos casos dos compostos **26** e **27**, respectivamente (**Figura 6**). Outras diferentes atividades já foram documentadas, como: anti-inflamatória (DAYAKAR *et al.*, 2017; WILHELM *et al*., 2014), antiviral (VERNEKAR *et al*., 2015; WANG *et al*., 2011; WANG Q. *et al.*, 2010), antibacteriana (DEMARAY *et al*., 2008; KLIMESOVA *et al*., 2004; MAO *et al*., 2017; THATIPAMULA *et al*., 2015; WANG X. *et al*., 2010). É possível encontrar também aplicações desses derivados na área de materiais (BARANIAK *et al.*, 2011; DEBIA *et al*. 2018; SHIE *et al*., 2014) e de biotecnologia (CHAVAN *et al*., 2017; MENENDEZ *et al*., 2000; WU *et al.*, 2018).

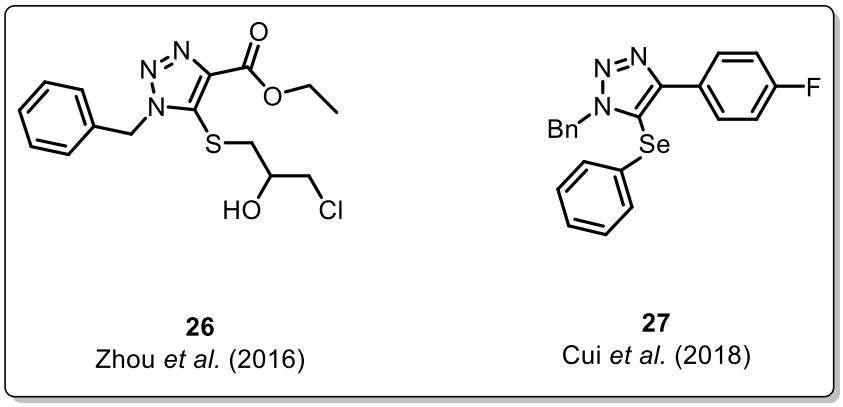


Figura 6. Estrutura de diferentes 1,2,3-triazóis.

Como precursores na geração de triazóis, tem-se as azidas orgânicas que são amplamente utilizadas na longa lista de grupos funcionais capazes de potencializar moléculas (NAINAR *et al*., 2016), através do mecanismo de cicloadição 1,3 dipolar mostrado genericamente na **Figura 7**.

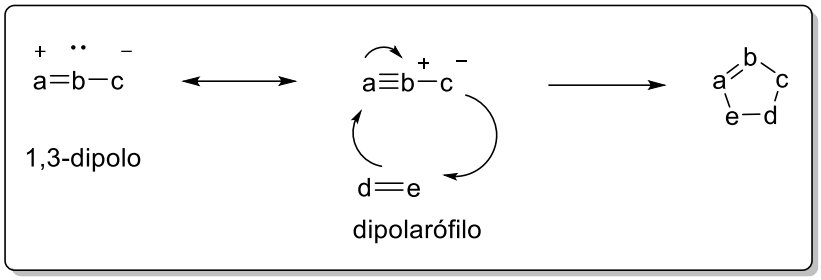


Figura 7. Mecanismo genérico de cicloadição 1,3 dipolar em azidas orgânicas (CARY, 2007).

Em geral, as azidas orgânicas são intermediários valiosos, reativos e versáteis, que podem reagir em N-1 com eletrófilos e em N-3 com nucleófilos, sob várias condições de reação (**Figura 8**) (BRASE *et al*. 2005; KOSIOVA *et al.*, 2006).

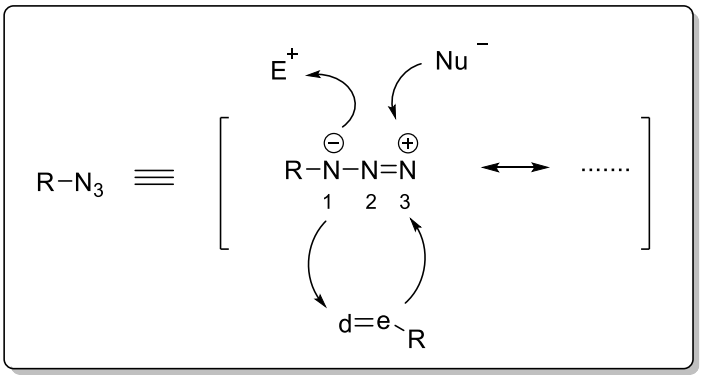


Figura 8. Reações de azidas com compostos deficientes de elétrons (eletrófilos) em N-1 e compostos ricos em elétrons (nucleófilos) em N-3.

A justificativa para as diferentes reatividades e alta seletividade descritas para as azidas arílicas em reações organo-*Click* pode ser explicada pelo mecanismo mostrado na **Figura 9**. Nesse caso, o mesomerismo de estruturas de ressonância entre o grupo azida e o anel aromático é o fator fundamental para determinar a reatividade dessas azidas arílicas em síntese orgânica (BRASE *et al*., 2005). Algumas das suas propriedades físico-químicas também podem ser explicadas por esse efeito mesomérico, onde o grupo azida está conectado a diferentes grupos arílicos (**28**-**32**, **Figura 9**).

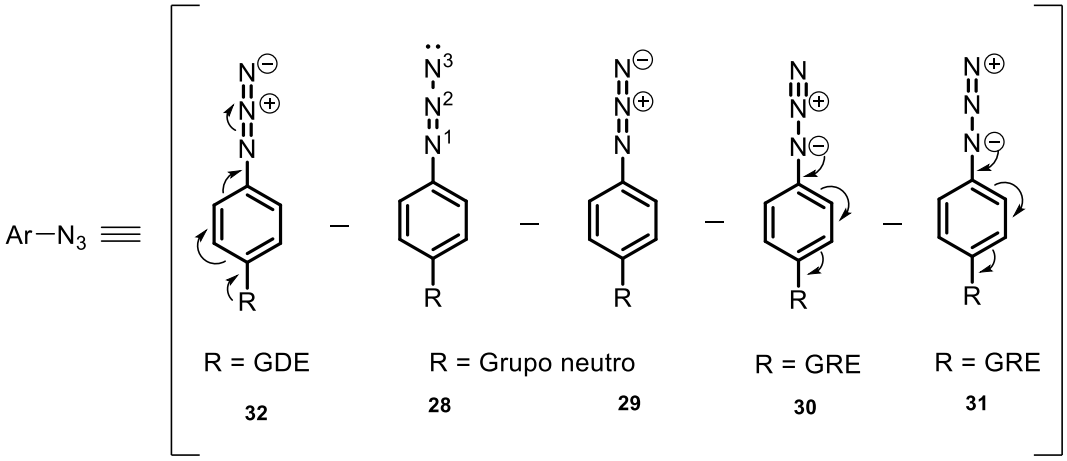


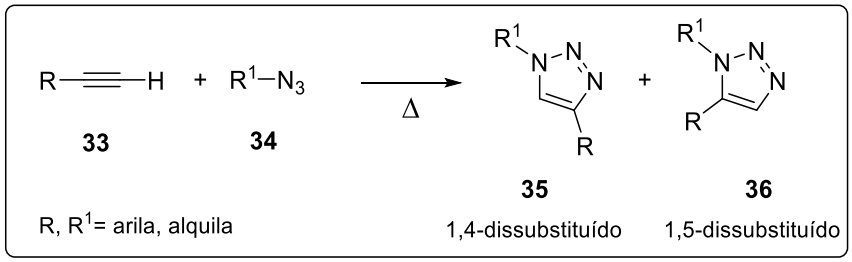
Figura 9. Estruturas mesoméricas de azidas arílicas.

A excelente reatividade e alta regioseletividade das azidas arílicas com nucleófilos é explicada com base nas estruturas mesoméricas contribuintes **30** e **31** (ataque do nucleófilo ao N-3) em comparação com **28**, **29** ou **32** (RAMACHARY *et al.*, 2013). A exploração das reações organocatalíticas com azidas arílicas funcionalizadas será demostrada no **Capítulo 2** deste trabalho, mostrando a influência dos grupos doadores (GDE) e retiradores (GRE) de elétrons ao seu redor como um fator chave para aumentar ou diminuir a taxa de reação.

2.2 Cicloadição 1,3-dipolar

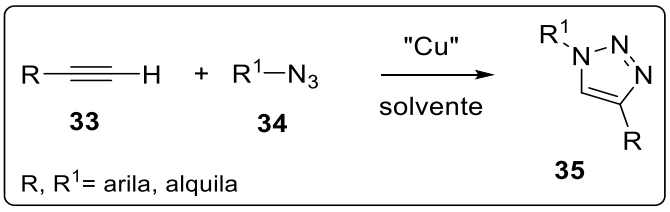
Por várias décadas, reações de cicloadição 1,3-dipolar vêm despertando grande interesse na pesquisa especialmente por sua versatilidade. Além disso, tendo em vista o grande número de dipolos e dipolarófilos em potencial envolvidos nessas reações, são consideradas estratégicas para a formação de sistemas de anéis heterocíclicos de cinco membros (KRIM *et al.*, 2013; NAINAR *et al.*, 2016; THI *et al.* 2016;)

Para a síntese de triazóis substituídos, em 1963, a cicloadição de Huisgen foi pioneira em reações de cicloadição entre alquinos terminais **33** e azidas orgânicas **34**. Esta metodologia apresenta como desvantagem a formação de uma mistura regioisomérica (**35**-**36**) de 1,2,3-triazóis (1,4- e 1,5-dissubstituídos) apresentado no **Esquema 5.**



Esquema 5

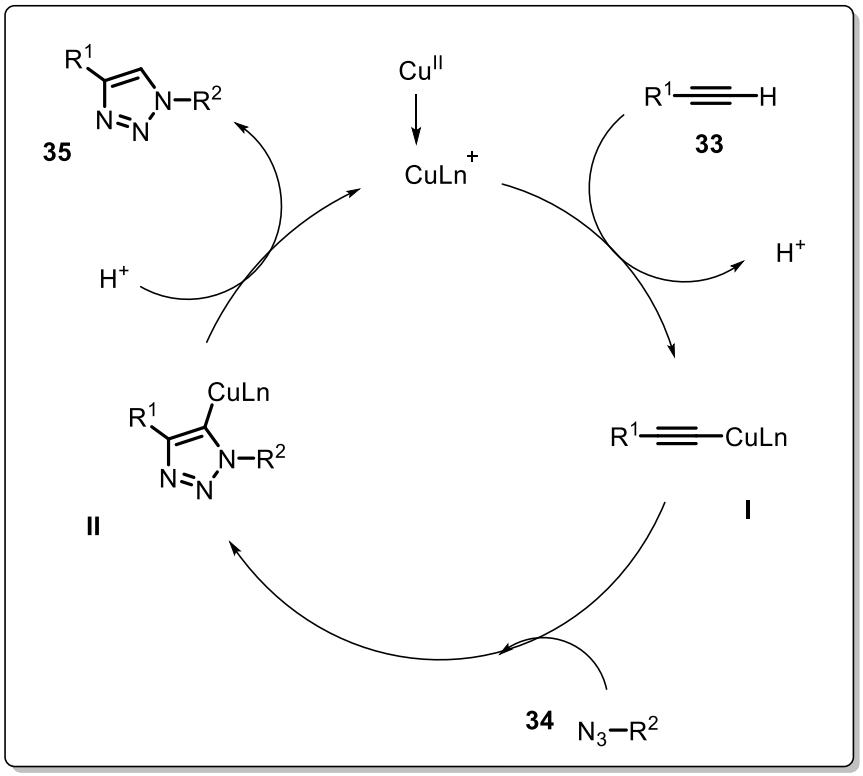
Contudo, este tipo de reação se popularizou quando independentemente Sharpless (ROSTOVTSEV *et al*., 2002) e Meldal (TORNØE *et al*., 2002) utilizaram a reação entre alquinos terminais **33** e azidas orgânicas **34**, na presença de sais de cobre como catalisadores (CuAAC). Através desse método de acoplamento foi obtido apenas os regioisômeros 1,4-dissubstituídos **35** (BODNAR *et al*., 2016; MAO *et al*., 2017; SRIVASTAVA *et al*., 2018; THI *et al*., 2016). A partir de então, essas metodologias desenvolvidas foram importantes para o avanço das reações de cicloadição do tipo 1,3-dipolar, pois foi observado que elas não ocorrem seletivamente na ausência de Cu(I) tampouco com alquinos internos. Além disso, apresentam maior sensibilidade a azidas estericamente impedidas. Esta reação é considerada uma das principais reações incluídas no contexto de *"Click Chemistry"* (ROSTOVTSEV *et al*., 2002; TORNØE *et al*., 2002; ZHANG *et al*., 2017) demostrada no **Esquema 6**.



Esquema 6

Para este tipo de reação, a literatura relata o desenvolvimento de sistemas catalíticos a partir de sais de cobre(I), comumente CuI, os quais podem ser utilizados diretamente, na ausência de agente redutor e sais de cobre(II) que, na presença de agentes redutores, geram espécies de cobre(I) *in situ*. Os sais de cobre(II) comumente utilizados para esta finalidade são $CuSO_4.5H_2O$ e $Cu(OAc)_2$ e os agentes redutores mais eficazes são o ácido ascórbico e seu correspondente sal sódico (HIMO *et al*., 2002; KOLB *et al*., 2003; ROSTOVTSEV *et al*., 2002; WORRELL *et al*., 2013).

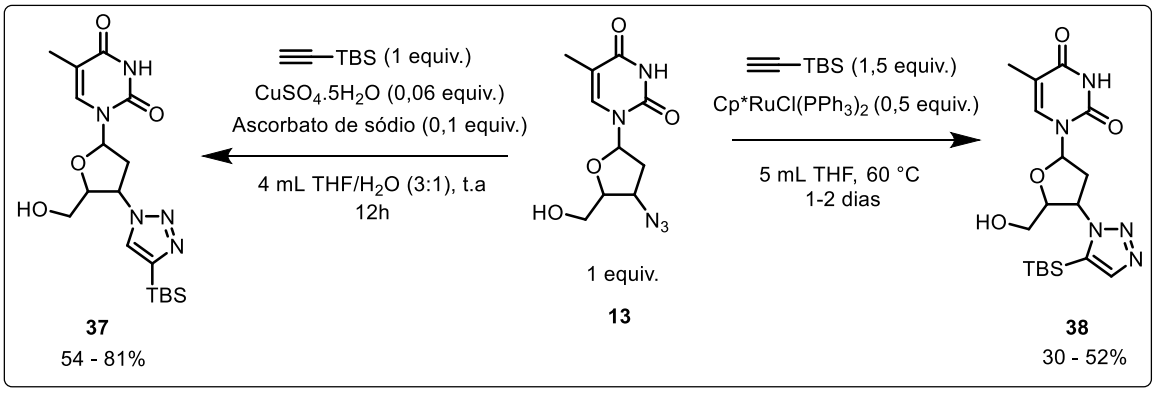
A seguir, está descrito o mecanismo clássico das reações de *"Click Chemistry"* descrito por BRASE e colaboradores em 2005 (**Esquema 7**).



Esquema 7

Primeiramente, ocorre a complexação entre o Cu(II) e o alquino terminal para a formação do acetileto de cobre **I**. Após a formação do acetileto de cobre **I** ocorre a reação com a azida orgânica, gerando o complexo azida-acetileto **II** , levando a formação da triazolina de cobre **II**. Na última etapa do mecanismo ocorre uma etapa de protonação do intermediário triazolina de cobre **II**, para finalmente levar a formação do produto final o 1,2,3-triazol 1,4-dissubstituído **35** e a regeneração do catalisador para o meio reacional.

As reações de CuAAC favorecem a formação de triazóis dissubstituídos, como mostra os trabalhos de Mao (2017) e Vernekar (2015). No trabalho de Vernekar e colaboradores (2015) são reportadas diferentes estratégias sintéticas para a obtenção de triazóis utilizando catálise de cobre para obter o regioisômero, 1,4-dissubstituídos **37** e catálise de rutênio (RuAAC) para obter o regioisômero, 1,5-dissubstituídos **38** (**Esquema 8**).



Esquema 8

Vários métodos para a síntese de compostos heterocíclicos nitrogenados foram relatados utilizando a cicloadição 1,3-dipolar, no entanto, a presença de metais de transição no meio reacional restringiu sua aplicação, em vista de seus efeitos adversos (BASKIN *et al.*, 2007; GAETKE *et al*., 2003; GIERLICH *et al*., 2006; JOMOVA *et al*., 2011; LALLANA *et al*., 2009; KENNEDY *et al*., 2011), uma vez que poderiam induzir danos em algum sistema biológico (WILHELM *et al*., 2014). O cobre, por exemplo, tem sido associado à toxicidade celular, a danos em processos metabólicos e oxidativos (DHEER *et al*., 2017).

2.3 Organocatálise

Para superar as limitações apontadas no item anterior, tais como a toxicidade, uma ferramenta eficiente é a organocatálise. Esta abordagem envolve as cargas presentes em *β*-enamina-azidas ou enolato-azidas para preparar 1,2,3-triazóis funcionalizados (DUARTE *et al.*, 2017; RAMACHARY *et al.*, 2017).

A organocatálise pode ser definida como a aceleração de reações por compostos orgânicos de baixo peso molecular (catalisadores) na ausência de metais (DHEER *et al*., 2017). Alguns atributos notáveis desta reação, de acordo com Danence e colaboradores (2011), incluem:

- Estrutura simples do catalisador;
- Alta eficiência (altos rendimentos e curto tempo de reação na maioria dos casos);
- Condições brandas (baixa temperatura, reação livre de metais);
- Regioespecificidade (exclusão completa dos regioisômeros);

- Complexidade (três substituintes);
- Tolerância de grupos funcionais (por exemplo, grupos cetonas, ésteres, nitrito, trifluormetano, halogêneo e hidroxila).

Como exemplos de organocatalisadores nitrogenados tem-se a glicina **39**, a *L*-prolina **40**, a (*S*)-pirrolidina-2-carboxamida **41**, a pirrolidina **42**, a piperidina **43**, a dietilamina **44**, a trietilamina **45**, o DBU (1,8-diazabiciclo[5.4.0]undec-7-eno) **46** e o TBD (1,5,7-triazobiciclo[4.4.0]dec-5-eno) **47**, como mostra a **Figura 10** (DANENCE *et al*., 2011; RAMACHARY *et al.*, 2016).

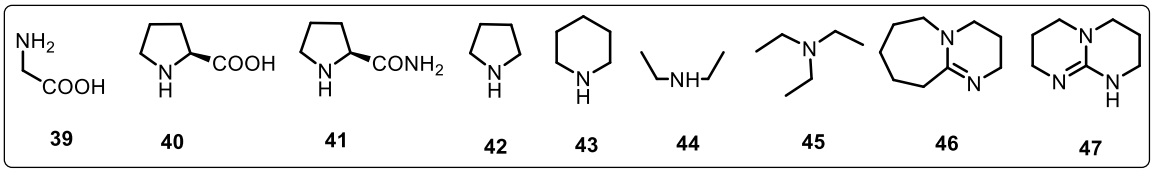


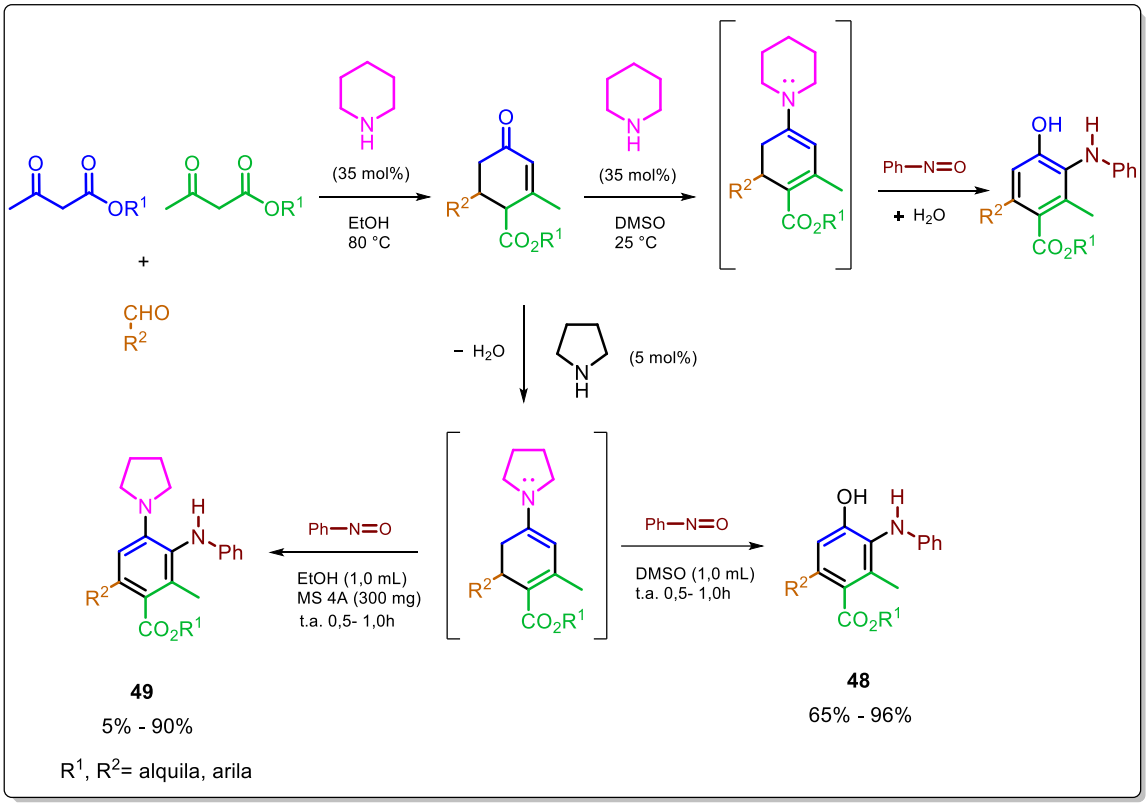
Figura 10. Exemplos de organocatalisadores.

Sob diferentes condições de reação, compostos carbonílicos poderiam facilmente gerar uma enamina ou um enolato. Nesse caso, ambas as espécies atuam como dipolarófilos nas cicloadições 1,3-dipolares organocatalisadas com azidas orgânicas (RAMACHARY *et al.*, 2015; RAMACHARY *et al.*, 2016; SHASHANK *et al*., 2014).

Desde 2002 o grupo de pesquisa de Ramachary vêm investigando reações de cetonas *α*- e *β*-insaturadas catalisadas por amina de forma direta através de reações do tipo Diels-Alder. Neste trabalho os autores demonstraram pela primeira vez reações diretas de Diels-Alder a partir de cetonas insaturadas catalisadas por amina para fornecer derivados de cicloexanonas. A reação ocorreu por meio da formação *in situ* de dienos e dienófilos na forma de 2-amino-1,3-butadienos e enonas ativadas pelo íon imínio, ou seja, uma estratégia de ativação baseada em enamina, e os rendimentos obtidos foram de até 80%. Ainda assim, os autores não conseguiram atribuir uma proposta mecanística concisa.

Na sequência, o grupo de Ramachary e colaboradores (2006) conseguiu elucidar o mecanismo via enamina sugerido anteriormente. Neste estudo é relatado um processo seletivo organocatalítico para a síntese em cascata de *o*-hidroxidiarilaminas **48** altamente substituídas e *o*-pirrolidin-1-diarilanilinas **49**. Através da combinação direta de outras reações nomeadas como:

Knoevenagel, Michael, condensação e descarboxilação como mostra a **Esquema 9**.



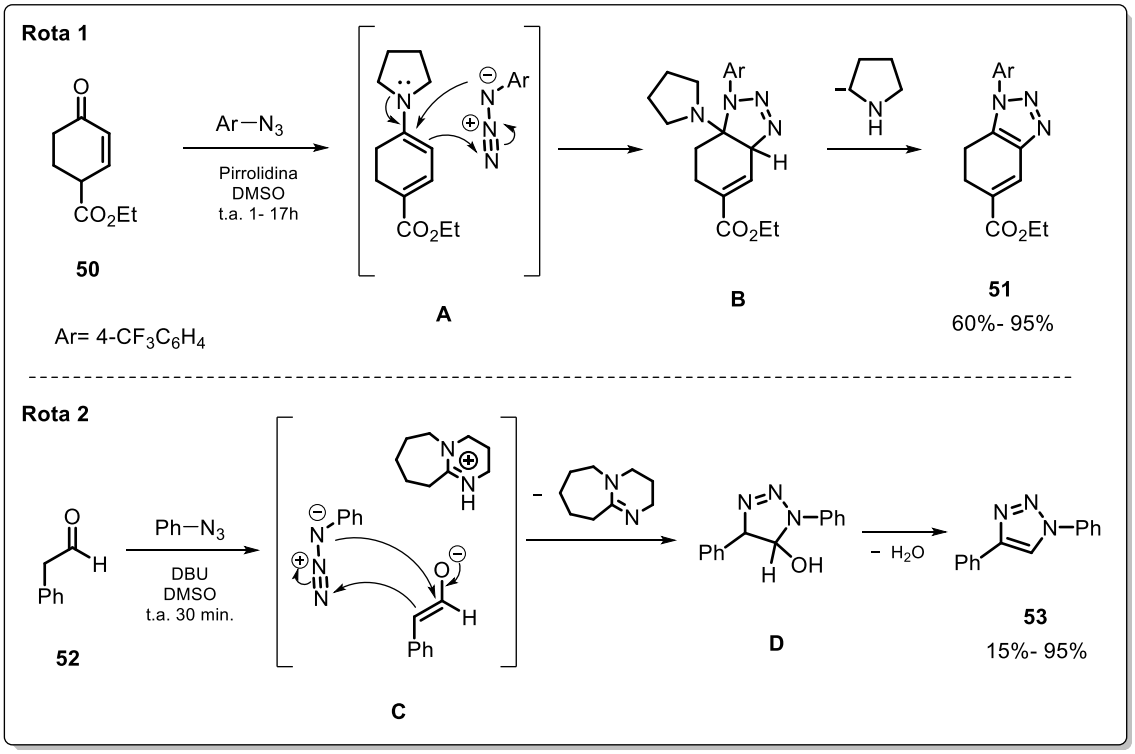
Esquema 9

Em 2013 e 2014 Ramachary e colaboradores aplicaram seu protocolo organocatalítico desenvolvendo mecanismos concertados de cicloadição 1,3-dipolar via enamina (Rota 1) e também via enolato (Rota 2) para sintetizar diferentes 1,2,3-triazóis, conforme o **Esquema 10**.

Os autores sugerem que ao utilizarem bases secundárias, como por exemplo pirrolidina, o mecanismo ocorre via enamina (Rota 1). Primeiramente, através de uma reação de condensação entre o organocatalisador e o composto carbonílico **50** gerando um íon imínio **A**, o qual, tautomeriza em uma enamina ativada para reagir com a azida orgânica através de uma reação de cicloadição 1,3-dipolar formando o aduto triazolina **B**. Em seguida ocorre uma etapa de transferência de hidrogênio, proporcionado a eliminação e regeneração do organocatalisador, o qual retorna para o meio reacional para finalmente formar o composto triazólico de interesse **51**.

Na presença de bases terciárias, o mecanismo ocorre via enolato (Rota 2). Inicialmente, o organocatalisador reage com o aldeído gerando um íon

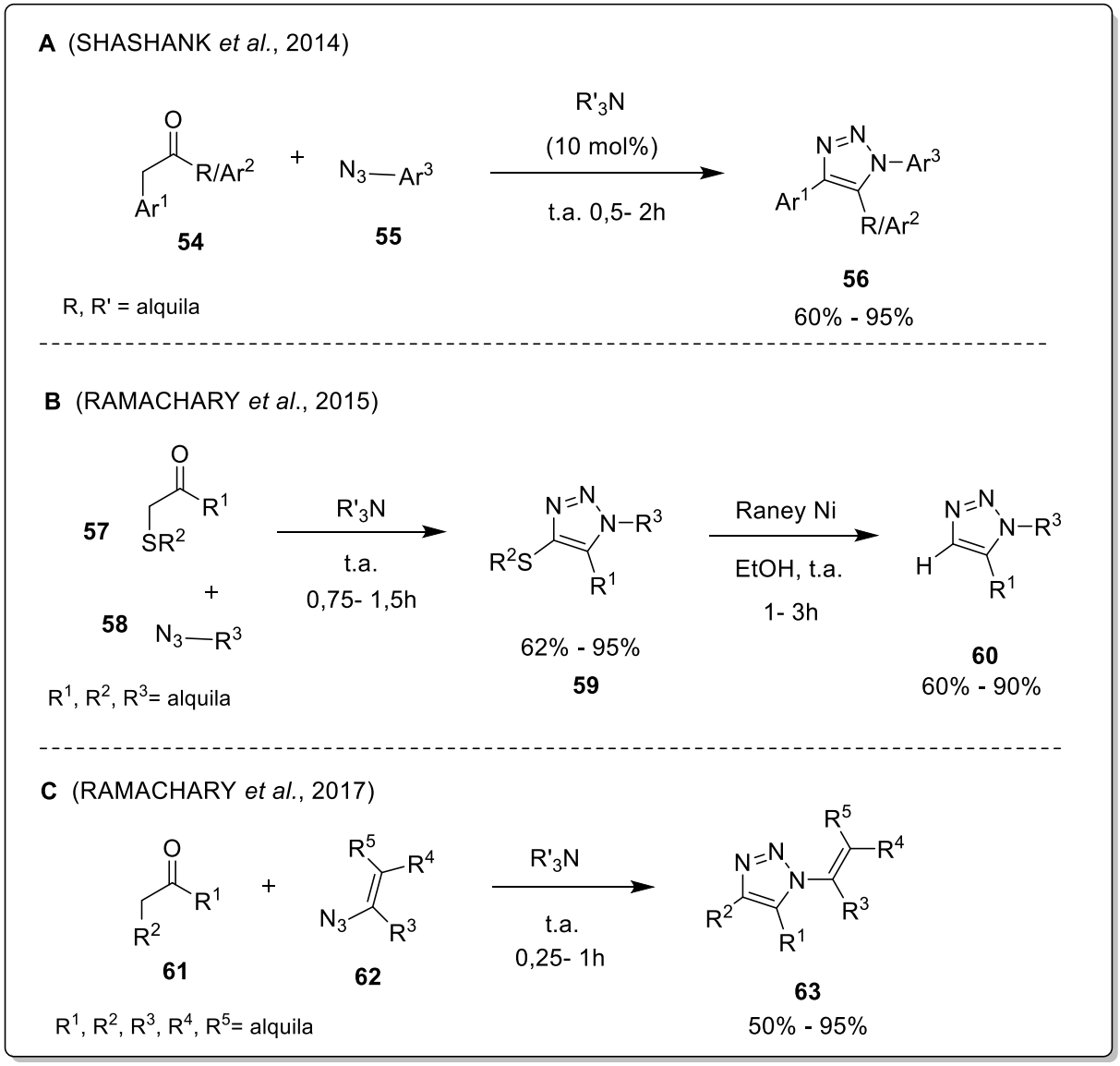
enolato **C** e uma base protonada. Logo, fornece seletivamente o aduto triazolina **D** por meio da reação de cicloadição 1,3-dipolar. Pela natureza básica do organocatalisador ocorre uma etapa de abstração de um próton, seguido da eliminação de uma molécula de água e, assim, proporcionando a aromatização do núcleo do 1,2,3-triazol. Por fim, o organocatalisador é regenerado e retorna para o meio reacional formando o produto desejado **53**.



Esquema 10

Dentre os diferentes trabalhos envolvendo a organocatálise desenvolvidos por Ramachary e colaboradores (RAMACHARY *et al.*, 2015; RAMACHARY *et al.*, 2017; SHASHANK *et al*., 2014), destaca-se o desenvolvimento de um protocolo catalítico geral para a síntese regiosseletiva de compostos triazólicos. As reações ocorrem na presença de azidas orgânicas arílicas ou vinílicas e cetonas *α*-funcionalizadas com grupos alifáticos, arílicos ou sulfurados, como demostrado no **Esquema 11**. A partir de azidas arilicas **55** (**Esquema 11-A**) obteve-se os produtos 1,4-diaril-5-metil-(alquil)-1,2,3-triazóis **56** (SHASHANK *et al*., 2014); partindo de tiocetonas **57** obteve-se os 4-tio-1,2,3-triazóis-1,5-dissubstituídos **59**, **Esquema 11-B** (RAMACHARY *et al.*, 2015) e para a síntese dos *N*-vinil-1,2,3-triazóis-1,4,5-trissubstituídos **63** foram utilizadas as azidas vinílicas **62**, conforme demonstrado no **Esquema 11-C**

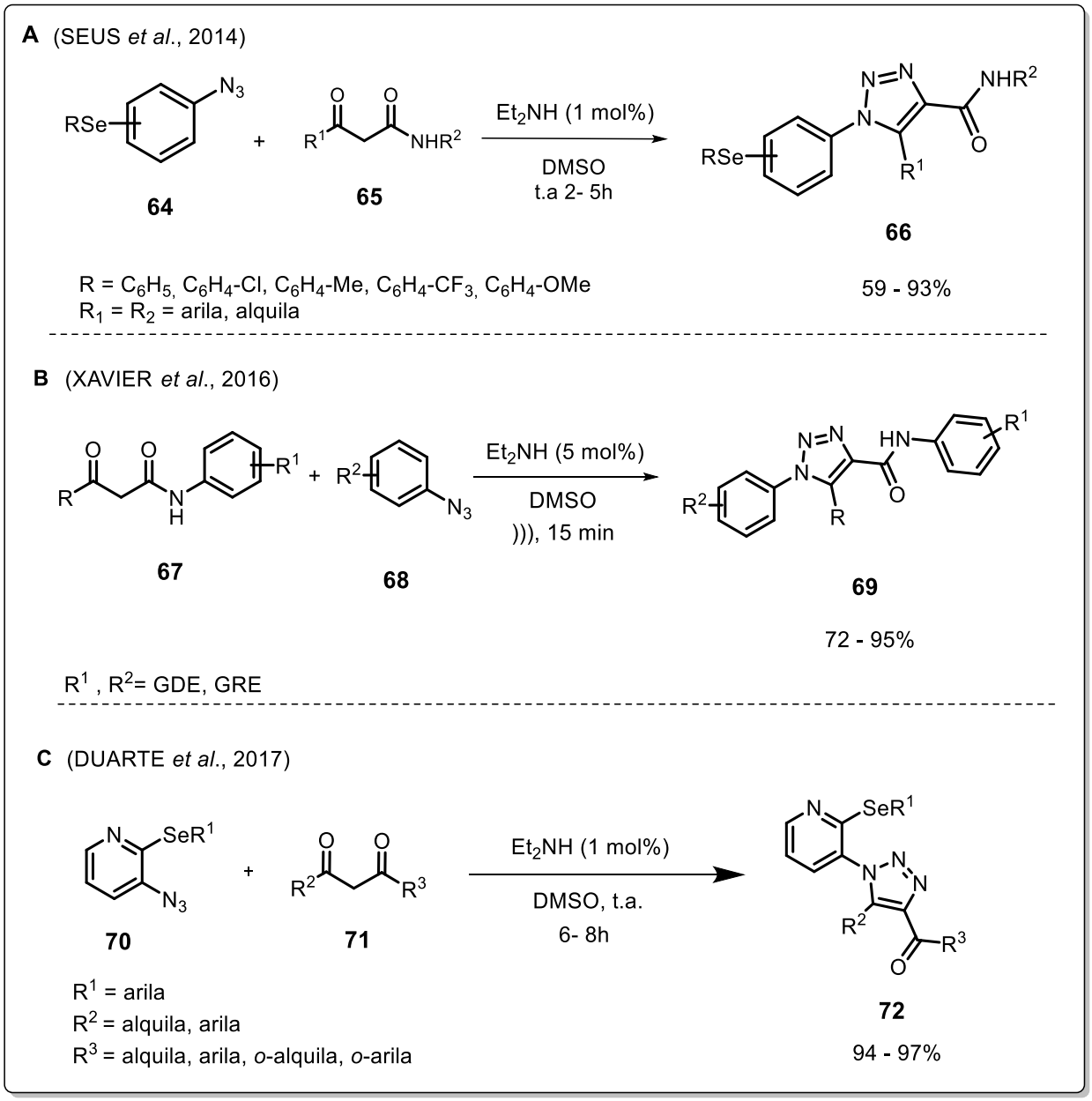
(RAMACHARY *et al.*, 2017). Os trabalhos citados utilizaram DBU (1,8-diazabiciclo[5,4,0]-undec-7-eno) como organocatalisador e DMSO (dimetilsulfóxido) como solvente, obtendo bons rendimentos.



Esquema 11

Nesse contexto, nosso grupo de pesquisa vem publicando diferentes protocolos de sínteses de triazóis funcionalizados via organocatálise. Desta forma, em 2014 Seus e colaboradores descreveram a síntese de 14 moléculas arilsselaniltriazoil-carboxilatos **66** (**Esquema 12-A**), utilizando dietilamina como catalisador. Já no trabalho desenvolvido por Xavier e colaboradores (2016), foi desenvolvida a síntese de *N*-aril-1,2,3-triazoil carboxamidas **69** (**Esquema 12-B**), descrevendo o uso de ultrassom como fonte de energia para essas reações de cicloadição enamino-azidas. As reações foram realizadas com uma

variedade de *β*-cetoamidas e arilazidas substituídas dando origem a 18 compostos com rendimentos que variam de bons a excelentes (72-95%). Mais tarde, Duarte e colaboradores (2017), por sua vez, propuseram a obtenção de arilselanil-piridin-3-il-1,2,3-triazóis **72** (**Esquema 12-C**) via cicloadição 1,3-dipolar mediada por dietilamina.



Esquema 12

A utilização de derivados triazólicos funcionalizados é considerada, na literatura, uma estratégia ideal para síntese de uma ampla variedade de produtos complexos. Isso ocorre porque esses compostos possuem baixa toxicidade, são mais propensos a elevar a solubilidade de compostos quando

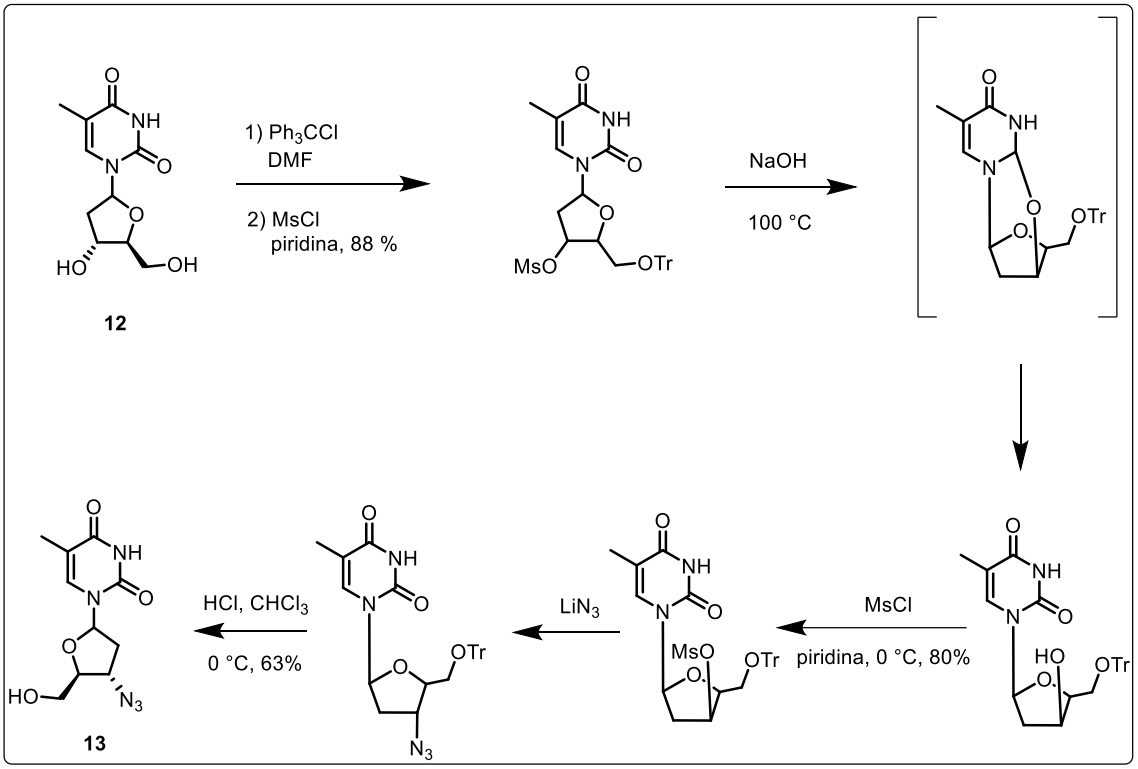
presentes na estrutura, além de serem altamente estáveis (JANA *et al*., 2016; KUMAR *et al.*, 2013; ZHANG *et al*., 2017). Com isso, podem atuar como unidades de ligação que podem conectar dois farmacóforos para gerar um novo medicamento bifuncional (MANNEGANTI *et al.,*2015). Entretanto, apesar dessas importantes características, o núcleo do 1,2,3-triazol não ocorre na natureza (RAJASEKAR *et al.*, 2019).

Com relação às propriedades químicas, os triazóis possuem alta estabilização aromática e forte momento de dipolo, proporcionando que os mesmos se associem a alvos biológicos por meio de interações químicas através da formação de ligações de hidrogênio e de interações dipolo-dipolo (BODNÁR *et al*., 2016; KOSIOVA *et al*., 2007; MACAN *et al*., 2019; SALMAN *et al*., 2019; THI *et al*., 2016). Portanto, são mais do que apenas ligantes passivos (SALMAN *et al*., 2019). São relativamente resistentes à degradação metabólica, estáveis à hidrólise ácida e básica, bem como a condições redutoras e oxidativas (BODNÁR *et al*., 2016; THI *et al*., 2016). Além disso, apresentam afinidade para interações com o DNA, proteínas ou células (KUMAR *et al.*, 2013).

Essas observações estão relacionadas com o estudo da relação estrutura-atividade, que no decorrer dos anos identificou posições e grupos funcionais ativos e inativos de acordo com a atividade. Esses resultados vão depender dos substituintes, alifáticos ou aromáticos, presentes nas posições 1,4; 1,5; ou 1,4,5 do núcleo triazólico e, por essa razão, o *design* e o desenvolvimento de métodos catalíticos verdes e eficientes despertam grande interesse em grupos de pesquisa na área de química orgânica, a fim de gerar uma síntese regiosseletiva de compostos totalmente funcionalizados (LIN, *et al.* 2010; VERNEKAR *et al*., 2015; WANG X. *et al.* 2010;). Portanto, ainda são necessários estudos sobre as combinações de diferentes substratos e condições reacionais para a síntese de estruturas heterocíclicas altamente funcionalizadas e complexas, como triazóis derivados de zidovudina e ésteres graxos.

2.4 Zidovudina - AZT

A zidovudina, também conhecido por AZT, azidotimidina ou retrovir é um dos análogos da timidina mais estudados e foi sintetizado pela primeira vez por Horwitz, da Fundação do Câncer de Michigan em 1964, porém, não apresentou atividade anticancerígina (WANG *et al*., 2011; ZHAN *et al*., 2011). Esta síntese tem como material de partida a timidina **12** e é realizada em seis etapas reacionais com um rendimento global de 30% (**Esquema 13**) (SOUZA *et al.* 2014). No início da década de 70 foi comprovada a sua atividade antiviral, sendo o primeiro composto a apresentar atividade anti-HIV (Vírus da Imunodeficiência Humana) (WANG *et al*., 2011; ZHAN *et al*., 2011).



Esquema 13

A zidovudina foi o primeiro medicamento aprovado nos EUA pela FDA (*Food and Drug Administration*) desde 1987 para prevenir e tratar a AIDS, e também faz parte da Lista de Medicamentos Essenciais da Organização Mundial da Saúde (CHEN *et al.*, 2018; SOUZA *et al.* 2014; TIAN *et al.* 2018; VASILYEVA *et al.*, 2015; ZHANG *et al*., 2017). Atua como um inibidor da transcriptase reversa no tratamento de infecções pelo HIV e, quando combinado com agentes antitumorais, vem demostrando atividade anticancerígena pronunciada (THI *et al.* 2016).

O vírus da imunodeficiência humana (HIV), o agente causador da AIDS, continua sendo um desafio global urgente, pois não constitui apenas um grave problema de saúde, mas também tem importantes consequências sociais e econômicas em todo o mundo (CASTRO *et al.*, 2018; KIM *et al.*, 2018).

Estimativas recentes do UNAIDS (The Joint United Nations Programme on HIV/AIDS) indicam que aproximadamente 37,9 milhões de pessoas vivem com HIV-1 globalmente e que houve 1,7 milhões de novas infecções e 770 mil mortes por AIDS em 2018. Um declínio significativo quando comparado com 3,4 milhões de novas infecções (50%) em 2001 e 2,3 milhões de mortes por AIDS (67%) em 2005 (NAIDU *et al.*, 2018).

Conforme o relatório da UNAIDS Brasil, de junho de 2019, no mundo cerca de 24,5 milhões de pessoas tiveram acesso ao tratamento antirretroviral, o qual gera um impacto no aumento da expectativa de vida dos portadores de HIV. No Brasil, de 2009 a 2018, 593 mil pessoas tiveram acesso a terapias antirretrovirais, através do Sistema Único de Saúde, de acordo com Ministério da Saúde do Brasil.

O HIV é um patógeno que se transforma rapidamente para escapar do sistema imunológico. Além disso, causa imunodeficiência, o que muitas vezes leva a uma alta suscetibilidade a infecções oportunistas por vários outros patógenos, incluindo vírus, bactérias e protozoários (CASTRO *et al.*, 2018).

O tratamento atual é denominado terapia antirretroviral e consiste em combinações de duas ou mais drogas, visando processos virais específicos (NAIDU *et al.*, 2018). O mecanismo de ação do AZT incorporado à terapia de combinação antirretroviral se dá através da inibição a atividade da transcriptase reversa do HIV, tornando-se eficaz na interrupção da replicação do HIV e abrandamento da progressão da AIDS (ECKER *et al.*, 2018).

Desde o avanço da terapia antirretroviral, a qualidade de vida e o tempo de vida dos pacientes infectados pelo HIV-1 melhoraram significativamente (NAIDU *et al.*, 2018). Atualmente, mais de 20 drogas que são usadas em 14 combinações para o tratamento da infecção pelo HIV-1 foram aprovadas e podem atuar pelos seguintes mecanismos de ação: inibidores da transcriptase reversa, inibidores de protease, inibidores da integrase, inibidores da fusão (IFs) e antagonista do receptor 5 da quimiocina (CHEN *et al.*, 2018).

Apesar da introdução da terapia antirretroviral, uma cura completa e permanente ainda é indefinida (KIM *et al.*, 2018). Além disso, a terapia antirretroviral pode apresentar efeitos colaterais adversos, eventual desenvolvimento de resistência a medicamentos e toxicidades a longo prazo. Portanto, novos e mais potentes agentes anti-HIV ainda são necessários (CASTRO *et al.*, 2018; NAIDU *et al.*, 2018; WU *et al.*, 2018; YAN *et al*., 2018).

A principal limitação no uso clínico da zidovudina, especificamente, está associada aos seus efeitos colaterais. Esta molécula pode causar toxicidade na medula óssea, no fígado, no músculo esquelético e no coração (SOUZA *et al.* 2014). Também pode apresentar uma toxicidade moderada, como anemia, neutropenia e trombocitopenia (ECKER *et al.*, 2018).

Neste contexto, várias estratégias têm sido relatadas levando ao desenvolvimento de novos análogos de nucleosídeos com atividade mais potente, menores efeitos colaterais e que possam potencialmente modular processos metabólicos, proporcionando acesso fácil e rápido a uma grande variedade de compostos (KRIM *et al.*, 2013; LI *et al*., 2006; SOUZA *et al.* 2014).

2.4.1 Compostos derivados do AZT

O AZT e seus derivados exibem características estruturais interessantes como substratos orgânicos versáteis para gerar compostos nitrogenados funcionalizados (ZHANG *et al*., 2017) e, por isso, diferentes nucleosídeos modificados ainda são estudados na área de síntese orgânica (ECKER *et al.*, 2018; LI *et al*., 2006; PATHAK *et al*., 2002).

Na literatura, nota-se que a timidina é um nucleosídeo de grande interesse, uma vez que a incorporação de diferentes substituintes em sua posição 3' normalmente modifica significativamente suas propriedades biológicas. Por exemplo, a 3'-azido-3'-desoxitimidina ou zidovudina (AZT) foi o primeiro e ainda é o análogo nucleosídeo mais aplicado na terapia anti-HIV (SOLYEV *et al.* 2014). As estruturas da timidina **12** e do AZT **13** (RAVANELLO, 2014) estão demostradas na **Figura 11**. O grupo azido do AZT, sendo um dipolo, é suscetível à reações de cicloadição com dipolarófilos, dentre os quais foram selecionadas cetonas *α*-funcionalizadas para este estudo que será abordado no **Capítulo 1** deste trabalho.

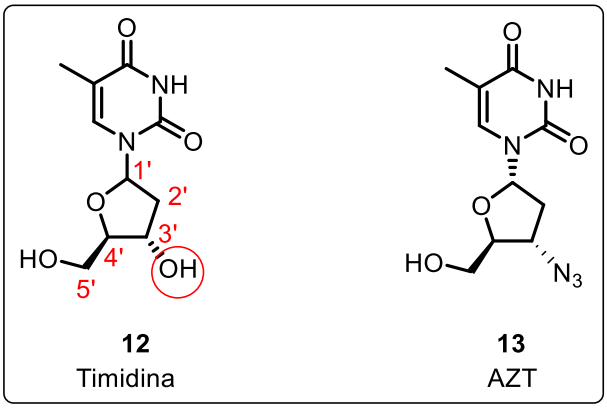


Figura 11. Estruturas da timidina e do AZT.

Uma ampla gama de modificações estruturais é realizada em análogos de pirimidina e uracila objetivando inúmeras aplicações biológicas, podendo ser destacadas as atividades antiviral **73**, anticancerígena **74**, inibidor da enzima Timidina Fosforilase (TP) **75** e atividade antimicrobiana **76**, apresentadas na **Figura 12**.

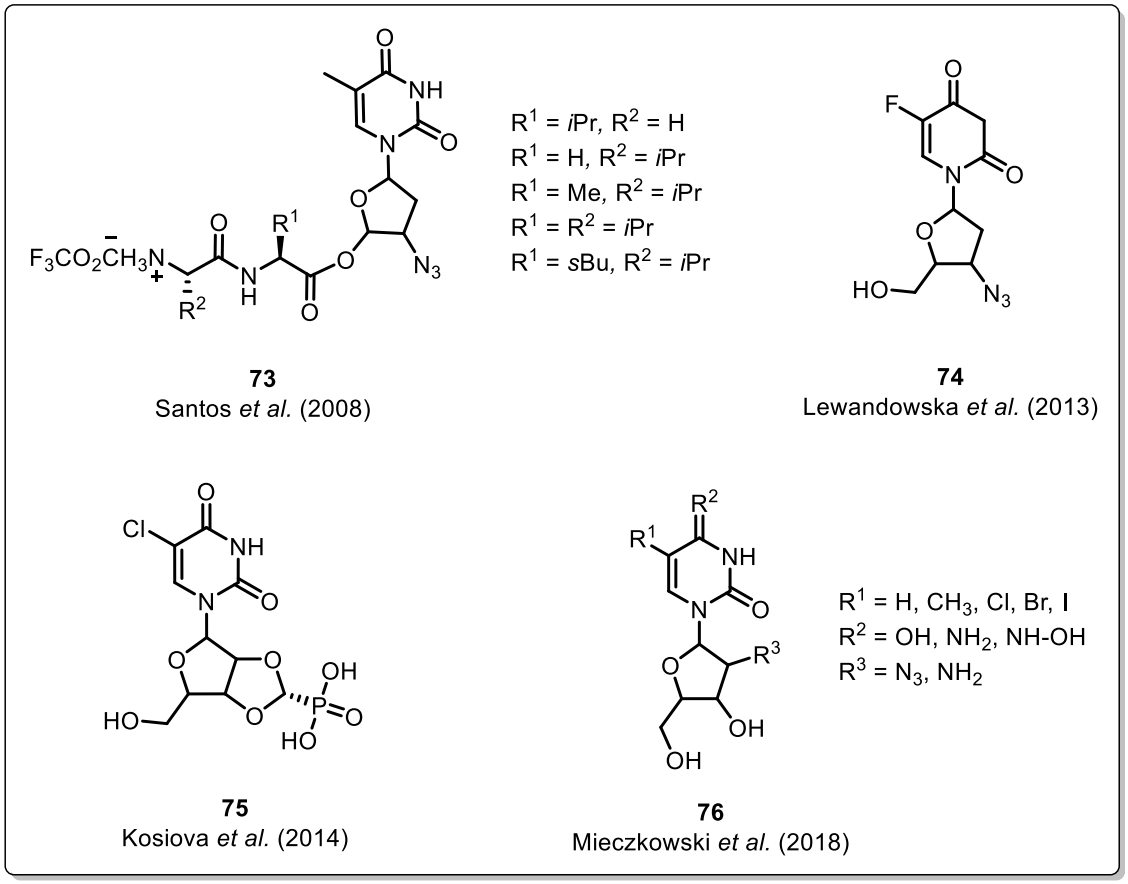


Figura 12. Estruturas de nucleosídeos derivados do AZT.

2.4.2 1*H*-1,2,3-triazol-zidovudina

Os análogos de nucleosídeos sintéticos têm um elevado potencial como agentes antibacterianos, antifúngicos, antivirais e anticancerígenos, como já citado anteriormente. Esses agentes são importantes ferramentas para o estudo dos principais processos do metabolismo celular, pois se comportam como antimetabólitos, ou seja, competem com nucleosídeos fisiológicos e, consequentemente, interagem com um grande número de alvos intracelulares para induzir citotoxicidade (KOSIOVA *et al*., 2007; KRIM *et al.*, 2013).

Metodologias sintéticas simples e eficientes foram desenvolvidas para a síntese de nucleosídeos modificados ligados a triazóis, tendo em conta os seus perfis biológicos destacados (SRIVASTAVA *et al*., 2018). Com base no exposto é razoável sugerir que, a construção de análogos triazol-AZT poderá vir a mostrar boas atividades de citotoxicidade.

Em 1989, Wigerinck e colaboradores relataram análogos de triazol-zidovudina. No entanto, na época, estes foram obtidos através de condições de reações clássicas (térmicas) de Huisgen (ou seja, na ausência de um catalisador de Cu), que geralmente resultaram em misturas de regioisômeros 1,4- e 1,5-dissubstituídos, uma vez que existia pouca possibilidade de separação por procedimentos cromatográficos clássicos.

Métodos clássicos, na presença de metais de transição como o cobre, ainda são bastante empregados para obter os compostos triazol-zidovidina 1,4- ou 1,5-dissubstituídos, como mostra a **Figura 13**. Destacando os trabalhos de Poecke e colaboradores que desenvolveram derivados **77** com potencial de inibição a timidina quinase mitocondrial (TK-2); os análogos **78** reportados por Kumar e colaboradores que foram elaborados com o intuito de obter atividade antiproliferativa de células tumorais; os derivados **79** desenvolvidos também para atividade antiviral; os compostos **79** foram propostos para inibição do vírus da dengue por Vernekar e colaboradores. E por fim, Zhang e colaboradores utilizaram a metodologia convencional de *click* a fim de associar peptídeos a estrutura do triazol-zidovudina, formando os compostos **80** (**Figura 13**).

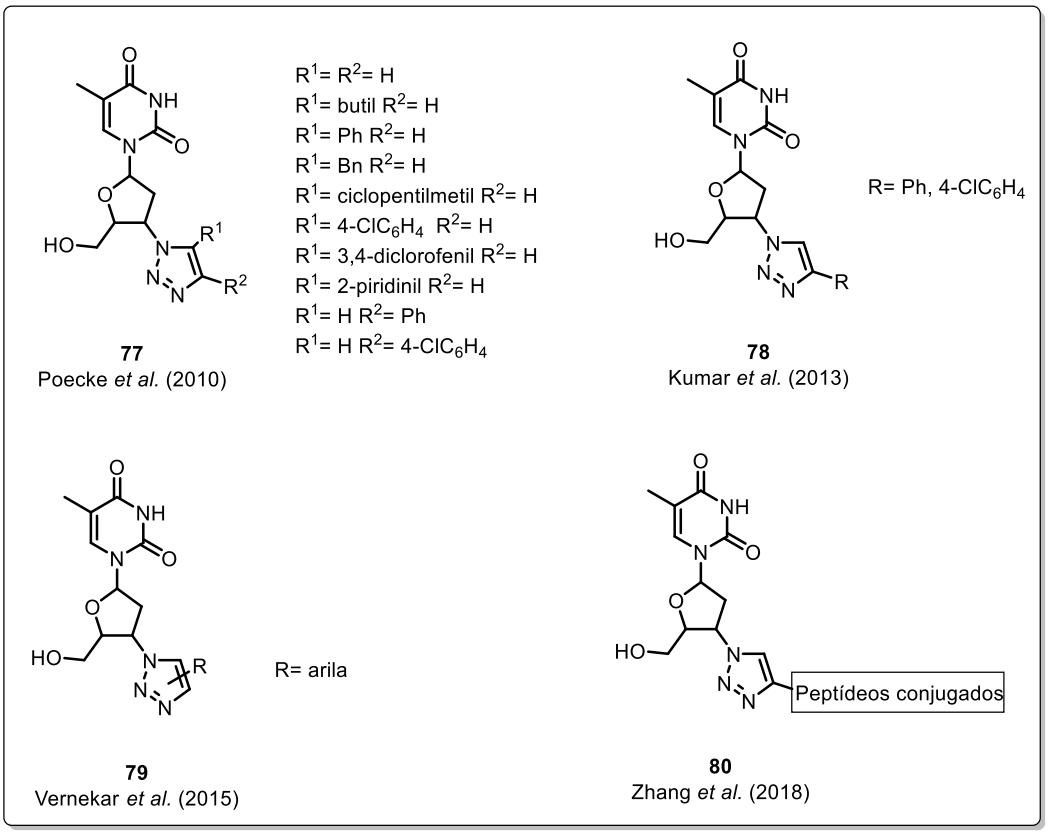
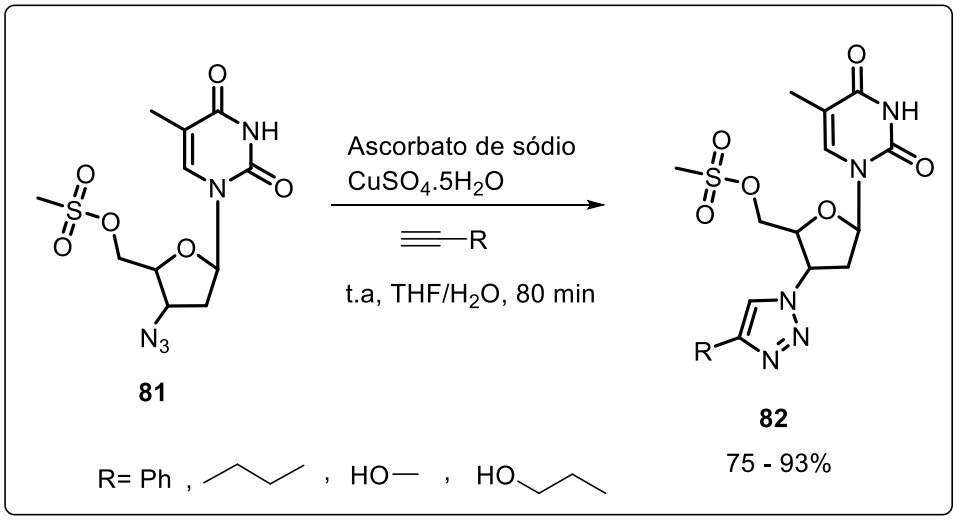


Figura 13. Análogos de triazol-zidovidina.

Em 2018, Munchen e colaboradores sintetizaram análogos de zidovidina que foram utilizados como substratos para síntese de 3'-triazoil-5'-aril-calcogenotimidina **82**. Os autores utilizaram uma metodologia clássica de cicloadição 1,3-dipolar para a inserção do núcleo triazólico no azidonucleosídeo, obtendo rendimentos que variaram de 75 a 93% (**Esquema 14**).



Esquema 14

A partir das contribuições da literatura científica, fica evidente que 1*H*-1,2,3-triazol-zidovudina podem ser considerados compostos com alto valor agregado, tanto do ponto de vista de síntese orgânica como em biotecnologia. Necessita-se, porém, de mais estudos de síntese para gerar novas funcionalizações, empregando metodologias em condições mais brandas e estudos biotecnológicos de relação estrutura-atividade (*SAR*) a fim de desenvolver novos e promissores compostos biologicamente ativos.

2.5 Ésteres de ácidos graxos - EAG

Os ácidos graxos são ácidos carboxílicos geralmente derivados de triacilgliceróis ou fosfolipídios formados a partir da clivagem de gorduras e óleos. São ácidos carboxílicos alifáticos de cadeia longa, que geralmente são saturados ou insaturados e variam de 4 a 28 átomos de carbono (VENEPALLY *et al*., 2017).

A literatura mostra que uma variedade de compostos interessantes de ácidos graxos modificados por meio de transformações simples são moléculas promissoras e apresentam atividades biológicas como, por exemplo, atividade anticâncer (RAHMAN *et al*., 2005). Da mesma forma, avaliando a relação estrutura-atividade, a introdução de cadeias carbônicas em moléculas orgânicas também pode produzir alterações importantes em suas propriedades químicas e físicas, como o aumento da permeabilidade desses compostos graxos na parede celular, que é basicamente composta por lipídios (BECK *et al*., 2012; RICHARD *et al*., 2008).

Há relatos de trabalhos que propõem o desenvolvimento de compostos de cadeia longa derivados de ésteres graxos com diversas atividades biológicas, incluindo atividade neuroprotetora **83**, atividade antimicrobiana **84** e atividade antioxidante de novas poli-hidroquinolinas graxas **85**, como demostrado na **Figura 14**.

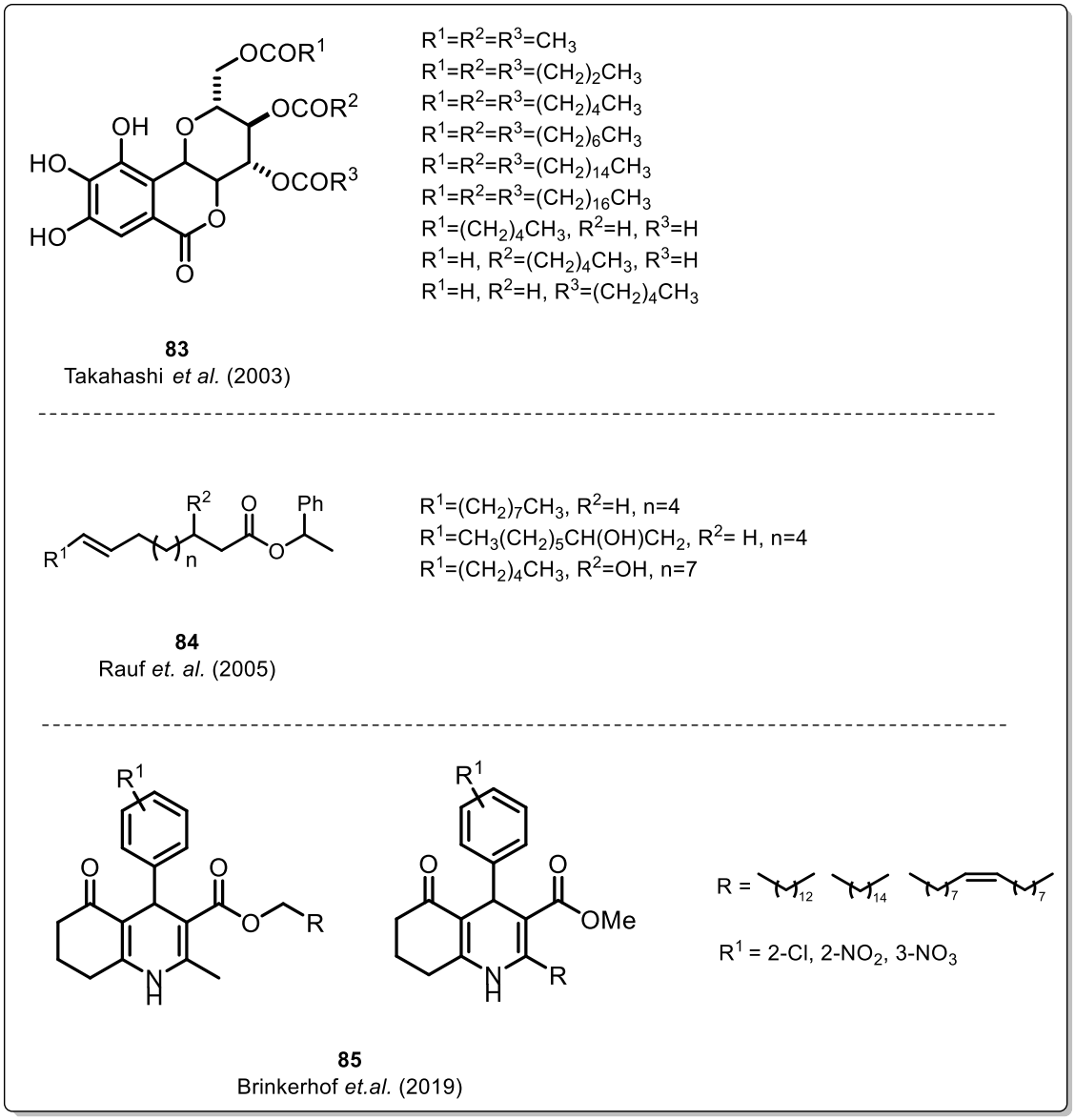
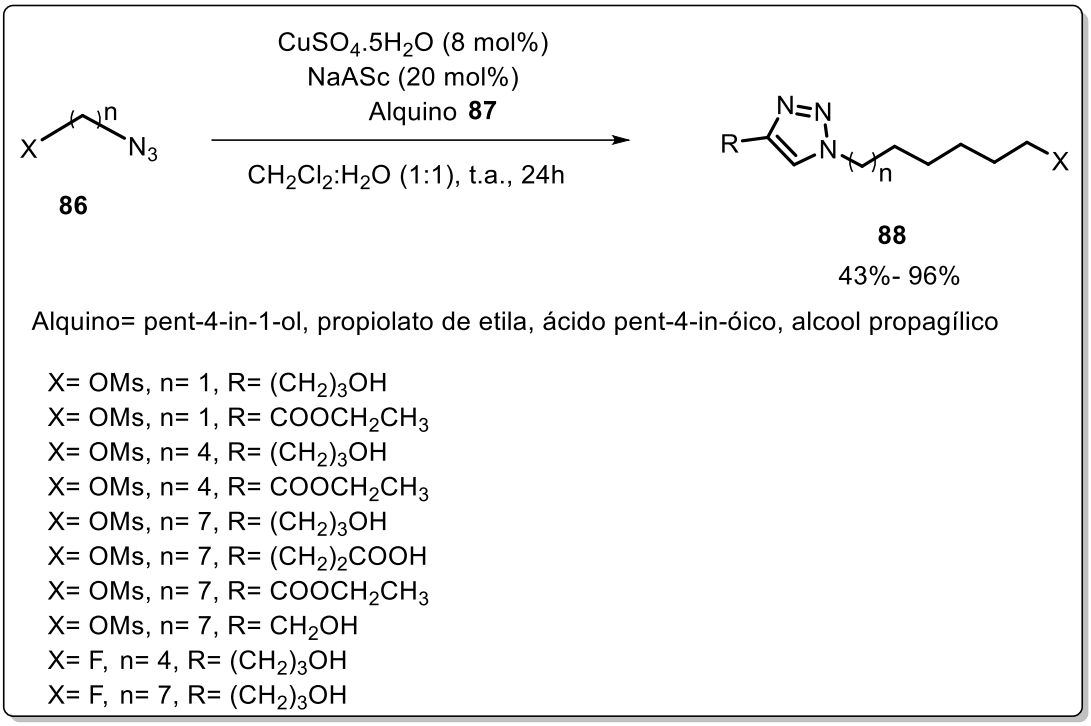


Figura 14. Exemplos de moléculas bioativas derivadas de ácidos graxos.

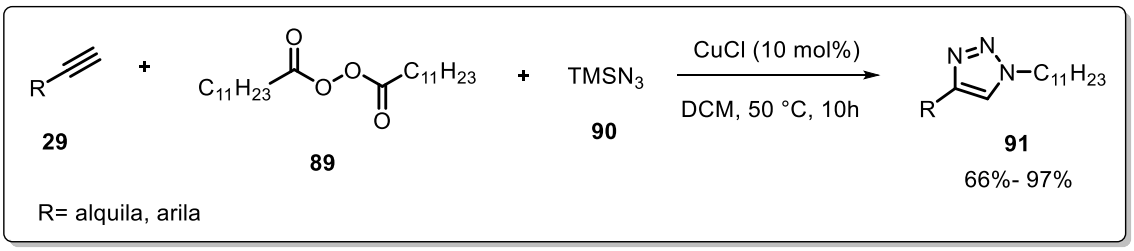
2.5.1 Compostos derivados de 1*H*-1,2,3-triazol graxos

Gontijo e colaboradores propuseram em 2015, a síntese de alquil-triazóis de cadeia longa **88** como uma nova classe de agentes antitumorais. A síntese procedeu através da reação alquino-azida catalisada por sais de cobre (CuAAC), na presença de ascorbato de sódio como agente redutor. A reação ocorreu à temperatura ambiente e na presença de uma combinação de diclorometano e água como solvente (**Esquema 15**).



Esquema 15

Mais recentemente, Israr e colaboradores em 2018, propuseram a síntese de triazóis funcionalizados com cadeia longa **91** a partir de reações entre o alquino terminal **32** com o peróxido **89** na presença de azidotrimetilsilano **90**. As reações se deram através da catálise de cobre utilizando diclorometano como solvente, obtendo 26 exemplos com bons rendimentos (**Esquema 16**).

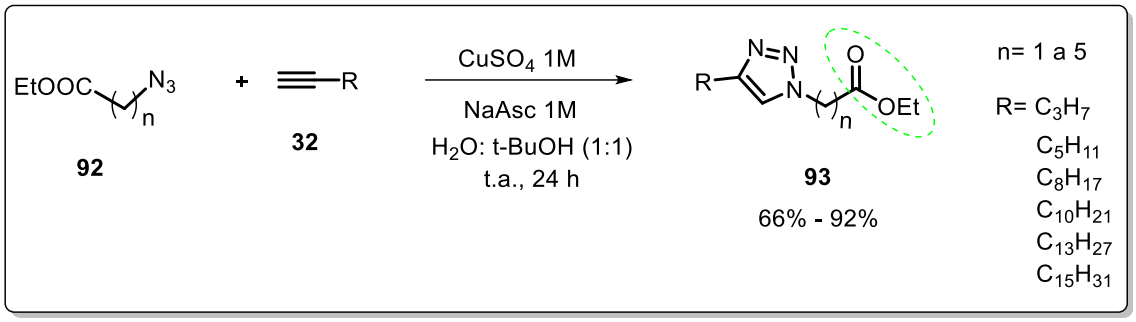


Esquema 16

2.5.2 1*H*-1,2,3-triazol-esteres graxos

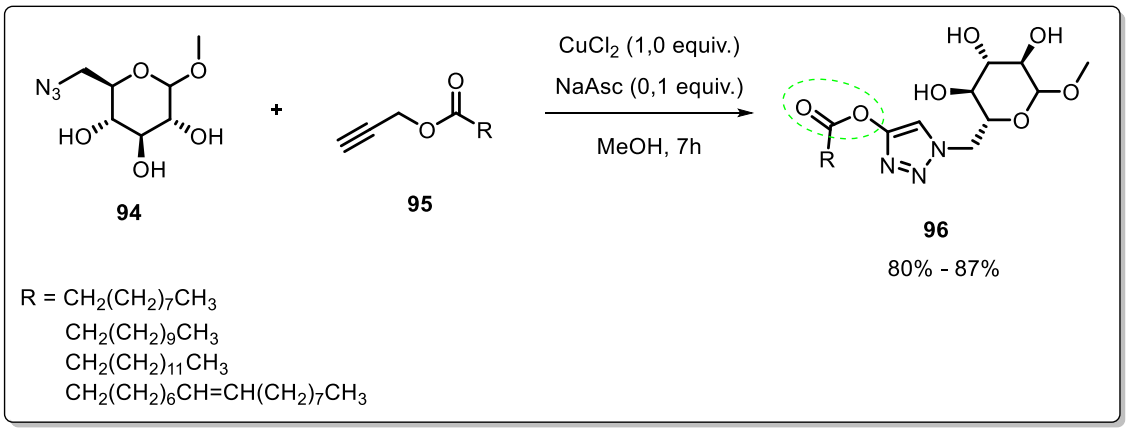
Em 2017, Ghiano e colaboradores avaliaram a atividade antitubercular de triazóis contendo ésteres graxos **93**, sintetizados através de reações de CuAAC. Os autores obtiveram 25 exemplos com rendimentos que variaram de

moderados a excelentes considerando a complexidade da molécula (**Esquema 17**).



Esquema 17

E, por último, foi recentemente reportado por Salman e colaboradores (2019) a síntese de triazóis funcionalizados contendo ésteres graxos. A síntese propôs a obtenção de uma nova série de triazóis alquilados **96** partindo de um grupo azido multi-hidroxila **94** e um éster de alquil-propargila de cadeia longa **95**, via reação de *click* utilizando metanol como solvente. Esses derivados apresentaram excelentes rendimentos (**Esquema 18**).



Esquema 18

3 HIPÓTESE E OBJETIVOS

3.1 Hipótese

Como hipótese deste trabalho é sugerido que sistemas organocatalíticos são altamente versáteis, podendo ser aplicados com diferentes substratos e em diferentes atividades biológicas. Levando em consideração que cada série de compostos desenvolvidos apresenta uma especificidade e sensibilidade celular, ou seja, de acordo com os substituintes da molécula sintetizada tem-se uma resposta diferente frente a um determinado alvo, pela interação única que possuem entre a droga e o alvo escolhido.

3.2 Objetivo Geral

Sintetizar e caracterizar análogos de 1,2,3-triazóis substituídos derivados da zidovudina e de ésteres graxos através de reações de cicloadição via organocatálise e, avaliar o potencial biológico desses análogos da zidovudina frente a testes antioxidantes e, dos análogos de ésteres graxos frente a proliferação de células cancerígenas de bexiga, através de análise citotóxica.

3.3 Objetivos Específicos

- Sintetizar análogos de 1,2,3-triazóis substituídos derivados de zidovudina via organocatálise;
- Avaliar o potencial antioxidante de 1,2,3-triazóis substituídos derivados de zidovudina através de ensaios antioxidantes, como ROS e TBARS;
- Sintetizar análogos de 1,2,3-triazóis substituídos derivados de ésteres graxos via organocatálise;
- Observar o potencial antiproliferativo de 1,2,3-triazóis substituídos derivados de ésteres graxos em linhagem celular humana de câncer de bexiga através do ensaio citotóxico MTT.

4 CAPÍTULOS

4.1 Manuscrito 1 – Organocatalysis in the synthesis of 1,2,3-triazoyl-zidovudine derivatives: synthesis and antioxidant activity

Manuscrito submetido à revista *Organic & Biomolecular Chemistry*

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Organocatalysis in the synthesis of 1,2,3-triazoyl-zidovudine derivatives: synthesis and antioxidant activity

Carolina B. Gomes,[a] Renata A. Balaguez,[a] Allya M. E. Larroza,[a] Thiago A. Smaniotto,[b] Micaela Domingues,[b] Angela M. Casaril,[b] Márcio S. Silva,[a] Oscar E. D. Rodrigues,[c] Lucielli Savegnago[b] and Diego Alves*[a]

We describe herein the organocatalyzed synthesis and preliminary results of antioxidant activities of a range of 1,2,3-triazoyl-zidovudine derivatives. These hybrid compounds were synthesized in moderate to excellent yields by the reaction of zidovudine **1** with a range of functionalized keto compounds **2**, such as β-keto-esters, β-diketones, β-keto-amides, α-keto-nitriles and β-keto-sulfones, in the presence of a catalytic amount of DBU (10 mol%). Furthermore, the synthesized compounds were screened for their *in vitro* antioxidant activity. The compounds **3a**, **3d**, **3g**, and **3l** inhibited the formation of reactive oxygen species (ROS) and lipid peroxidation in the prefrontal cortex and hippocampus of mice, with similar potency and efficacy.

Introduction

Highly substituted 1,2,3-triazoles are an important and useful class of heterocycles, which have received considerable attention, because of their application in organic synthesis, materials science and in medicinal chemistry.[1] Particularly, 1,2,3-triazoles derivatives exhibit a broad spectra of biological properties, such as anti-inflammatory, antifungal, antibacterial, anticancer, antivirus and antituberculosis.[2]

The great interest to develop synthetic methodologies to obtain 1,2,3-triazoles emerged when Huisgen proposed, in 1963, the cycloaddition reaction [3 + 2] employing an organic azide and a terminal alkyne.[3] Inspired this pioneering work, a number of catalytic strategies employing transition metals, such as copper, ruthenium, silver and iridium, have been used to address the reactivity and selectivity issues inherent to the seminal strategy.[4]

However, the requirements of transition-metals as catalysts in cycloaddition reactions restricted the biological evaluation of many triazoles, because some of these metals can induce damage in different biological systems even in trace amounts.[5] In view of these restricted applications, recent studies have been directed toward the development of metal-free methodologies for triazole synthesis. Organocatalytic approaches involving [3 + 2] cycloaddition have been reported for the synthesis of functionalized 1,2,3-triazoles.[6] In some reactions, carbonyl compounds can generate enamines or enolates and act as dipolarophiles in organocatalyzed 1,3-dipolar cycloadditions with organic azides.[7] There remains, however, a need for an in-depth study on the synthesis of more highly functionalized and complex 1,2,3-triazoles from various combinations of substrates.

In this context, zidovudine (AZT, 3'-Azido-3'-deoxythymidine) is one of the most usable synthetic molecule in medicine which was originally synthesized as an antitumoral agent.[8] It is an FDA (Food and Drug Administration - USA) approved drug for preventing and treating AIDS and is also on the World Health Organization's List of Essential Medicines.[9] Zidovudine derivatives show several pharmacological activities, including antitumor, antimicrobial, antioxidant, antiproliferative and antiviral activities.[10]

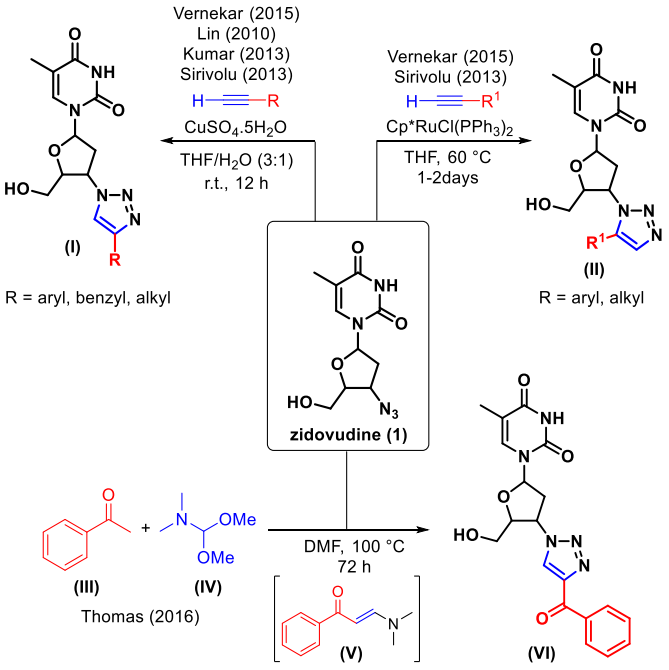


Figure 1 Examples of synthesized 1,2,3-triazolyl-zidovudine derivatives.

Hybrid molecules containing zidovudine and the 1,2,3-triazole nucleus are an interesting family of compounds featuring promising and broad biological applications due to the

[a] *Laboratório de Síntese Orgânica Limpa, Universidade Federal de Pelotas, UFPel. PO Box 354 - CEP 96010-900, Pelotas, RS, Brazil. Tel./Fax: +55 53 32757533; e-mail: diego.alves@ufpel.edu.br*

[b] *Programa de Pós-Graduação em Biotecnologia (PPGB), Grupo de Pesquisa em Neurobiotecnologia - GPN, Universidade Federal de Pelotas, UFPel, Postal Code 96010-900, Pelotas, RS, Brazil.*

[c] *LabSelen-NanoBio - Departamento de Química, Universidade Federal de Santa Maria, UFSM, 97115-900, Santa Maria, RS, Brazil.*

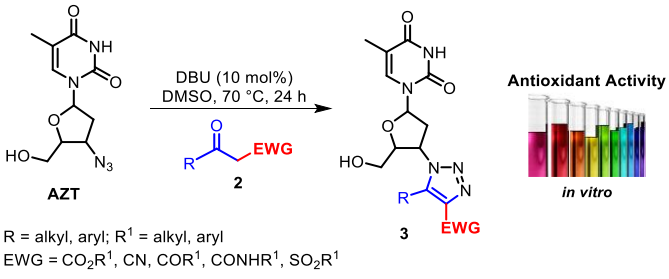
Electronic Supplementary Information (ESI) available: spectroscopic characterization of the compounds and additional results can also be found in the ESI. See DOI: 10.1039/x0xx00000x

Please do not adjust margins

Please do not adjust margins

combination of the well-known activity of the zidovudine[8-10] with that of the 1,2,3-triazole core.[1,2,11] Based on this, Vernekar,[12] Lin,[13] Kumar[14] and Sirivolu[15] in different works reported azide-alkyne cycloaddition reactions to access 1,4- or 1,5-regioisomers of 1,2,3-triazolyl zidovudine **(I)** and **(II)**. The synthesized compounds were obtained in moderate to excellent yields and screened for their antitumor and antiviral activities (Figure 1). More recently, Thomas et al. in 2016 described the metal-free synthesis of 4-acyl-1,2,3-triazole zidovudine derivative **(VI)** from readily available acetophenone **(III)**, *N*,*N*-dimethylformamide dimethyl acetal **(IV)** and zidovudine. This reaction is enabled by the *in-situ* formation of an enaminone intermediate **(V)** followed by its 1,3-dipolar cycloaddition reaction with zidovudine.[16]

In view of the exposed above and in continuation of our research endeavors in the synthesis of functionalized 1,2,3-triazoles, we report herein the organocatalyzed synthesis and preliminary results of antioxidant activities of a range of 1,2,3-triazoyl-zidovudine derivatives (Scheme 1).



Scheme 1. General propose.

Experimental

General information: The reactions were monitored by TLC carried out on Merck silica gel (60 F254) by using UV light as visualizing agent and 5% vanillin in 10% H_2SO_4 and heat as developing agents. Hydrogen nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 400 MHz on Bruker Avance III HD 400 spectrometer. Spectra were recorded in DMSO-d_6 solutions. Chemical shifts are reported in ppm, referenced to tetramethylsilane (TMS) as the external reference. Coupling constants (*J*) are reported in Hertz. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of double doublets), t (triplet), q (quartet) and m (multiplet). Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 100 MHz on Bruker Avance III HD 400 spectrometer. Chemical shifts are reported in ppm, referenced to the solvent peak of DMSO-d_6. Low-resolution mass spectra were obtained with a Shimadzu GC-MS-QP2010 mass spectrometer. High resolution mass spectra (HRMS) were recorded on a Bruker Micro TOF-QII spectrometer 10416. The solvents and reagents were used as received or purified using standard procedures.

General procedure for the synthesis of 1,2,3-triazoyl-zidovudine derivatives 3a-p: The appropriate keto compound **2** (0.36 mmol) was first added to a solution of zidovudine **1** (0.3 mmol) in DMSO (0.6 mL), followed by DBU (10 mol %) as catalyst. The reaction mixture was stirred in an open flask at 70 °C for 24 hours. After completion of the reaction, the crude product was purified by column chromatography on silica gel with a mixture of hexane/ethyl acetate (1:2) as eluent to afford the desired product **3a-p**. Spectral data for the products prepared are listed below.

Ethyl 1-(2-(hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate 3a. Yield: 0.093 g (82%); Yellow solid; mp 203-205 °C. ^{1}H NMR ^{1}H (400 MHz, DMSO-d_6) δ (ppm): 11.41 (s, 1H), 7.86 (s, 1H), 6.56-6.53 (m, 1H), 5.39 (s, 1H), 5.28-5.26 (m, 1H), 4.37 (q, *J* = 7.0 Hz, 2H), 4.32-4.31 (m, 1H), 3.77-3.68 (m, 2H), 2.84-2.78 (m, 1H), 2.74-2.68 (m, 1H), 2.63 (s, 3H), 1.87 (s, 3H), 1.36 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.8, 161.2, 150.5, 139.1, 136.1, 135.7, 109.8, 84.5, 84.4, 61.1, 60.4, 57.7, 36.8, 14.2, 12.3, 8.8. MS (relative intensity) m/z: 381 (M$^+$48), 225 (5), 192 (46), 190 (100), 188 (50), 156 (46), 154 (26). HRMS-ESI: *m/z* calculated for $C_{16}H_{22}N_5O_6$ [M + H]$^+$: 380.1580. Found: 380.1567.

Ethyl 1-(2-(hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)-5-phenyl-1*H*-1,2,3-triazole-4-carboxylate 3b. Yield: 0.117 g (88%); Yellow solid; mp 82-84 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.31 (s, 1H), 7.74 (s, 1H), 7.57-7.50 (m, 5H), 6.56-6.53 (m, 1H), 5.17-5.15 (m, 1H), 4.92-4.90 (m, 1H), 4.41-4.40 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.57-3.51 (m, 1H), 3.42-3.37 (m, 1H), 2.73-2.54 (m, 2H), 1.76 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.6, 160.2, 150.4, 141.0, 136.3, 136.0, 130.2, 130.0, 128.4, 125.7, 109.7, 84.7, 84.6, 61.3, 60.2, 58.9, 37.4, 13.8, 12.2. MS (relative intensity) m/z: 441 (M$^+$ 3), 316 (25), 316 (25), 225 (2), 219 (13), 218 (100), 217 (7), 172 (41). HRMS-ESI: *m/z* calculated for $C_{21}H_{24}N_5O_6$ [M + H]$^+$: 442.1727. Found: 442.1726.

***tert*-Butyl 1-(2-(hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3-yl)-5-methyl-1H-1,2,3-triazole-4-carboxylate 3c**. Yield: 0.072 g (59%); Orange liquid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.36 (s, 1H), 7.80 (s, 1H), 6.50-6.46 (m, 1H), 6.33-6.30 (m, 1H), 5.21-5.16 (m, 1H), 4.26-4.23 (m, 1H), 3.73-3.6 (m, 2H), 2.76-2.70 (m, 1H), 2.67-2.59 (m, 1H), 2.54 (s, 3H), 1.81 (s, 3H), 1.54 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 163.8, 160.4, 150.5, 138.4, 136.7, 136.1, 109.8, 84.5, 84.4, 81.2, 61.1, 57.6, 36.8, 27.9, 12.3, 8.9. HRMS-ESI: *m/z* calculated for $C_{16}H_{26}N_5O_6$ [M + H]$^+$: 408.1883. Found: 408.1890.

1-(4-(4-Acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione 3d. Yield: 0.094 g (90%); beige solid; mp 212-214 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): δ 11.44 (s, 1H), 7.90 (s, 1H), 6.61-6.58 (m, 1H), 5.42 (s, 1H), 5.32-5.28 (m, 1H), 4.37-4.34 (m, 1H), 3.81-3.71 (m, 2H), 2.88-2.80 (m, 1H), 2.78-2.70 (m, 1H), 2.67 (s, 3H), 2.66 (s, 3H), 1.91 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 193.2, 163.5, 150.3, 142.6, 137.3, 135.9, 109.5, 84.2, 84.1, 60.8, 57.2, 36.5, 27.3, 12.1, 8.5. MS (relative intensity) m/z: 349 (M$^+$ 6), 225 (14), 224 (100), 206 (9), 156 (13). HRMS-ESI: *m/z* calculated for $C_{15}H_{20}N_5O_5$ [M + H]$^+$: 350.1464. Found: 350.1470.

1-(4-(5-Ethyl-4-propionyl-1*H*-1,2,3-triazol-1-yl)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione 3e. Yield: 0.103 g (91%); White solid; mp 188-190

Please do not adjust margins

Please do not adjust margins

°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 11.27 (s, 1H), 7.78 (s, 1H), 6.54-6.51 (m, 1H), 5.31 (s, 1H), 5.25-5.21 (m, 1H), 4.31-4.30 (m, 1H), 3.73-3.61 (m, 2H), 3.10-2.96 (m, 4H), 2.73-2.63 (m, 2H), 1.82 (s, 3H), 1.15-1.08 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 195.9, 163.6, 150.4, 142.3, 141.7, 136.1, 109.7, 84.51, 84.48, 61.0, 57.2, 37.3, 32.4, 15.9, 12.7, 12.2, 7.8. MS (relative intensity) m/z: 377 (M^+ 11), 253 (10), 252 (68), 155 (9), 154 (100). HRMS-ESI: *m/z* calculated for $C_{17}H_{24}N_5O_5$ $[M + H]^+$: 378.1777. Found: 378.1791.

1-(4-(4-Benzoyl-5-phenyl-1*H*-1,2,3-triazol-1-yl)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione 3f. Yield: 0.127 g (89%); White solid; mp 210-212 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 11.37 (s, 1H), 8.10 (d, *J* = 7.2 Hz, 2H), 7.77 (s, 1H), 7.68-7.64 (m, 1H), 7.56-7.52 (m, 7H), 6.64-6.60 (m, 1H), 5.25-5.22 (m, 1H), 5.00-4.98 (m, 1H), 4.48-4.46 (m, 1H), 3.60-3.55 (m, 1H), 3.46-3.41 (m, 1H), 2.77 (ddd, *J* = 13.7, 5.9, 1.9 Hz, 1H), 2.58-2.56 (m, 1H), 1.77 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 186.1, 163.7, 150.5, 143.0, 141.3, 136.9, 136.1, 133.2, 130.2, 130.1, 130.0, 128.7, 128.4, 125.9, 109.8, 84.8, 84.7, 61.4, 58.9, 37.5, 12.3. MS (relative intensity) m/z: 473 (M^+ 9), 349 (6), 348 (27), 251 (17), 250 (100), 249 (11), 248 (6), 172 (16). HRMS-ESI: *m/z* calculated for $C_{25}H_{24}N_5O_5$ $[M + H]^+$: 474.1777. Found: 474.1790.

1-(2-(Hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)-5-methyl-*N*-phenyl-1*H*-1,2,3-triazole-4-carboxamide 3g. Yield: 0.105 g (82%); White solid; mp 110-112 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 11.37 (s, 1H), 10.35 (s, 1H), 7.82-7.81 (m, 3H), 7.35-7.31 (m, 2H), 7.11-7.07 (m, 1H), 6.53-6.50 (m, 1H), 5.36 (t, *J* = 5.1 Hz, 1H), 5.26-5.22 (m, 1H), 4.33-4.30 (m, 1H), 3.76-3.64 (m, 2H), 2.80-2.74 (m, 1H), 2.71-2.65 (m, 1H), 2.63 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 163.8, 159.6, 150.5, 138.6, 138.2, 137.4, 136.1, 128.6, 123.7, 120.4, 109.8, 84.5, 84.4, 61.1, 57.6, 36.9, 12.4, 8.5. MS (relative intensity) m/z: 426 (M^+26), 301 (11), 225 (2), 204 (12), 203 (100), 202 (15). HRMS-ESI: *m/z* calculated for $C_{20}H_{23}N_6O_5$ $[M + H]^+$: 427.1730. Found: 427.1741.

***N*-(4-Chlorophenyl)-1-(2-(hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)-5-methyl-1*H*-1,2,3-triazole-4-carboxamide 3h**. Yield: 0.108 g (78%); White solid; mp 248-250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 11.24 (s, 1H), 10.42 (s, 1H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.69 (s, 1H), 7.26 (d, *J* = 8.8 Hz, 2H), 6.40-6.36 (m, 1H), 5.26 (s, 1H), 5.13-5.11 (m, 1H), 4.18-4.17 (m, 1H), 3.58-3.51 (m, 2H), 2.66-2.60 (m, 1H), 2.57-2.54 (m, 1H), 2.50 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 163.8, 159.7, 150.5, 138.1, 137.6 (2C), 136.2, 128.5, 127.4, 122.0, 109.8, 84.5, 84.3, 61.2, 57.7, 36.9, 12.4, 8.5. MS (relative intensity) m/z: 460 (M^+ 31), 335 (10), 239 (32), 238 (20), 237 (100), 236 (25), 235 (2), 225 (5), 154 (8). HRMS-ESI: *m/z* calculated for $C_{20}H_{22}ClN_6O_5$ $[M + H]^+$: 461.1340.

1-(2-(Hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)-*N*-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxamide 3i. Yield: 0.123 g (90%); White solid; mp 106-108 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.33 (s, 1H), 10.20 (s, 1H), 7.81 (s, 1H), 7.71 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.53-6.49 (m, 1H), 5.34-5.32 (m, 1H), 5.25-5.23 (m, 1H), 4.31-4.30 (m, 1H), 3.74 (s, 3H), 3.71-3.64 (m, 2H), 2.80-2.72 (m, 1H), 2.71-2.65 (m, 1H), 2.62 (s, 3H), 1.83 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.7, 159.2, 155.6, 150.4, 138.3, 137.0, 136.1, 131.6, 122.0, 113.7, 109.7, 84.4, 84.3, 61.1, 57.5, 55.2, 36.8, 12.2, 8.4. MS (relative intensity) m/z: 457 (M^+ 24), 456 (100), 234 (8), 233 (40), 232 (15), 225 (3), 150 (4). HRMS-ESI: *m/z* calculated for $C_{21}H_{25}N_6O_6$ $[M + H]^+$: 457.1836. Found: 457.1833.

1-(2-(Hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)-5-phenyl-1*H*-1,2,3-triazole-4-carbonitrile 3j. Yield: 0.104 g (88%); Yellow solid; mp 102-104 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 11.36 (s, 1H), 7.76 (s, 1H), 7.69-7.65 (m, 5H), 6.55-6.51 (m, 1H), 5.27-5.25 (m, 1H), 5.15-5.12 (m, 1H), 4.47-4.45 (m, 1H), 3.62-3.56 (m, 1H), 3.52-3.47 (m, 1H), 2.76 (ddd, *J* = 14.0, 6.1, 2.4 Hz, 1H), 2.64-2.56 (m, 1H), 1.77 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 163.7, 150.5, 144.1, 136.1, 131.3, 129.6, 129.5, 123.0, 119.4, 112.4, 109.8, 84.7, 84.5, 61.3, 59.8, 37.5, 12.3. MS (relative intensity) m/z: 394 (M^+ 4), 270 (17), 269 (100), 225 (0.8), 201 (12), 171 (45), 170 (8). HRMS-ESI: *m/z* calculated for $C_{19}H_{19}N_6O_4$ $[M + H]^+$: 395.1468. Found: 395.1467.

5-(4-Bromophenyl)-1-(2-(hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)-1*H*-1,2,3-triazole-4-carbonitrile 3k. Yield: 0.125 g (88%); Orange solid; mp 222-224 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 10.31 (s, 1H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.50 (s, 1H), 7.35 (d, *J* = 8.6 Hz, 2H), 6.41-6.38 (m, 1H), 5.27-5.23 (m, 1H), 4.71 (s, 1H), 4.52-4.50 (m, 1H), 3.79-3.76 (m, 1H), 3.56-3.52 (m, 1H), 2.75 (ddd, *J* = 13.8, 6.5, 4.0 Hz, 1H), 2.66-2.62 (m, 1H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 164.0, 150.4, 142.8, 136.3, 132.9, 130.6, 126.0, 121.6, 120.2, 111.4, 110.8, 86.5, 84.7, 61.1, 58.7, 38.5, 12.3. MS (relative intensity) m/z: 472 (M^+ 5), 445 (4), 349 (97), 348 (18), 347 (100), 249 (24), 248 (23), 246 (1), 225 (2), 154 (9). HRMS-ESI: *m/z* calculated for $C_{19}H_{18}BrN_6O_4$ $[M + H]^+$: 473.0573. Found: 473.0578.

5-(4-Fluorophenyl)-1-(2-(hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)-1*H*-1,2,3-triazole-4-carbonitrile 3l. Yield: 0.105 g (85%); Yellow solid; mp 124-126 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 10.80 (s, 1H),7.63-7.61 (m, 1H), 7.59-7.53 (m, 2H), 7.36-7.29 (m, 2H), 6.56-6.49 (m, 1H), 5.30-5.24 (m, 1H), 4.98 (s, 1H), 4.56-4.54 (m, 1H), 3.83-3.81 (m, 1H), 3.61-3.59 (m, 1H), 2.91-2.76 (m, 2H), 1.88-1.85 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 163.7, 163.6 (d, *J* = 251.6 Hz), 150.1, 142.5, 135.6, 131.1 (d, *J* = 8.8 Hz), 119.8, 118.4 (d, *J* = 3.46 Hz), 116.6 (d, *J* = 22.2 Hz), 111.2, 110.2, 85.4, 84.3, 60.8, 58.5, 38.1, 11.9. MS (relative intensity) m/z: 412 (M^+ 4), 287 (100), 189 (22), 159 (21), 288 (16), 225 (0.9), 188 (10). HRMS-ESI: *m/z* calculated for $C_{19}H_{18}FN_6O_4$ $[M + H]^+$: 413.1374. Found: 413.1370.

1-(2-(Hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)-5-(4-methoxyphenyl)-1*H*-1,2,3-triazole-4-carbonitrile 3m. Yield: 0.102 g (80%); Orange solid; mp 195-197 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 10.78 (s, 1H), 7.66-7.64 (m, 1H), 7.47-7.43 (m, 2H), 7.11-7.09 (m, 2H), 6.57-6.51 (m, 1H), 5.31-5.28 (m, 1H), 4.96 (s, 1H), 4.56-4.54 (m, 1H), 3.90-3.76 (m, 4H), 3.64-3.52 (m, 1H), 2.94-2.83 (m, 1H), 2.81-2.69 (m, 1H), 1.88-1.86 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 163.7, 161.3, 150.2, 143.4, 135.7, 130.2, 119.5, 114.8, 114.1, 111.6, 110.3, 85.6, 84.4, 61.0, 58.4, 55.0, 38.3, 12.0. MS (relative intensity) m/z: 424 (M^+ 11), 299 (90), 231 (25), 225 (1), 201 (100), 200 (68). HRMS-ESI: *m/z* calculated for $C_{20}H_{21}N_6O_5$ $[M + H]^+$: 425.1573. Found: 425.1564.

1-(5-(Hydroxymethyl)-4-(5-phenyl-4-(phenylsulfonyl)-1*H*-1,2,3-triazol-1-yl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-

Please do not adjust margins

Please do not adjust margins

dione 3n. Yield: 0.133 g (87%); Orange solid; mp 200-202 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.30 (s, 1H), 7.78-7.76 (m, 2H), 7.74-7.70 (m, 2H), 7.65-7.56 (m, 5H), 7.48-7.46 (m, 2H), 6.51-6.48 (m, 1H), 5.14-7.12 (m, 1H), 4.84-4.79 (m, 1H), 4.42-4.39 (m, 1H), 3.52-3.47 (m, 1H), 3.39-3.35 (m, 1H), 2.76-2.70 (m, 1H), 2.47-2.39 (m, 1H), 1.74 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.6, 150.4, 144.4, 140.3, 139.3, 136.0, 134.1, 130.6, 130.3, 129.5, 128.6, 127.4, 123.9, 109.7, 84.7, 84.4, 61.4, 59.6, 37.2, 12.2. MS (relative intensity) m/z: 509 (M^+ 1), 384 (15), 288 (6), 287 (17), 286 (100), 285 (5). HRMS-ESI: *m/z* calculated for $C_{24}H_{24}N_5O_6S$ [M + H]$^+$: 510.1447. Found: 510.1451.

1-(4-(4-((4-Chlorophenyl)sulfonyl)-5-phenyl-1*H*-1,2,3-triazol-1-yl)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione 3o. Yield: 0.124 g (76%); Orange solid; mp 109-111 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.30 (s, 1H), 7.77-7.75 (m, 2H), 7.71-7.66 (m, 3H), 7.63-7.56 (m, 3H), 7.48-7.46 (m, 2H), 6.51-6.47 (m, 1H), 5.14-5.11 (m, 1H), 4.83-4.78 (m, 1H), 4.42-4.39 (m, 1H), 3.52-3.47 (m, 1H), 3.37-3.34 (m, 1H), 2.73 (dd, *J* = 12.3, 6.5 Hz, 1H), 2.47-2.40 (m, 1H), 1.74 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.6, 150.4, 144.1, 139.4, 139.2, 139.0, 136.0, 130.6, 130.3, 129.7, 129.4, 128.6, 123.8, 109.7, 84.6, 84.4, 61.3, 59.7, 37.2, 12.2. MS (relative intensity) m/z: 332 (18), 320 (48), 126 (18), 99 (64), 69 (100). HRMS-ESI: *m/z* calculated for $C_{24}H_{23}ClN_5O_6S$ [M + H]$^+$: 544.1058. Found: 544.1057.

1-(5-(Hydroxymethyl)-4-(4-((4-methoxyphenyl)sulfonyl)-5-phenyl-1*H*-1,2,3-triazol-1-yl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione 3p. Yield: 0.144 g (89%); Orange solid; mp 111-113 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.30 (s, 1H), 7.71-7.67 (m, 3H), 7.64-7.56 (m, 3H), 7.47-7.46 (m, 2H), 7.10 (d, *J* = 9.0 Hz, 2H), 6.51-6.48 (m, 1H), 5.12 (s, 1H), 4.82-4.80 (m, 1H), 4.41-4.38 (m, 1H), 3.84 (s, 3H), 3.52-3.48 (m, 1H), 3.39-3.35 (m, 1H), 2.72 (dd, *J* = 14.4, 7.9 Hz, 1H), 2.47-2.41 (m, 1H), 1.75 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.6, 163.5, 150.4, 145.2, 138.7, 136.0, 131.7, 130.5, 130.3, 129.8, 128.6, 124.0, 114.7, 109.7, 84.6, 84.4, 61.3, 59.6, 55.8, 37.2, 12.1. MS (relative intensity) m/z: 539 (M^+3), 414 (15), 317 (19), 316 (100), 315 (11), 225 (2), 171 (17). HRMS-ESI: *m/z* calculated for $C_{25}H_{26}N_5O_7S$: [M + H]$^+$: 540.1553. Found: 540.1549.

Antioxidant Activity Assay:

Inhibition of reactive oxygen species (ROS) formation and inhibition of thiobarbituric acid reactive species (TBARS) formation: In order to evaluate the antioxidant effect of AZT derivatives, the formation of ROS and lipid peroxidation was measured in the prefrontal cortex and hippocampus of *Swiss* male mice.

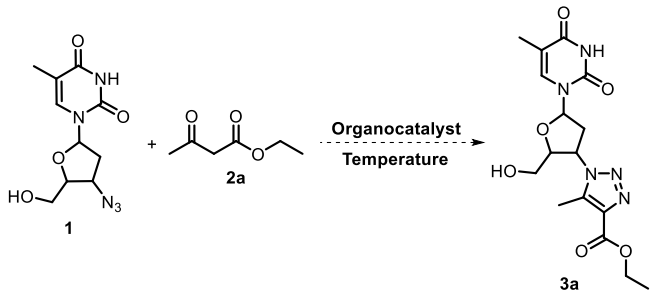
The formation of ROS was determined as described by Loetchutinat.[17] Sodium azide induces the formation of ROS, which oxidize dichlorofluorescein diacetate to dichlorofluorescein (DCF), a fluorescent form. The fluorescence is read spectrofluorimetrically at 520nm wavelength and excitation at 488 nm. The TBARS assay was performed as a measure of lipid peroxidation.[18] Briefly, sodium nitroprusside was used to induce lipid peroxidation. The malondialdehyde, a product of lipid peroxidation, reacts with thiobarbituric acid to form a chromophore that is detected by spectrophotometer at 532 nm.[18]

Statistical analysis: The results were analyzed using GraphPad Prism 8.0 software. Percentage of inhibition or ROS formation and lipid peroxidation were analyzed by one-way ANOVA analysis of variance followed by Tukey's post hoc test. Values of half maximal inhibitory concentration (IC_{50}) and maximal inhibition (I_{max}) were also calculated with GraphPad Prism 8.0 and were analyzed by one-way ANOVA analysis of variance followed by Tukey's post hoc test in order to compare the efficacy and potency of the compounds. Results are expressed as mean ± standard error medium (S.E.M) and were considered significant when $p < 0.05$.

Results and discussion

Initial experiments to optimize the reaction conditions were carried out using zidovudine **1** and ethyl acetoacetate **2a** as standard reaction substrates (Table 1). On the basis of the conditions described in our previous report,[19] we started the reaction screening with zidovudine **1** (0.3 mmol) and ethyl acetoacetate **2a** (0.33 mmol) in DMSO (0.6 mL), using 10 mol% of pyrrolidine as the organocatalyst, in reactions at room temperature and 70 °C (Table 1, Entries 1-2). Unfortunately, under these reaction conditions the desired product **3a** was not obtained in both experiments and the respective start materials **1** and **2a** were recovered. Similar results were obtained under identical reaction conditions using 10 mol% of Et_2NH as the organocatalyst[20] (Table 1, Entries 3-4).

Table 1 Optimization of the reaction conditions.[a]



Entry	Organocatalyst (mol%)	Temperature (°C)	Yield (%)[(b)]
1	Pyrrolidine (10)	25	nd
2	Pyrrolidine (10)	70	nd
3	Diethylamine (10)	25	nd
4	Diethylamine (10)	70	nd
5	DBU (10)	25	15
6	**DBU (10)**	**70**	**82**
7	DBU (20)	70	80
8	DBU (5)	70	53

[a] Reactions were performed with zidovudine **1** (0.3 mmol) and ethyl acetoacetate **2a** (0.33 mmol) in DMSO (0.6 mL) under an air atmosphere for 24 h. [b] Yields are given for isolated products. nd: not detected.

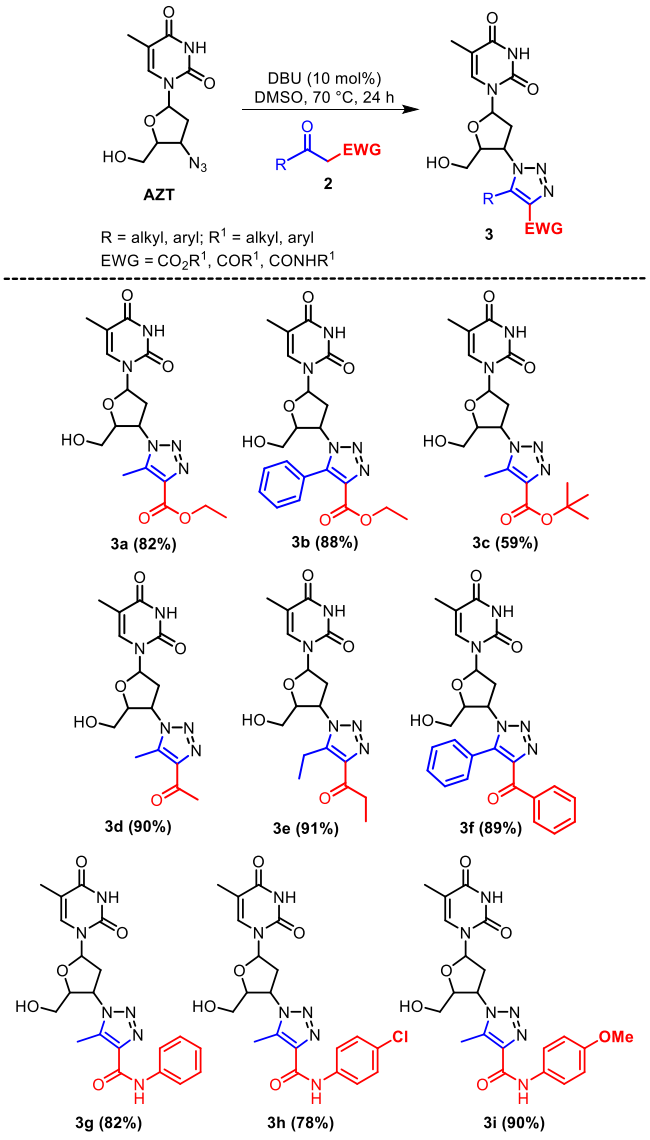
Another possibility for the organocatalytic [3 + 2] cycloadditions synthesis of 1,2,3-triazoles is by the enolate-azide pathway employing tertiary amines, such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene).[21] Using this 10 mol% of this organocatalyst, product **3a** was obtained 15% yield after 24 h at room temperature (Table 1, Entry 5). Inspired by this result,

Please do not adjust margins

Please do not adjust margins

additional experiments using DBU as the organocatalyst were performed. To our delight, a remarkable improvement in chemical yield (82% of **3a**) was achieved when the reaction was carried out at 70 °C (Table 1, Entry 6). Furthermore, on increasing the organocatalyst charge from 10 to 20 mol %, a slight decrease in the yield of compound **3a** was observed (Table 1, Entry 7). On reducing the catalyst charge from 10 to 5 mol %, a decrease in the reaction yield was observed, and in this case, there was incomplete consumption of starting materials (Table 1, Entry 8).

After analyzing these results, we determined that the best reaction conditions for obtaining 1,2,3-triazoyl-zidovudine derivative **3a** used zidovudine **1** (0.3 mmol), ethyl acetoacetate **2a** (0.33 mmol), DBU (10 mol%) as the organocatalyst, and DMSO (0.6 mL) as the solvent at 70 °C under an air atmosphere for 24 (Table 1, Entry 6).

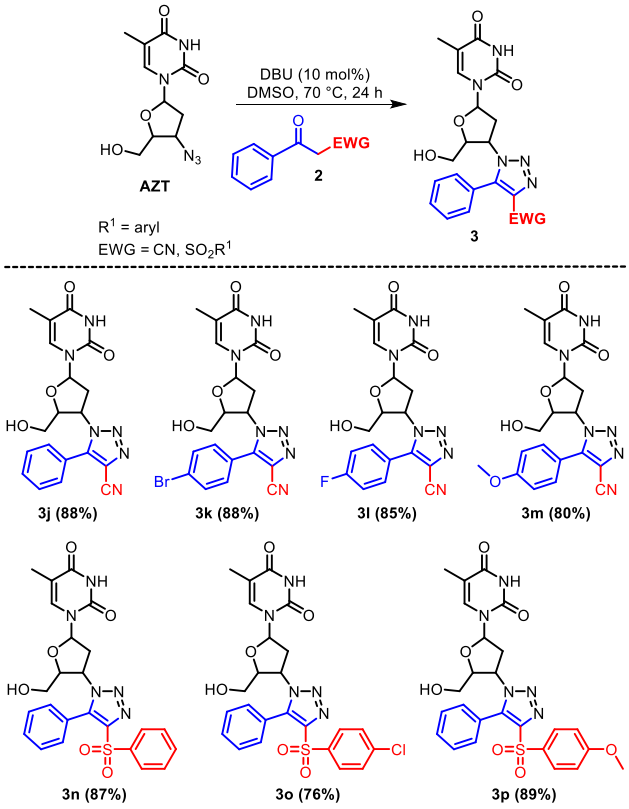


Scheme 2 Synthesis of 1,2,3-triazoyl-zidovudine derivatives **3a-i**.

The scope of the proposed methodology was then extended to a range of β-keto compounds **2**, such as β-keto-esters, β-diketones and β-keto-amides, under optimized reaction conditions (Scheme 2). Zidovudine **1** reacted efficiently with different β-keto-esters to give the corresponding 1,2,3-triazoyl-zidovudine carboxylates **3a-c** in moderate to good yields. High yields of desired 4-acyl-1,2,3-triazole zidovudine derivatives **3d-f** were obtained using β-diketones bearing methyl, ethyl and phenyl substituents. In addition, the reaction performed with 3-oxo-*N*-phenylbutanamide yielded the 1,2,3-triazoyl-zidovudine carboxamide **3g** in 82%. In addition, β-keto-amides containing either an electron-withdrawing group (EWG) or an electron-donating group (EDG) at the aromatic ring delivered the desired 1,2,3-triazoyl-zidovudine carboxamides **3h-j** in good isolated yields. The reactions were found to be slightly sensitive to electronic effects in the aromatic ring of β-keto-amides.

In the next series of experiments, we extend the applicability of the optimized reaction conditions reacting zidovudine **1** with α-keto-nitriles or β-keto-sulfones (Scheme 3). Our protocol worked well and were not sensitive to the electronic effect at the aromatic ring in the α-keto-nitriles. Consequently, α-keto nitriles containing EWG (4-Br and 4-F) and an EDG (4-OMe) at the aromatic ring delivered the corresponding 1,2,3-triazoyl-zidovudine carbonitriles **3j-m** in good yields.

Finally, when the reactions were carried out with β-keto-sulfones containing different electron demands, 4-sulfonyl-1,2,3-triazole zidovudine derivatives **3n-p** were obtained in yields ranging from 76% to 89%.



Scheme 3 Synthesis of 1,2,3-triazoyl-zidovudine derivatives **3j-p**.

Please do not adjust margins

Please do not adjust margins

All the synthesized molecules were screened for *in vitro* antioxidant activity; however, only 1,2,3-triazole zidovudine derivatives **3a**, **3d**, **3g** and **3l** showed antioxidant effects against ROS formation (Figure 2) and lipid peroxidation (Figures 3). The efficacy and potency of the compounds was analysed by comparing their half maximal inhibitory concentration (IC_{50}) and maximal inhibition (I_{max}), respectively.

Increased ROS formation induced by sodium azide was inhibited by compounds **3a**, **3d**, **3g**, and **3l**, both in the prefrontal cortex and hippocampus of mice. The compound **3a** was effective at concentrations ranging from 10 to 500 µM in the prefrontal cortex, but inhibited ROS formation only at 500 µM in hippocampus (Figure 2A). The compound **3d** was effective at concentrations ranging from 50 to 500 µM in the prefrontal cortex and at 100 and 500 µM in the hippocampus (Figure 2B). The compound **3g** was able to inhibit the formation of ROS at concentrations ranging from 50 to 500 µM in the prefrontal cortex and in the hippocampus of mice (Figure 2C). The compound **3l** presented antioxidant activity at concentrations ranging from 10 to 500 µM in prefrontal cortex and from 50 to 500 µM in the hippocampus (Figure 2D).

Based on the I_{max} values, the activity of these compounds follow the order **3a** ≥ **3d** ≥ **3l** ≥ **3g** in the prefrontal cortex and **3d** ≥ **3l** ≥ **3g** ≥ **3a** in the hippocampus of mice, indicating that all tested compounds presented similar potency in inhibiting ROS formation. Data regarding the efficacy of the compounds in inhibiting ROS formation was determined through IC_{50} values and is depicted in Table 2. In the prefrontal cortex, the compounds follow the order **3d** ≤ **3l** < **3a** = **3g** and the one-way ANOVA revealed significant differences between **3a** × **3d** ($p = 0.02$) and **3d** × **3g** ($p = 0.02$). The IC_{50} values in the hippocampus follow the order **3g** ≤ **3d** = **3l** < **3a** and one-way ANOVA revealed that all compounds were more efficient than compound **3a** ($p < 0.001$).

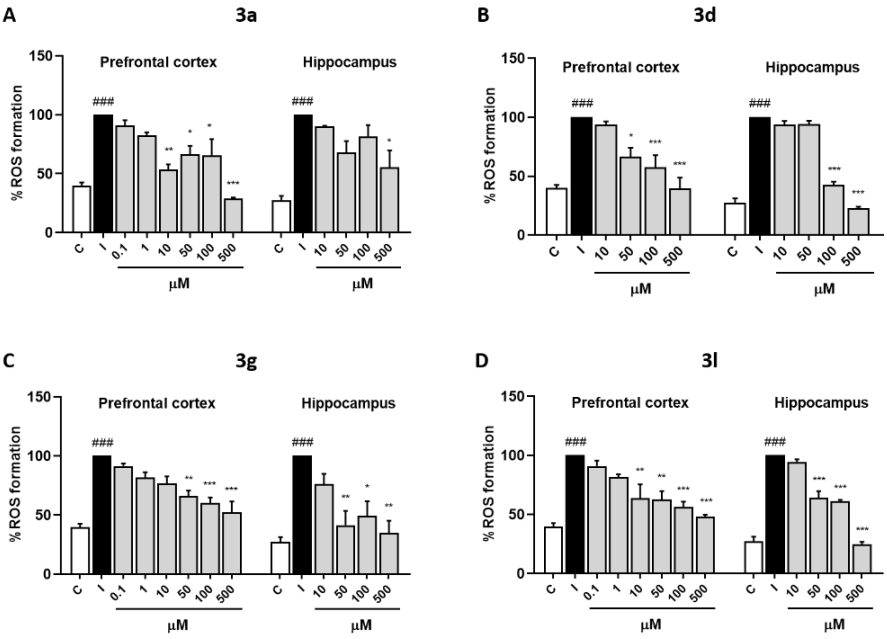


Figure 2. Levels of ROS formation (%) in the prefrontal cortex and hippocampus of mice. A) **3a**, B) **3d**, C) **3g** and D) **3l**. ### $p < 0.001$ when compared to the control group (white bars). *** $p < 0.001$, ** $p < 0.01$ and * $p < 0.05$ when compared with the induced group (black bars). Results are presented as mean ± S.E.M (n = 3 replicates). (One-way ANOVA followed by Tukey's post hoc test).

Table 2 Effect of 1,2,3-triazole zidovudine derivatives against ROS formation in the prefrontal cortex and hippocampus of mice indicated by half maximal inhibitory concentration (IC_{50}) and maximum inhibition (I_{max}).

Compounds	IC_{50} µM		I_{max} (%) 500 µM	
	Cortex	Hippocampus	Cortex	Hippocampus
3a	> 500	> 500	71.00±0.76	44.70±14.47
3d	200.80±48.55	128.00±25.72	60.60±9.42	77.00±1.05
3g	> 500	70.95±32.01	47.70±9.18	65.20±10.43
3l	295.90±96.25	138.00±34.52	51.70±1.24	75.40±2.20

IC_{50}: Required concentration to inhibit 50% of RS formation. N/A (not applicable). I_{max}: maximum inhibition (%) of RS formation at a concentration of 500 µM.

Here, sodium nitroprusside was used to induce lipid peroxidation in the prefrontal cortex and hippocampus of mice. As depicted in Figure 3A, the compound **3a** reduced the lipid peroxidation at concentrations ranging from 10 to 500 µM in the prefrontal cortex and from 50 to 500 µM in the hippocampus of mice. Compound **3d** inhibited TBARS formation at concentrations ranging from 50 to 500 µM in both brain structures (Figure 3B). Compound **3g** was effective at inhibiting TBARS in the prefrontal cortex at concentrations ranging from 10 to 500 µM and at 100 and 500 µM in the hippocampus (Figure 3C). As depicted in Figure 3D, the compound **3l** reduced the lipid peroxidation at concentrations ranging from 1 to 500 µM in the prefrontal cortex and from 50 to 500 µM in the hippocampus of mice. The I_{max} values for the 1,2,3-triazole zidovudine derivatives follow the order **3l** ≥ **3a** ≥ **3d** ≥ **3g** in the

Please do not adjust margins

Please do not adjust margins

prefrontal cortex and **3a** ≥ **3l** ≥ **3g** ≥ **3d** in the hippocampus, indicating that all compounds present similar potency at inhibiting lipid peroxidation in both brain structures. Data regarding the efficacy of the compounds in inhibiting lipid peroxidation was determined through IC_{50} values and is depicted in Table 3. In the prefrontal cortex, the compounds follow the order **3l** < **3g** ≤ **3a** ≤ **3d** and the one-way ANOVA revealed significant difference only between compounds **3l** × **3d** ($p = 0.02$). The IC_{50} values in the hippocampus follow the order **3a** ≤ **3l** ≤ **3g** ≤ **3d** and the one-way ANOVA revealed a statistically significant difference between **3a** × **3d** ($p = 0.02$) and **3a** × **3g** ($p = 0.04$).

Oxidative stress is present as a consequence of reduced antioxidant defenses and/or increased ROS generation.[22] Excessive ROS can lead to damage in biomolecules such as, lipids, proteins, carbohydrates and DNA, which can trigger the development and progression of several pathologies. Taken together, these results indicate that the 1,2,3-triazoyl-zidovudine derivatives tested here present antioxidant proprieties, opening up possibilities of translation of these compounds to treatment of several pathologies related to oxidative stress, such as, major depressive disorder, anxiety, multiple sclerosis, and Alzheimer disease. In accordance to our results, some authors reported previously *in vitro* antioxidant effects of other zidovudine derivatives, showing that they can neutralize the ROS formation.[10b,10c] The antioxidant activity of these compounds emphasizes the importance of investigating them as potential pharmacological strategies against oxidative stress in the brain, which is often found in psychiatric and neurodegenerative diseases.

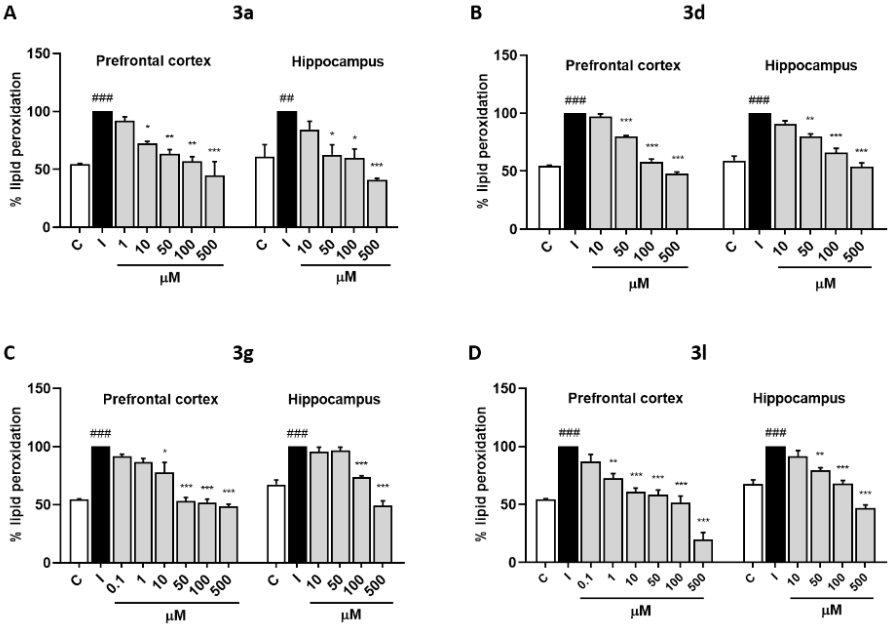


Figure 3. Levels of lipid peroxidation (%) in prefrontal cortex and hippocampus of mice. A) **3a**, B) **3d**, C) **3g** and D) **3l**. ### p <0.001 and ## p <0.01 when compared to the control group (white bras). *** p < 0.001, ** p < 0.01 and * p < 0.05 when compared to the induced group (black bars). Results are presente d as mean ± S.E.M (n = 3 replicates). (One-way ANOVA followed by Tukey's post hoc test).

Table 3 Effect of 1,2,3-triazole zidovudine derivatives against TBARS formation in the prefrontal cortex and hippocampus of mice indicated by half maximal inhibitory concentration (IC_{50}) and maximum inhibition (I_{max}).

Compounds	IC_{50} μM		I_{max} (%) 500 μM	
	Cortex	Hippocampus	Cortex	Hippocampus
3a	236.10±61.45	214.60±52.60	55.10±11.90	59.00±1.29
3d	334.80±60.55	> 500	52.00±1.27	46.20±3.40
3g	201.20±50.15	461.40±68.40	51.40±1.92	50.70±3.99
3l	48.47±13.16	388.70±54.14	80.10±5.98	53.20±2.70

IC_{50}: Required concentration to inhibit 50% of TBARS formation. I_{max}: maximum inhibition (%) of TBARS formation at a concentration of 500 μM. Results are presented as mean ± S.E.M (n = 3 replicates). (One-way ANOVA followed by Tukey's post hoc test).

Conclusions

In summary, the organocatalyzed synthesis and preliminary results of antioxidant activities of hybrids containing zidovudine and the 1,2,3-triazole nucleus were described. These new compounds were regioselectively synthesized in moderate to excellent yields (59-91% yield) by the reaction of zidovudine with a range of keto compounds, such as β-keto-esters, β-diketones, β-keto-amides, α-keto-nitriles and β-keto-sulfones. Noteworthy, the synthesized compounds were able to inhibit the production of reactive species and lipid peroxidation in the prefrontal cortex and hippocampus of mice. These results emphasize the importance of investigating 1,2,3-triazole zidovudine derivatives as potential pharmacological strategies against oxidative stress in the brain, which is often found in psychiatric and neurodegenerative diseases. Further studies are needed to better characterize the pharmacological potential of these compounds.

Please do not adjust margins

Please do not adjust margins

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for the financial support and scholarships from the Brazilian agencies CNPq (310943/2016-7, 409782/2018-1 and 308015/2019-3), FAPERGS (PRONEM 16/2551-0000240-1) and FINEP. This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001. CNPq is also acknowledged for the fellowship for O.E.D.R., L.S. and D.A. We are grateful to Prof. Thiago Barcellos from University of Caxias do Sul (UCS) for providing the HRMS analysis.

Notes and references

(a) W. Dehaen and V. A. Bakulev, *Chemistry of 1,2,3-triazoles*, Springer International Publishing, New York, 1st ed., 2014. For a recent set of reviews in this area, see themed issues: (b) *Chem. Soc. Rev.*, 2010, **39**, 1221. (c) *Acc. Chem. Res.*, 2011, **44**, 651.

(a) F. Cui, J. Chen, Z. Mo, S. Su, Y. Chen, X. Ma, H. Tang, H. Wang, Y. Pan and Y. Xu, *Org. Lett.*, **20**, 925. (b) K. R. Begnini, W. R. Duarte, L. P. Silva, J. H. Bussa, B. S. Goldani, M. Fronza, N. V. Segatto, D. Alves, L. Savegnago, F. K. Seixas and T. Collares, *Biomed. Pharmacother.*, 2017, **91**, 510. (c) J. Xie and C. T. Seto, *Bioorg. Med. Chem.*, 2007, **15**, 458. (d) T. Lee, M. Cho, S. Y. Ko, H. J. Youn, D. J. Baek, W. J. Cho, C. Y. Kang and S. Kirn, *J. Med. Chem.*, 2007, **50**, 585. (e) B. Parrish and T. Emrick, *Bioconjugate Chem.*, 2007, **18**, 263. (f) N. Pokhodylo, O. Shyyka and V. Matiychuk, *Med. Chem. Res.*, 2014, **23**, 2426. (g) E. A. Wilhelm, N. C. Machado, A. B. Pedroso, B. S. Goldani, N. Seus. S. Moura, L. Savegnago, R. G. Jacob and D. Alves, *RSC Adv*., 2014, **4**, 41437. (h) S. R. Chavan, K. S. Gavale, A. Khan, R. Joshi, N. Kumbhar D. Chakravarty and D. D. Dhavale, *ACS Omega*, 2017, **2**, 7203. (i) C. D. Hein, X. M. Liu and D. Wang, *Pharm. Res.*, 2008, **25**, 2216. (j) G. C. Tron, T. Pirali, R. A. Billington, P. L. Canonico, G. Sorba and A. A. Genazzani, *Med. Res. Rev.*, 2008, **28**, 278.

R. Huisgen, *Angew. Chem., Int. Ed.* 1963, **2**, 565.

Selected papers: (a) V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem. Int. Ed.*, 2002, **41**, 2596. (b) C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057. (c) A. Krasinski, Z. Radic, R. Manetsch, J. Raushel, P. Taylor, K. B. Sharpless and H. C. Kolb, *J. Am. Chem. Soc.*, 2005, **127**, 6686. (d) L. V. Lee, M. L. Mitchell, S. Huang, V. V. Fokin, K. B. Sharpless and C. Wong, *J. Am. Chem. Soc.*, 2003, **125**, 9588. (e) J. E. Hein, J. P. Tripp, L. B. Krasnova, K. B. Sharpless and V. V. Fokin, *Angew. Chem. Int. Ed.*, 2009, **48**, 8018. (f) L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin and G. Jia, *J. Am. Chem. Soc.*, 2005, **127**, 15998. (g) B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia and V. V. Fokin, *J. Am. Chem. Soc.*, 2008, **130**, 8923. (h) J. McNulty, K. Keskar and R. Vemula, *Chem. Eur. J*. 2011, **17**, 14727. (i) J. McNulty and K. Keskar, *Eur. J. Org. Chem.*, 2012, 5462. (j) S. Ding, G. Jia and J. Sun, *Angew. Chem. Int. Ed.*, 2014, **53**, 1877.

(a) J. A. Johnson, J. M. Baskin, C. R. Bertozzi, J. T. Koberstein and N. J. Turro, *Chem. Commun.*, 2008, 3064. (b) J. M. Baskin and C. R. Bertozzi, *QSAR Comb. Sci.*, 2007, **26**, 1211. (c) J. Gierlich, G. A. Burley, P. M. E. Gramlich, D. M. Hammond and T. Carell, *Org. Lett.*, 2006, **8**, 3639. (d) L. M. Gaetke and C. K. Chow, *Toxicology*, 2003, **189**, 147. (e) A. J. Link, M. K. S. Vink and D. A. Tirrell, *J. Am. Chem. Soc.*, 2004, **126**, 10598.

(a) M. F. Debets, S. S. Van Berkel, J. Dommerholt, A. J. Dirks, F. P. J. T. Rutjes and F. L. Van Delft, *Acc. Chem. Res.*, 2011, **44**, 805. (b) J. M. Baskin and C. R. Bertozzi, *Aldrichimica Acta*, 2010, **43**, 15.

(a) C. G. S. Lima, A. Ali, S. S. van Berkel, B. Westermann and M. W. Paixão, *Chem. Commun.*, 2015, **51**, 10784. (b) S. S. V. Ramasastry, *Angew. Chem., Int. Ed.*, 2014, **53**, 14310. (c) J. John, J. Thomas and W. Dehaen, *Chem. Commun.*, 2015, **51**, 10797.

W. Ostertag, G. Roesler, C. J. Krieg, J. Kind, T. Cole, T. Crozier, G. Gaedicke, G. Steinheider, N. Kluge and S. Dube, *Proc. Natl. Acad. Sci. U.S.A.,* 1974, **71**, 4980.

M. S. Kinch and E. Patridge, *Drug Discov. Today*, 2014, **19**, 1510.

Some examples: (a) L. Zhang, L. Zhang, T. Luo, J. Zhou, L. Sun and Y. Xu, *ACS Comb. Sci.*, 2012, **14**, 108. (b) D. Souza, D. O. C. Mariano, F. Nedel, E. Schultze, V. F. Campos, F. K. Seixas, R. S. Silva, T. S. Munchen, V. Ilha, L. Dornelles, A. L. Braga, J. B. T. Rocha, T. Collares and O. E. D. Rodrigues, *J. Med. Chem.,* 2015, **8,** 3329. (c) R. M. Rosa, B. C. Piccoli, F. D. Silva, L. Dornelles, J. B. T. Rocha, M. S. Sonego, K. R. Begnini, T. Collares, F. K. Seixas and O. E. D. Rodrigues, *Med. Chem. Commun.*, 2017, **8**, 408. (d) V. K. Sharma, S. K. Singh, P. M. Krishnamurthy, J. F. Alterman, R. A. Haraszti, A. Khvorova, A. K. Prasad and J. K. Watts, *Chem. Commun.*, 2017, **53**, 8906. (e) S. M. Park, J. Woo, E. Jeon and B. H. Kim, *Chem. Commun.*, 2010, **46**, 1523. (f) T. O. Olomola, R. Klein and P. T. Kaye, *Tetrahedron Lett.*, 2014, **70**, 9449. (g) M. H. Manyeruke, T. O. Olomola, S. Majumder, S. Abrahams, M. Isaacs, N. Mautsa, S. Mosebi, D. Mnkandhla, R. Hewer, H. C. Hoppe, R. Klein and P. T. Kaye, *Bioorg. Med. Chem.*, 2015, **23**, 7521. (h) T. A. D. Thi, N. T. K. Tuyet, C. P. The, H. T. Nguyen, C. B. Thi, T. D. Duy, M. D'hooghe and T. V. Nguyen, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 5190. (i) D. Baraniak, K. Kacprzak and L. Celewicz, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 723. (j) S. K. V. Vernekar, L. Qiu, J. Zacharias, R. J. Geraghty and Z. Wang, *Med. Chem. Commun.*, 2014, **5**, 603.

(a) A. Ayati, S. Emami and A. Foroumadi, *Eur. J. Med. Chem.*, 2016, **109**, 380. (b) D. Dheer, V. Singh and R. Shankar, *Bioorg. Chem.*, 2017, **71**, 30. (c) R. Kharb, P. C. Sharma and M. S. Yar, *J. Enzyme Inhib. Med. Chem.*, 2011, **26**, 1.

S. K. Vernekar, L. Qiu, J. Zhang, J. K. H. Li, R. J. Geraghty and Z. Wang, *J. Med. Chem.*, 2015, **58**, 4016.

J. Lin, V. Roy, L. Wanga, L. You, L. Agrofoglio, D. Deville-Bonne, T. McBrayer, S. Coats, R. Schinazi and S. Eriksson, S. *Bioorg. Med. Chem.*, 2010, **18**, 3261.

J. M. Kumar, M. M. Idris, G. Srinivas, P. V. Kumar, V. Meghah, M. Kavitha, C. R. Reddy, P. S. Mainkar, B. Pal, S. Chandrasekar and N. Nagesh, *Plos One*, 2013, **8**, e70798.

V. R. Sirivolu, S. K. V. Vernekar, T. Ilina, N. S. Myshakina, M. A. Parniak and Z. Wang, *J. Med. Chem.*, 2013, **56**, 8765.

J. Thomas, V. Goyvaerts, S. Liekens and W. Dehaen, *Chem. Eur. J.*, 2016, **22**, 9966.

H. Ohkawa, N. Ohishi and K. Yagi, *Anal. Biochem.*, 1979, 95351.

C. Loetchutinat, S. Kothan, S. Dechsupa, J. Meesungnoen, J. -P. Jay-Gerin and S. Mankhetkorn, *Radiat. Phys. Chem.*, 2005, **72**, 323.

(a) M. T. Saraiva, G. P. Costa, N. Seus, R. F. Schumacher, G. Perin, M. W. Paixão, R. Luque and D. Alves, *Org. Lett.*, 2015, **17**, 6206. (b) M. T. Saraiva, R. Krüger, R. S. M. Baldinotti, E. J. Lenardão, C. Luchese, L. Savegnago, E. A. Wilhelm and D. Alves, *J. Braz. Chem. Soc.*, 2016, **27**, 41.

(a) N. Seus, B. Goldani, E. J. Lenardão, L. Savegnago, M. W. Paixão and D. Alves, *Eur. J. Org. Chem.*, 2014, 1059. (b) N. Seus, L. C. Gonçalves, A. M. Deobald, L. Savegnago, D. Alves and M. W.

Please do not adjust margins

Please do not adjust margins

Paixão, *Tetrahedron*, 2012, **68**, 10456. (c) D. M. Xavier, B. S. Goldani, N. Seus, R. G. Jacob, T. Barcellos, M. W. Paixão, R. Luque and D. Alves, *Ultrason. Sonochem.*, 2017, **34**, 107.

A. Ali, A. G. Correa, D. Alves, J. Zukerman-Schpector, B. Westermann, M. A. B. Ferreira, M. W. Paixão, *Chem. Commun.*, 2014, **50**, 11926.

L. Mandelker, *Vet. Clin. North Am. Small Anim. Pract.*, 2008, **38**, 199.

R. M. Freitas, F. C. F. Sousa, S. M. M. Vasconcelos, G. S. B. Viana and M. M. F. Fonteles, *Pharmacol. Biochem. Behav.* 2004, **78**, 327.

Please do not adjust margins

Organocatalysis in the synthesis of 1,2,3-triazoyl-zidovudine derivatives: synthesis and antioxidant activity

Carolina B. Gomes,[a] Renata A. Balaguez,[a] Allya M. E. Larroza,[a] Thiago A. Smaniotto,[b] Micaela Domingues,[b] Angela M. Casaril,[b] Márcio S. Silva,[a] Oscar E. D. Rodrigues,[c] Lucielli Savegnago[b] and Diego Alves*[a]

[a] *Laboratório de Síntese Orgânica Limpa, Universidade Federal de Pelotas, UFPel. PO Box 354 - CEP 96010-900, Pelotas, RS, Brazil.*

[b] *Programa de Pós-Graduação em Biotecnologia (PPGB), Grupo de Pesquisa em Neurobiotecnologia - GPN, Universidade Federal de Pelotas, UFPel, Postal Code 96010-900, Pelotas, RS, Brazil.*

[c] *LabSelen-NanoBio - Departamento de Química, Universidade Federal de Santa Maria, UFSM, 97115-900, Santa Maria, RS, Brazil.*

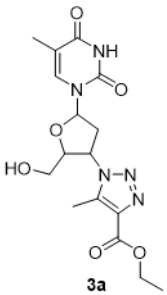
***Corresponding author:** E-mail: diego.alves@ufpel.edu.br, Phone / Fax: (+) 55 53 32757533.

Contents

General Information: The reactions were monitored by TLC carried out on Merck silica gel (60 F254) by using UV light as visualizing agent and 5% vanillin in 10% H_2SO_4 and heat as developing agents. Hydrogen nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 400 MHz on Bruker Avance III HD 400 spectrometer. Spectra were recorded in DMSO-d_6 solutions. Chemical shifts are reported in ppm, referenced to tetramethylsilane (TMS) as the external reference. Coupling constants (*J*) are reported in Hertz. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of double doublets), t (triplet), q (quartet) and m (multiplet). Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 100 MHz on Bruker Avance III HD 400 spectrometer. Chemical shifts are reported in ppm, referenced to the solvent peak of DMSO-d_6. Low-resolution mass spectra were obtained with a Shimadzu GC-MS-QP2010 mass spectrometer. High resolution mass spectra (HRMS) were recorded on a Bruker Micro TOF-QII spectrometer 10416. The solvents and reagents were used as received or purified using standard procedures.

General procedure for the synthesis of 1,2,3-triazoyl-zidovudine derivatives 3a-p: The appropriate keto compound **2** (0.36 mmol) was first added to a solution of zidovudine **1** (0.3 mmol) in DMSO (0.6 mL), followed by DBU (10 mol %) as catalyst. The reaction mixture was stirred in an open flask at 70 °C for 24 hours. After completion of the reaction, the crude product was purified by column chromatography on silica gel with a mixture of hexane/ethyl acetate (1:2) as eluent to afford the desired product **3a-p**. Spectral data for the products prepared are listed below.

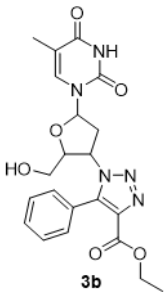
Spectral data of the products:



3a

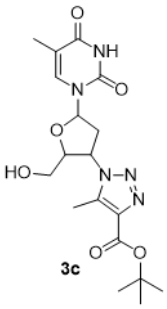
Ethyl 1-(2-(hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate 3a. Yield: 0.093 g (82%); Yellow solid; mp 203-205 °C. ^{1}H NMR ^{1}H (400 MHz, DMSO-d_6) δ (ppm): 11.41 (s, 1H), 7.86 (s, 1H), 6.56-6.53 (m, 1H), 5.39 (s, 1H), 5.28-5.26 (m, 1H), 4.37 (q, *J*

= 7.0 Hz, 2H), 4.32-4.31 (m, 1H), 3.77-3.68 (m, 2H), 2.84-2.78 (m, 1H), 2.74-2.68 (m, 1H), 2.63 (s, 3H), 1.87 (s, 3H), 1.36 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.8, 161.2, 150.5, 139.1, 136.1, 135.7, 109.8, 84.5, 84.4, 61.1, 60.4, 57.7, 36.8, 14.2, 12.3, 8.8. MS (relative intensity) m/z: 381 (M^+48), 225 (5), 192 (46), 190 (100), 188 (50), 156 (46), 154 (26). HRMS-ESI: *m/z* calculated for $C_{16}H_{22}N_5O_6$ [M + H]$^+$: 380.1580. Found: 380.1567.



3b

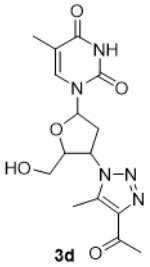
Ethyl 1-(2-(hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)-5-phenyl-1*H*-1,2,3-triazole-4-carboxylate 3b. Yield: 0.117 g (88%); Yellow solid; mp 82-84 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.31 (s, 1H), 7.74 (s, 1H), 7.57-7.50 (m, 5H), 6.56-6.53 (m, 1H), 5.17-5.15 (m, 1H), 4.92-4.90 (m, 1H), 4.41-4.40 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.57-3.51 (m, 1H), 3.42-3.37 (m, 1H), 2.73-2.54 (m, 2H), 1.76 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.6, 160.2, 150.4, 141.0, 136.3, 136.0, 130.2, 130.0, 128.4, 125.7, 109.7, 84.7, 84.6, 61.3, 60.2, 58.9, 37.4, 13.8, 12.2. MS (relative intensity) m/z: 441 (M^+ 3), 316 (25), 316 (25), 225 (2), 219 (13), 218 (100), 217 (7), 172 (41). HRMS-ESI: *m/z* calculated for $C_{21}H_{24}N_5O_6$ [M + H]$^+$: 442.1727. Found: 442.1726.



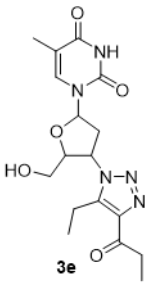
3c

***tert*-Butyl 1-(2-(hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3-yl)-5-methyl-1H-1,2,3-triazole-4-carboxylate 3c**. Yield: 0.072 g (59%); Orange liquid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.36 (s, 1H), 7.80 (s, 1H), 6.50-6.46 (m, 1H), 6.33-6.30 (m, 1H), 5.21-5.16 (m, 1H), 4.26-4.23 (m, 1H), 3.73-3.6 (m, 2H), 2.76-2.70 (m, 1H), 2.67-2.59 (m, 1H), 2.54 (s,

3H), 1.81 (s, 3H), 1.54 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 163.8, 160.4, 150.5, 138.4, 136.7, 136.1, 109.8, 84.5, 84.4, 81.2, 61.1, 57.6, 36.8, 27.9, 12.3, 8.9. MS (relative intensity) m/z: 407 (M+ 1), 334 (0.3), 264 (19), 224 (3), 182 (16), 139 (12), 127 (19), 99 (100).HRMS-ESI: *m/z* calculated for $C_{16}H_{26}N_5O_6$ [M + H]$^+$: 408.1883. Found: 408.1890.

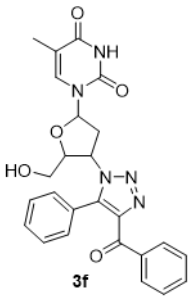


1-(4-(4-Acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione 3d. Yield: 0.094 g (90%); beige solid; mp 212-214 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): δ 11.44 (s, 1H), 7.90 (s, 1H), 6.61-6.58 (m, 1H), 5.42 (s, 1H), 5.32-5.28 (m, 1H), 4.37-4.34 (m, 1H), 3.81-3.71 (m, 2H), 2.88-2.80 (m, 1H), 2.78-2.70 (m, 1H), 2.67 (s, 3H), 2.66 (s, 3H), 1.91 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 193.2, 163.5, 150.3, 142.6, 137.3, 135.9, 109.5, 84.2, 84.1, 60.8, 57.2, 36.5, 27.3, 12.1, 8.5. MS (relative intensity) m/z: 349 (M$^+$ 6), 225 (14), 224 (100), 206 (9), 156 (13). HRMS-ESI: *m/z* calculated for $C_{15}H_{20}N_5O_5$ [M + H]$^+$: 350.1464. Found: 350.1470.



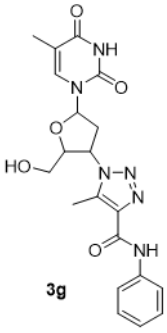
1-(4-(5-Ethyl-4-propionyl-1*H*-1,2,3-triazol-1-yl)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione 3e. Yield: 0.103 g (91%); White solid; mp 188-190 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 11.27 (s, 1H), 7.78 (s, 1H), 6.54-6.51 (m, 1H), 5.31 (s, 1H), 5.25-5.21 (m, 1H), 4.31-4.30 (m, 1H), 3.73-3.61 (m, 2H), 3.10-2.96 (m, 4H), 2.73-2.63 (m, 2H), 1.82 (s, 3H), 1.15-1.08 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 195.9, 163.6, 150.4, 142.3, 141.7, 136.1, 109.7, 84.51, 84.48, 61.0, 57.2, 37.3, 32.4, 15.9, 12.7, 12.2, 7.8. MS (relative intensity) m/z: 377 (M$^+$ 11), 253 (10), 252 (68), 155 (9), 154 (100). HRMS-ESI: *m/z* calculated for

$C_{17}H_{24}N_5O_5$ [M + H]$^+$: 378.1777. Found: 378.1791.



3f

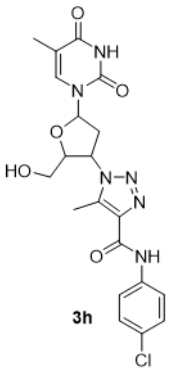
1-(4-(4-Benzoyl-5-phenyl-1*H*-1,2,3-triazol-1-yl)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione 3f. Yield: 0.127 g (89%); White solid; mp 210-212 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 11.37 (s, 1H), 8.10 (d, J = 7.2 Hz, 2H), 7.77 (s, 1H), 7.68-7.64 (m, 1H), 7.56-7.52 (m, 7H), 6.64-6.60 (m, 1H), 5.25-5.22 (m, 1H), 5.00-4.98 (m, 1H), 4.48-4.46 (m, 1H), 3.60-3.55 (m, 1H), 3.46-3.41 (m, 1H), 2.77 (ddd, J = 13.7, 5.9, 1.9 Hz, 1H), 2.58-2.56 (m, 1H), 1.77 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 186.1, 163.7, 150.5, 143.0, 141.3, 136.9, 136.1, 133.2, 130.2, 130.1, 130.0, 128.7, 128.4, 125.9, 109.8, 84.8, 84.7, 61.4, 58.9, 37.5, 12.3. MS (relative intensity) m/z: 473 (M$^+$ 9), 349 (6), 348 (27), 251 (17), 250 (100), 249 (11), 248 (6), 172 (16). HRMS-ESI: *m/z* calculated for $C_{25}H_{24}N_5O_5$ [M + H]$^+$: 474.1777. Found: 474.1790.



3g

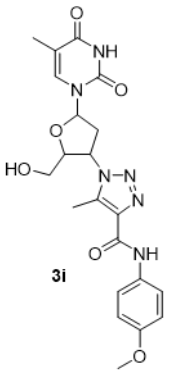
1-(2-(Hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)-5-methyl-*N*-phenyl-1*H*-1,2,3-triazole-4-carboxamide 3g. Yield: 0.105 g (82%); White solid; mp 110-112 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 11.37 (s, 1H), 10.35 (s, 1H), 7.82-7.81 (m, 3H), 7.35-7.31 (m, 2H), 7.11-7.07 (m, 1H), 6.53-6.50 (m, 1H), 5.36 (t, J = 5.1 Hz, 1H), 5.26-5.22 (m, 1H), 4.33-4.30 (m, 1H), 3.76-3.64 (m, 2H), 2.80-2.74 (m, 1H), 2.71-2.65 (m, 1H), 2.63 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 163.8, 159.6, 150.5, 138.6, 138.2, 137.4, 136.1, 128.6, 123.7, 120.4, 109.8, 84.5, 84.4, 61.1, 57.6, 36.9, 12.4, 8.5. MS (relative intensity) m/z: 426 (M$^+$26), 301 (11), 225 (2), 204 (12), 203 (100), 202 (15). HRMS-ESI: *m/z* calculated for $C_{20}H_{23}N_6O_5$ [M

+ H]$^+$: 427.1730. Found: 427.1741.



3h

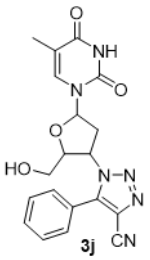
***N*-(4-Chlorophenyl)-1-(2-(hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)-5-methyl-1*H*-1,2,3-triazole-4-carboxamide 3h**. Yield: 0.108 g (78%); White solid; mp 248-250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 11.24 (s, 1H), 10.42 (s, 1H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.69 (s, 1H), 7.26 (d, *J* = 8.8 Hz, 2H), 6.40-6.36 (m, 1H), 5.26 (s, 1H), 5.13-5.11 (m, 1H), 4.18-4.17 (m, 1H), 3.58-3.51 (m, 2H), 2.66-2.60 (m, 1H), 2.57-2.54 (m, 1H), 2.50 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 163.8, 159.7, 150.5, 138.1, 137.6 (2C), 136.2, 128.5, 127.4, 122.0, 109.8, 84.5, 84.3, 61.2, 57.7, 36.9, 12.4, 8.5. MS (relative intensity) m/z: 460 (M$^+$ 31), 335 (10), 239 (32), 238 (20), 237 (100), 236 (25), 235 (2), 225 (5), 154 (8). HRMS-ESI: *m/z* calculated for $C_{20}H_{22}ClN_6O_5$ [M + H]$^+$: 461.1340.



3i

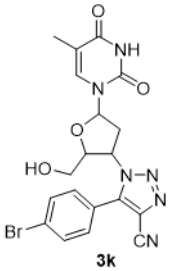
1-(2-(Hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)-*N*-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxamide 3i. Yield: 0.123 g (90%); White solid; mp 106-108 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.33 (s, 1H), 10.20 (s, 1H), 7.81 (s, 1H), 7.71 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.53-6.49 (m, 1H), 5.34-5.32 (m, 1H), 5.25-5.23 (m, 1H), 4.31-4.30 (m, 1H), 3.74 (s, 3H), 3.71-3.64 (m, 2H), 2.80-2.72 (m, 1H), 2.71-2.65 (m, 1H), 2.62 (s, 3H), 1.83 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.7, 159.2, 155.6, 150.4, 138.3, 137.0, 136.1, 131.6, 122.0, 113.7, 109.7, 84.4, 84.3, 61.1, 57.5, 55.2, 36.8, 12.2,

8.4. MS (relative intensity) m/z: 457 (M^+ 24), 456 (100), 234 (8), 233 (40), 232 (15), 225 (3), 150 (4). HRMS-ESI: *m/z* calculated for $C_{21}H_{25}N_6O_6$ [M + H]$^+$: 457.1836. Found: 457.1833.



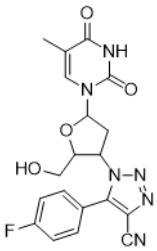
3j

1-(2-(Hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)-5-phenyl-1*H*-1,2,3-triazole-4-carbonitrile 3j. Yield: 0.104 g (88%); Yellow solid; mp 102-104 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 11.36 (s, 1H), 7.76 (s, 1H), 7.69-7.65 (m, 5H), 6.55-6.51 (m, 1H), 5.27-5.25 (m, 1H), 5.15-5.12 (m, 1H), 4.47-4.45 (m, 1H), 3.62-3.56 (m, 1H), 3.52-3.47 (m, 1H), 2.76 (ddd, *J* = 14.0, 6.1, 2.4 Hz, 1H), 2.64-2.56 (m, 1H), 1.77 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 163.7, 150.5, 144.1, 136.1, 131.3, 129.6, 129.5, 123.0, 119.4, 112.4, 109.8, 84.7, 84.5, 61.3, 59.8, 37.5, 12.3. MS (relative intensity) m/z: 394 (M^+ 4), 270 (17), 269 (100), 225 (0.8), 201 (12), 171 (45), 170 (8). HRMS-ESI: *m/z* calculated for $C_{19}H_{19}N_6O_4$ [M + H]$^+$: 395.1468. Found: 395.1467.



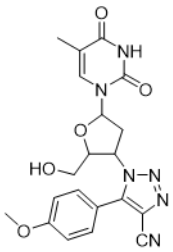
3k

5-(4-Bromophenyl)-1-(2-(hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)-1*H*-1,2,3-triazole-4-carbonitrile 3k. Yield: 0.125 g (88%); Orange solid; mp 222-224 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 10.31 (s, 1H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.50 (s, 1H), 7.35 (d, *J* = 8.6 Hz, 2H), 6.41-6.38 (m, 1H), 5.27-5.23 (m, 1H), 4.71 (s, 1H), 4.52-4.50 (m, 1H), 3.79-3.76 (m, 1H), 3.56-3.52 (m, 1H), 2.75 (ddd, *J* = 13.8, 6.5, 4.0 Hz, 1H), 2.66-2.62 (m, 1H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 164.0, 150.4, 142.8, 136.3, 132.9, 130.6, 126.0, 121.6, 120.2, 111.4, 110.8, 86.5, 84.7, 61.1, 58.7, 38.5, 12.3. MS (relative intensity) m/z: 472 (M^+ 5), 445 (4), 349 (97), 348 (18), 347 (100), 249 (24), 248 (23), 246 (1), 225 (2), 154 (9). HRMS-ESI: *m/z* calculated for $C_{19}H_{18}BrN_6O_4$ [M + H]$^+$: 473.0573. Found: 473.0578.



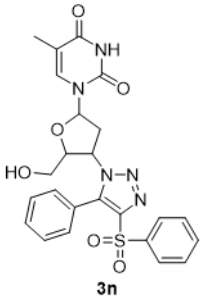
3l

5-(4-Fluorophenyl)-1-(2-(hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)-1*H*-1,2,3-triazole-4-carbonitrile 3l. Yield: 0.105 g (85%); Yellow solid; mp 124-126 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 10.80 (s, 1H),7.63-7.61 (m, 1H), 7.59-7.53 (m, 2H), 7.36-7.29 (m, 2H), 6.56-6.49 (m, 1H), 5.30-5.24 (m, 1H), 4.98 (s, 1H), 4.56-4.54 (m, 1H), 3.83-3.81 (m, 1H), 3.61-3.59 (m, 1H), 2.91-2.76 (m, 2H), 1.88-1.85 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 163.7, 163.6 (d, *J* = 251.6 Hz), 150.1, 142.5, 135.6, 131.1 (d, *J* = 8.8 Hz), 119.8, 118.4 (d, *J* = 3.46 Hz), 116.6 (d, *J* = 22.2 Hz), 111.2, 110.2, 85.4, 84.3, 60.8, 58.5, 38.1, 11.9. MS (relative intensity) m/z: 412 (M^+ 4), 287 (100), 189 (22), 159 (21), 288 (16), 225 (0.9), 188 (10). HRMS-ESI: *m/z* calculated for $C_{19}H_{18}FN_6O_4$ $[M + H]^+$: 413.1374. Found: 413.1370.

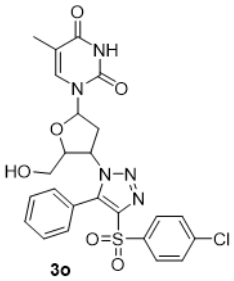


3m

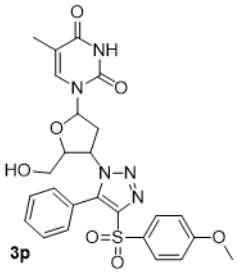
1-(2-(Hydroxymethyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl)-5-(4-methoxyphenyl)-1*H*-1,2,3-triazole-4-carbonitrile 3m. Yield: 0.102 g (80%); Orange solid; mp 195-197 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ(ppm): 10.78 (s, 1H), 7.66-7.64 (m, 1H), 7.47-7.43 (m, 2H), 7.11-7.09 (m, 2H), 6.57-6.51 (m, 1H), 5.31-5.28 (m, 1H), 4.96 (s, 1H), 4.56-4.54 (m, 1H), 3.90-3.76 (m, 4H), 3.64-3.52 (m, 1H), 2.94-2.83 (m, 1H), 2.81-2.69 (m, 1H), 1.88-1.86 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 163.7, 161.3, 150.2, 143.4, 135.7, 130.2, 119.5, 114.8, 114.1, 111.6, 110.3, 85.6, 84.4, 61.0, 58.4, 55.0, 38.3, 12.0. MS (relative intensity) m/z: 424 (M^+ 11), 299 (90), 231 (25), 225 (1), 201 (100), 200 (68). HRMS-ESI: *m/z* calculated for $C_{20}H_{21}N_6O_5$ $[M + H]^+$: 425.1573. Found: 425.1564.



1-(5-(Hydroxymethyl)-4-(5-phenyl-4-(phenylsulfonyl)-1*H*-1,2,3-triazol-1-yl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione 3n. Yield: 0.133 g (87%); Orange solid; mp 200-202 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.30 (s, 1H), 7.78-7.76 (m, 2H), 7.74-7.70 (m, 2H), 7.65-7.56 (m, 5H), 7.48-7.46 (m, 2H), 6.51-6.48 (m, 1H), 5.14-7.12 (m, 1H), 4.84-4.79 (m, 1H), 4.42-4.39 (m, 1H), 3.52-3.47 (m, 1H), 3.39-3.35 (m, 1H), 2.76-2.70 (m, 1H), 2.47-2.39 (m, 1H), 1.74 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.6, 150.4, 144.4, 140.3, 139.3, 136.0, 134.1, 130.6, 130.3, 129.5, 128.6, 127.4, 123.9, 109.7, 84.7, 84.4, 61.4, 59.6, 37.2, 12.2. MS (relative intensity) m/z: 509 (M^+ 1), 384 (15), 288 (6), 287 (17), 286 (100), 285 (5). HRMS-ESI: *m/z* calculated for $C_{24}H_{24}N_5O_6S$ $[M + H]^+$: 510.1447. Found: 510.1451.

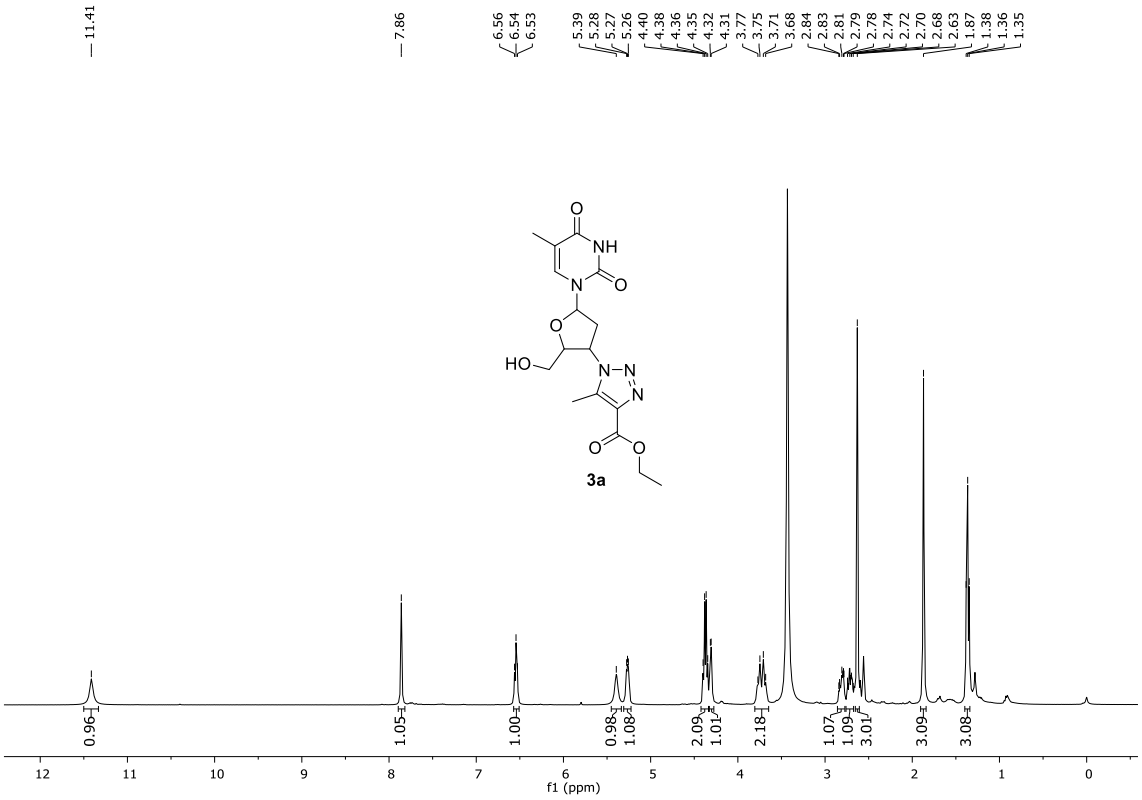


1-(4-(4-((4-Chlorophenyl)sulfonyl)-5-phenyl-1*H*-1,2,3-triazol-1-yl)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione 3o. Yield: 0.124 g (76%); Orange solid; mp 109-111 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.30 (s, 1H), 7.77-7.75 (m, 2H), 7.71-7.66 (m, 3H), 7.63-7.56 (m, 3H), 7.48-7.46 (m, 2H), 6.51-6.47 (m, 1H), 5.14-5.11 (m, 1H), 4.83-4.78 (m, 1H), 4.42-4.39 (m, 1H), 3.52-3.47 (m, 1H), 3.37-3.34 (m, 1H), 2.73 (dd, *J* = 12.3, 6.5 Hz, 1H), 2.47-2.40 (m, 1H), 1.74 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.6, 150.4, 144.1, 139.4, 139.2, 139.0, 136.0, 130.6, 130.3, 129.7, 129.4, 128.6, 123.8, 109.7, 84.6, 84.4, 61.3, 59.7, 37.2, 12.2. MS (relative intensity) m/z: 332 (18), 320 (48), 126 (18), 99 (64), 69 (100). HRMS-ESI: *m/z* calculated for $C_{24}H_{23}ClN_5O_6S$ $[M + H]^+$: 544.1058. Found: 544.1057.

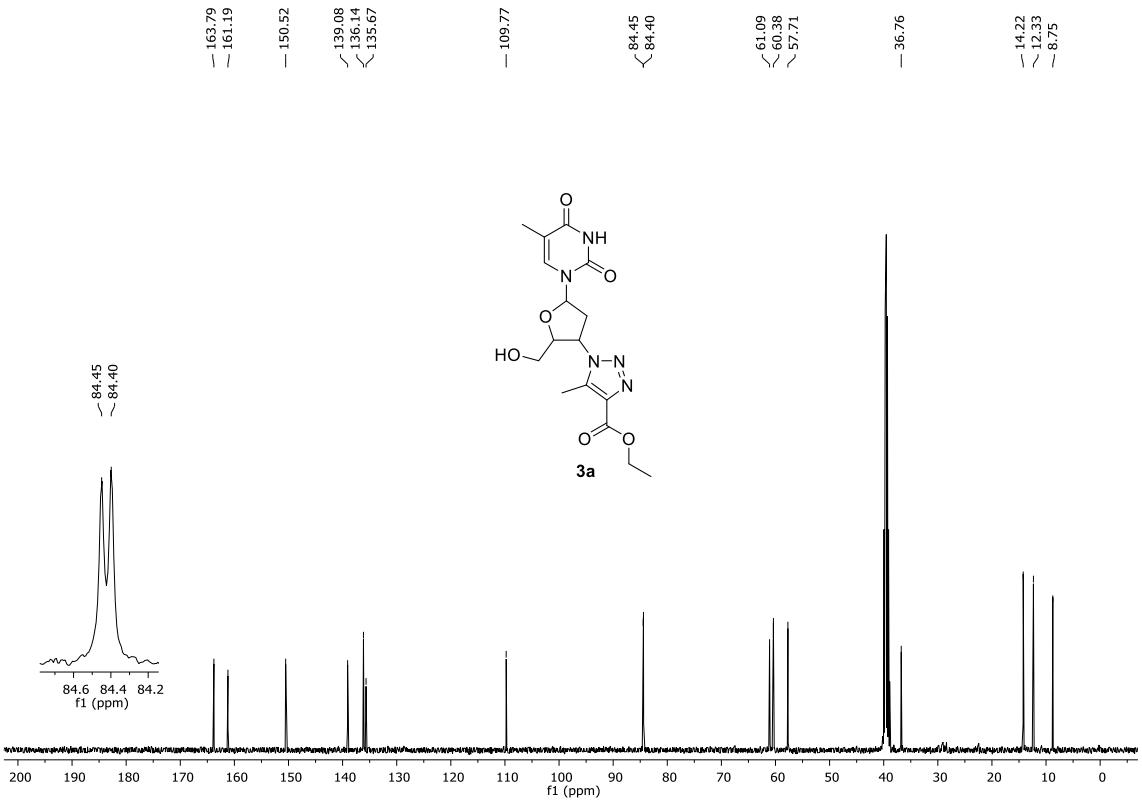


1-(5-(Hydroxymethyl)-4-(4-((4-methoxyphenyl)sulfonyl)-5-phenyl-1*H*-1,2,3-triazol-1-yl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione 3p. Yield: 0.144 g (89%); Orange solid; mp 111-113 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.30 (s, 1H), 7.71-7.67 (m, 3H), 7.64-7.56 (m, 3H), 7.47-7.46 (m, 2H), 7.10 (d, *J* = 9.0 Hz, 2H), 6.51-6.48 (m, 1H), 5.12 (s, 1H), 4.82-4.80 (m, 1H), 4.41-4.38 (m, 1H), 3.84 (s, 3H), 3.52-3.48 (m, 1H), 3.39-3.35 (m, 1H), 2.72 (dd, *J* = 14.4, 7.9 Hz, 1H), 2.47-2.41 (m, 1H), 1.75 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.6, 163.5, 150.4, 145.2, 138.7, 136.0, 131.7, 130.5, 130.3, 129.8, 128.6, 124.0, 114.7, 109.7, 84.6, 84.4, 61.3, 59.6, 55.8, 37.2, 12.1. MS (relative intensity) m/z: 539 (M^+3), 414 (15), 317 (19), 316 (100), 315 (11), 225 (2), 171 (17). HRMS-ESI: *m/z* calculated for $C_{25}H_{26}N_5O_7S$: $[M + H]^+$: 540.1553. Found: 540.1549.

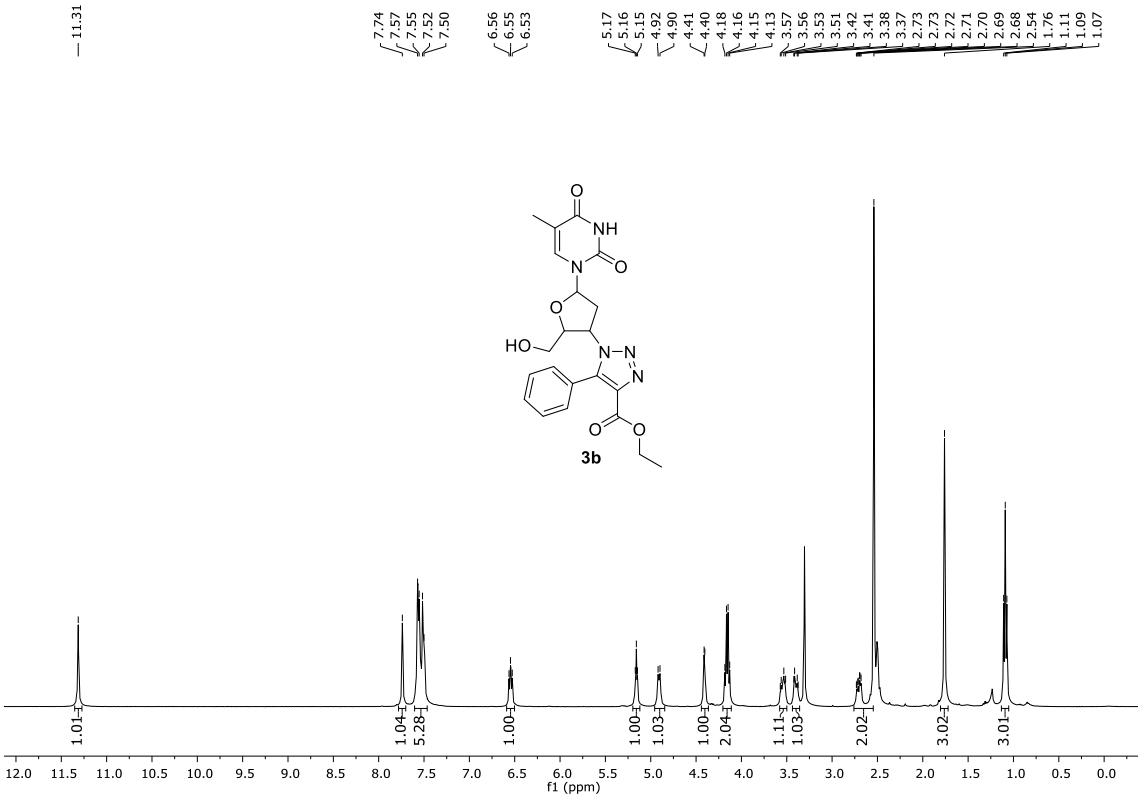
SELECTED SPECTRA



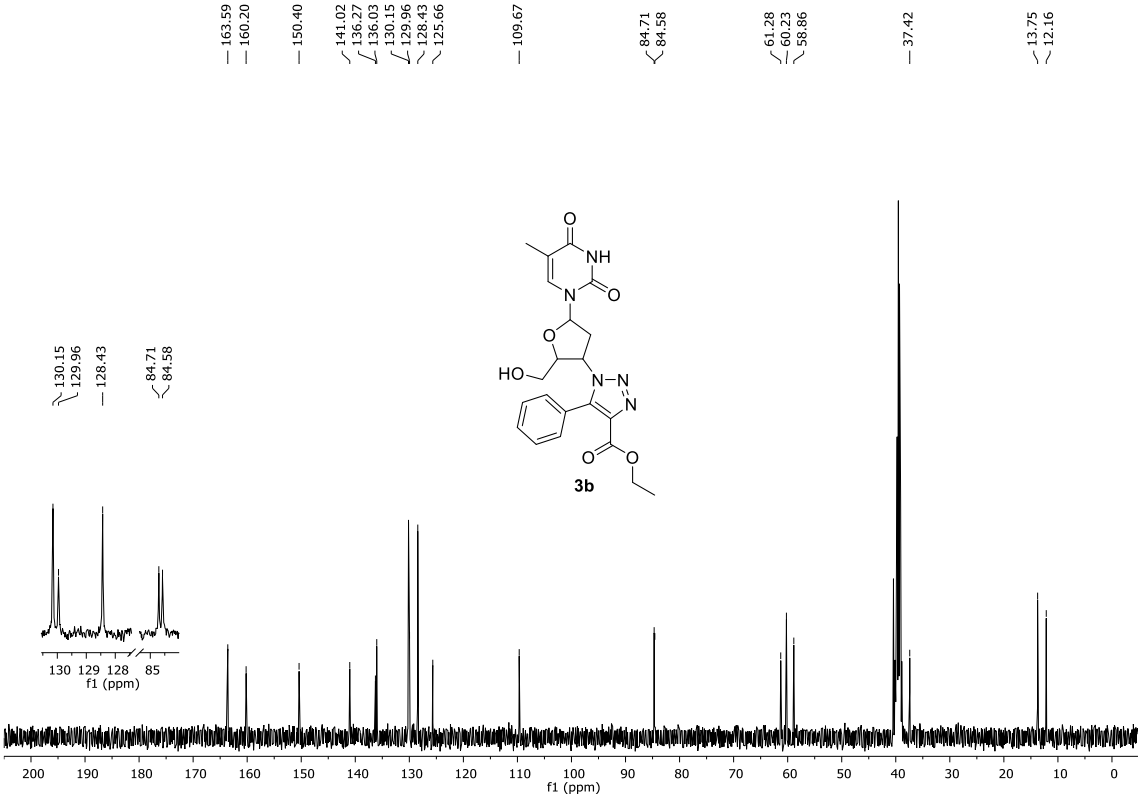
^{1}H NMR spectrum of compound **3a** (400 MHz, DMSO-d_6).



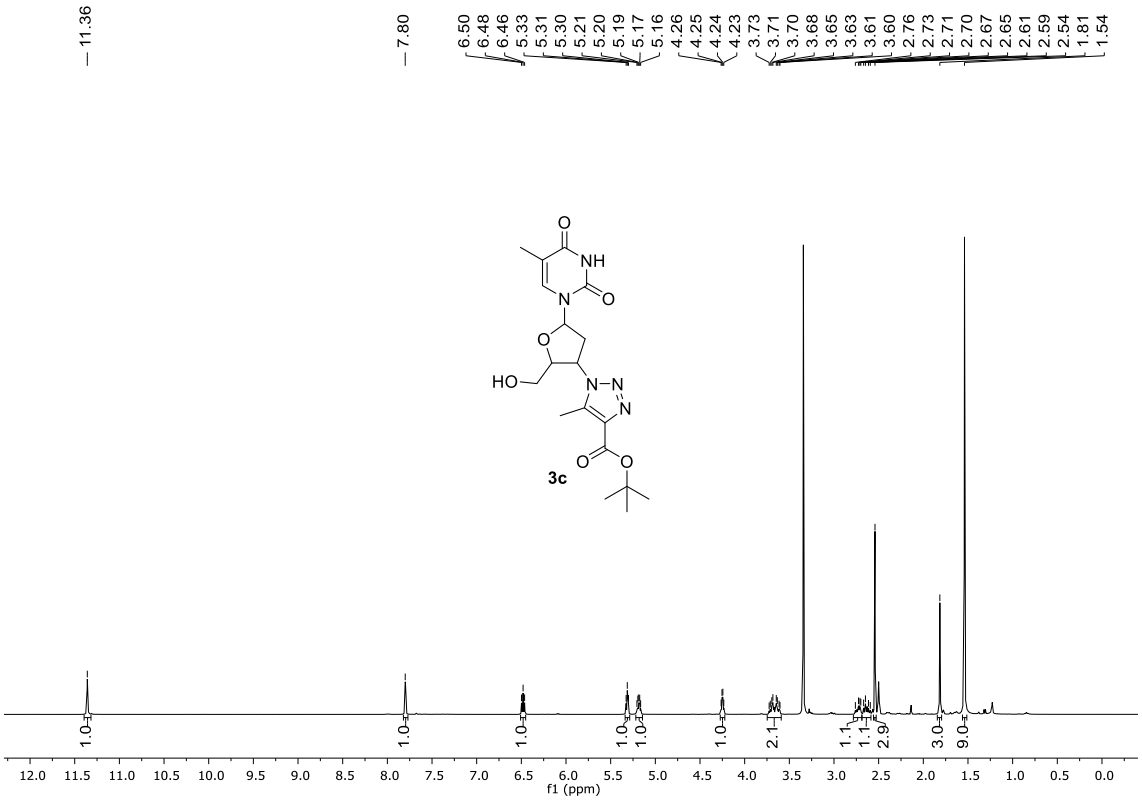
^{13}C NMR spectrum of compound **3a** (100 MHz, DMSO-d_6).



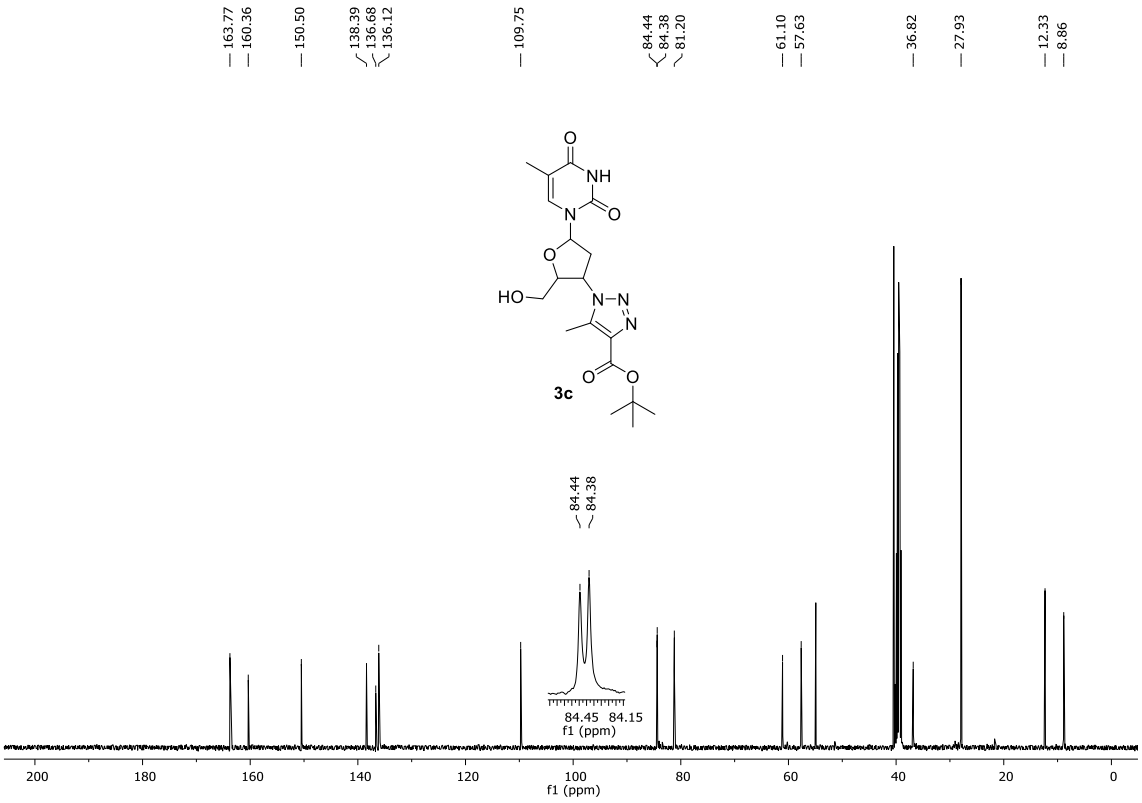
^{1}H NMR spectrum of compound **3b** (400 MHz, DMSO-d_6).



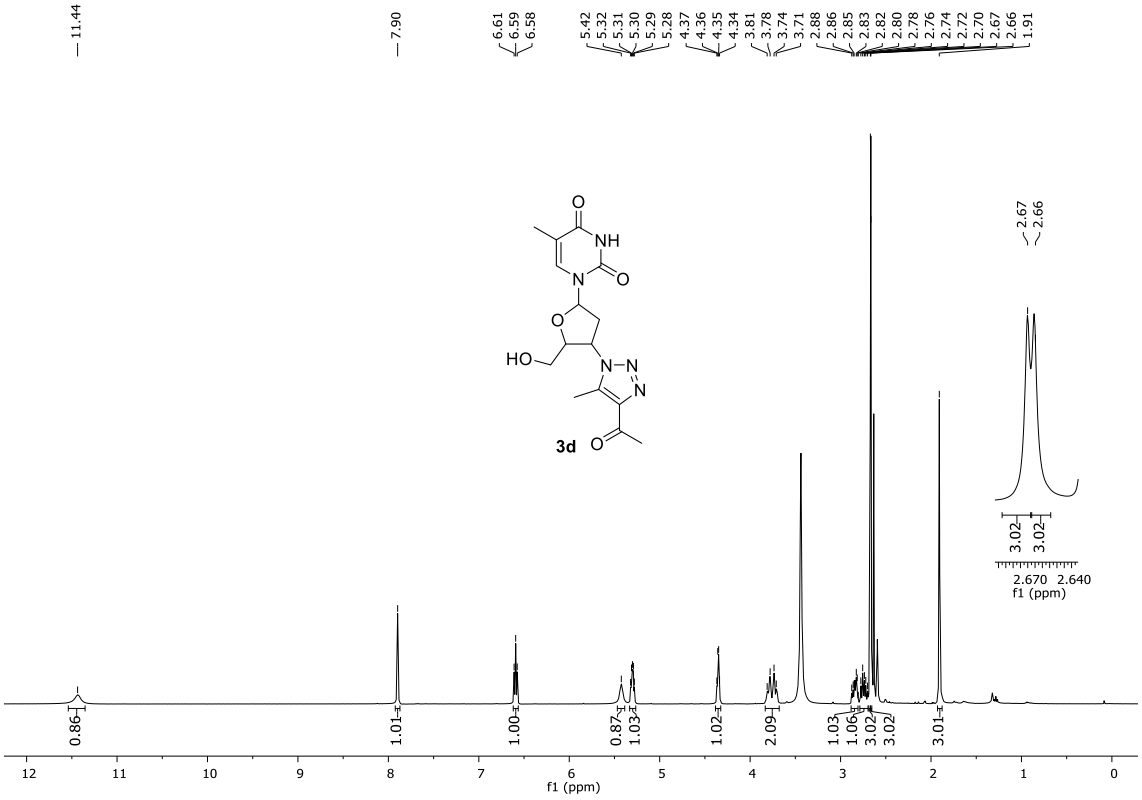
^{13}C NMR spectrum of compound **3b** (100 MHz, DMSO-d_6).



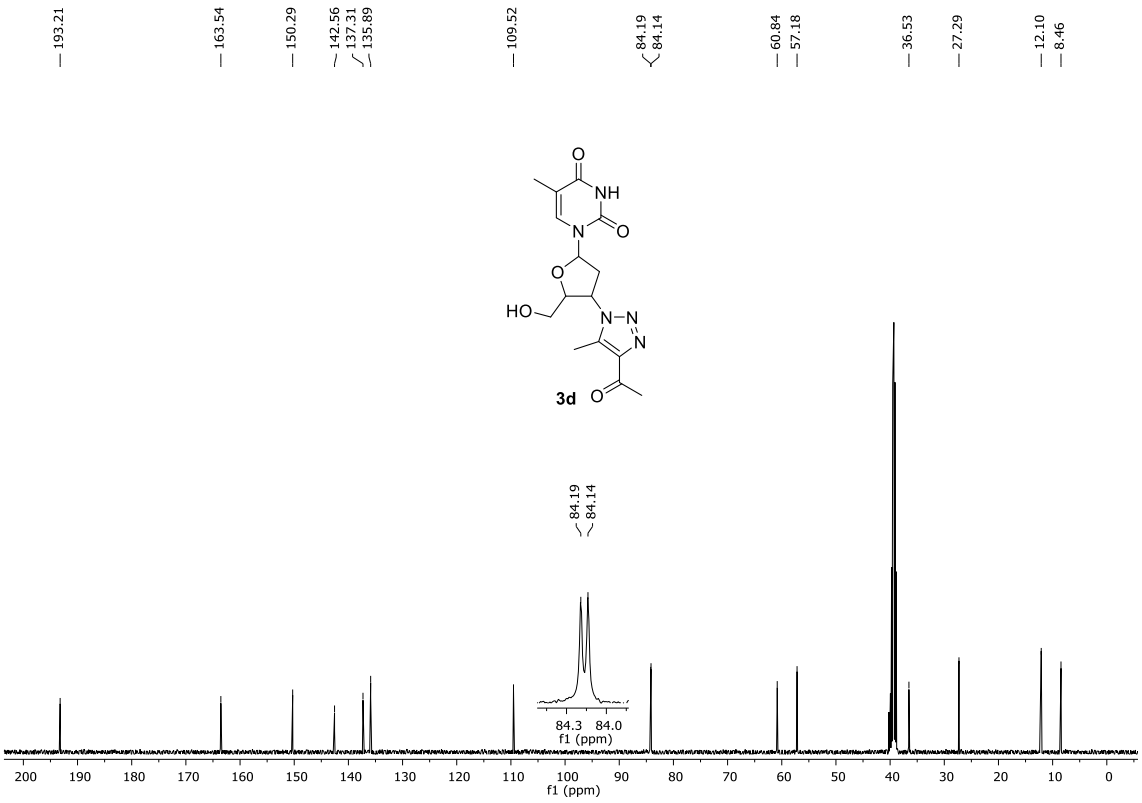
^{1}H NMR spectrum of compound **3c** (400 MHz, DMSO-d_6).



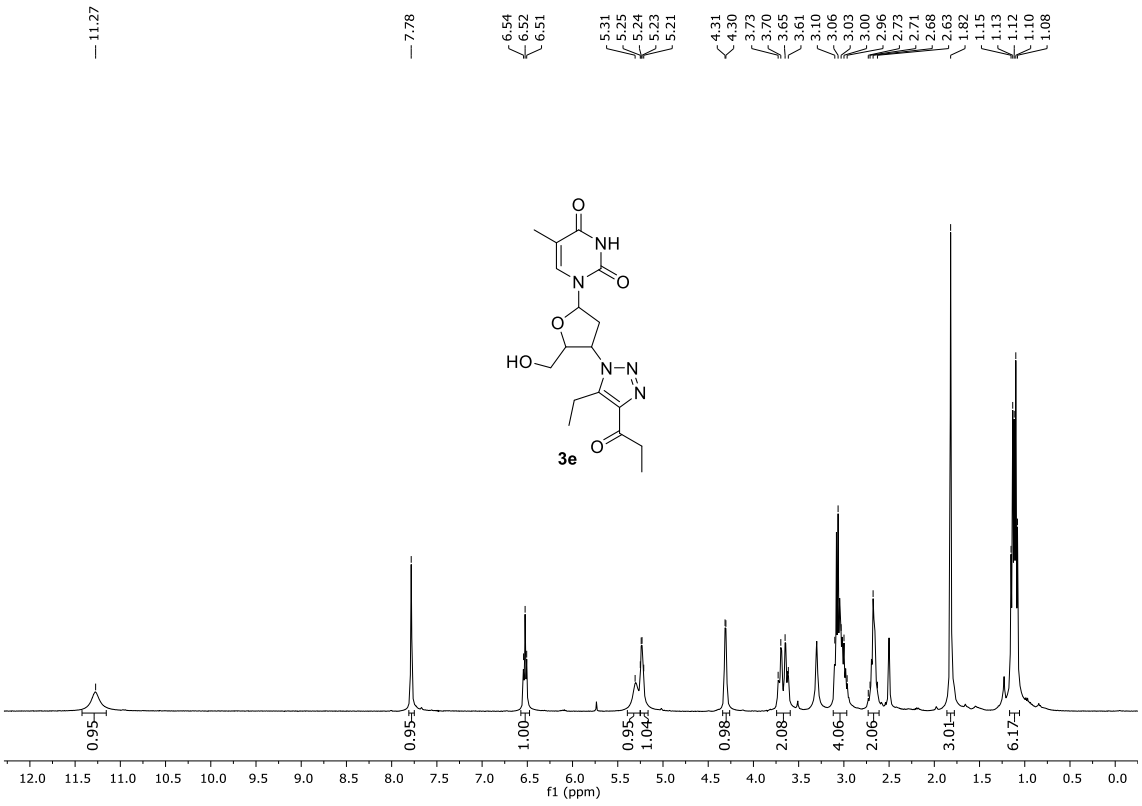
^{13}C NMR spectrum of compound **3c** (100 MHz, DMSO-d_6).



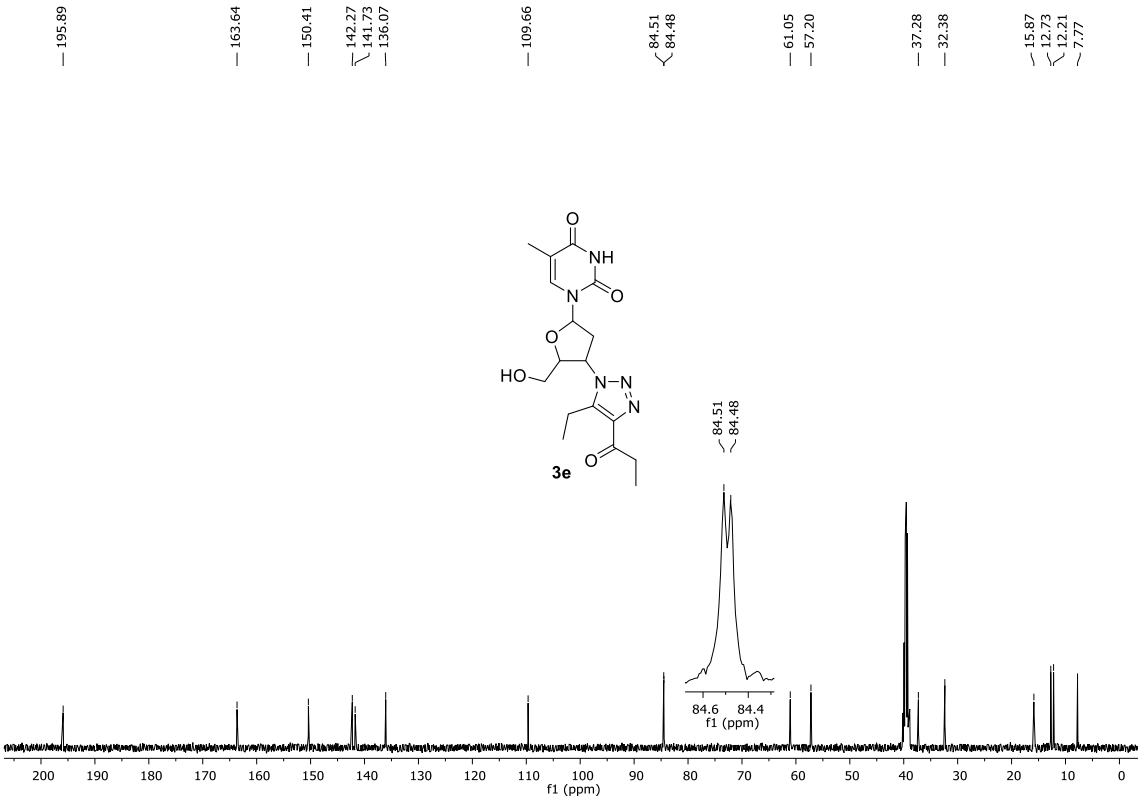
^{1}H NMR spectrum of compound **3d** (400 MHz, DMSO-d_6).



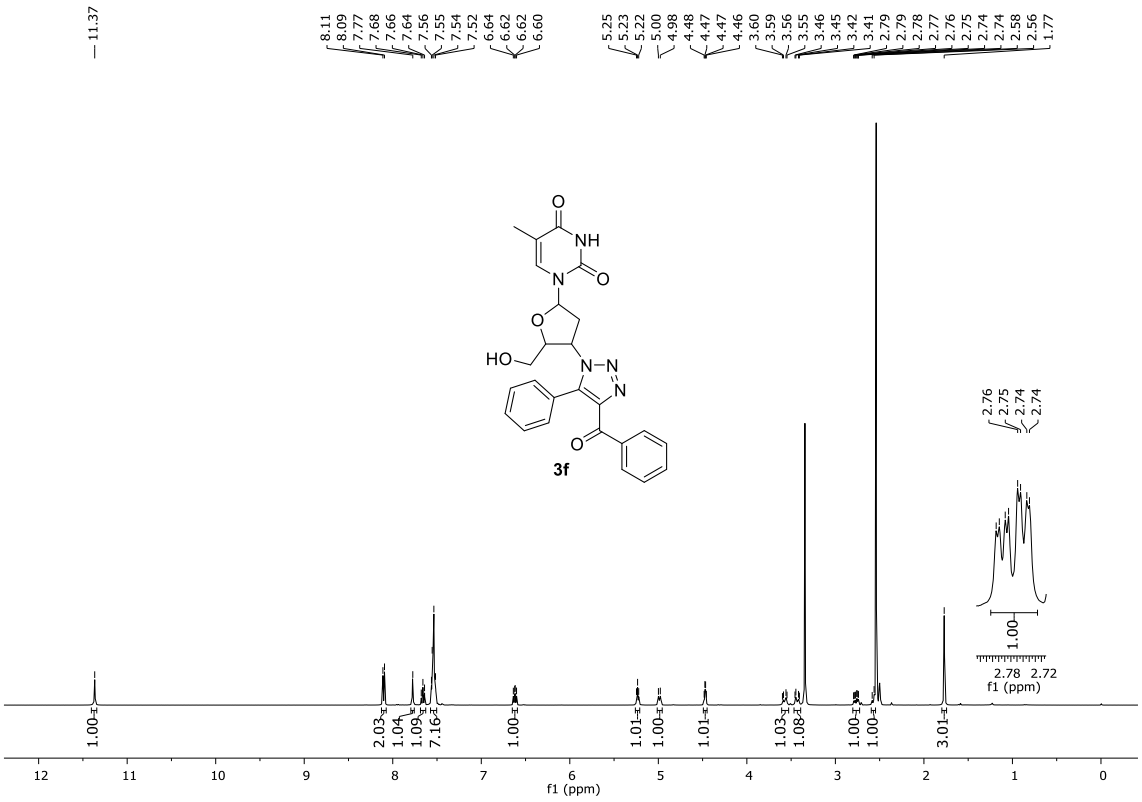
^{13}C NMR spectrum of compound **3d** (100 MHz, DMSO-d_6).



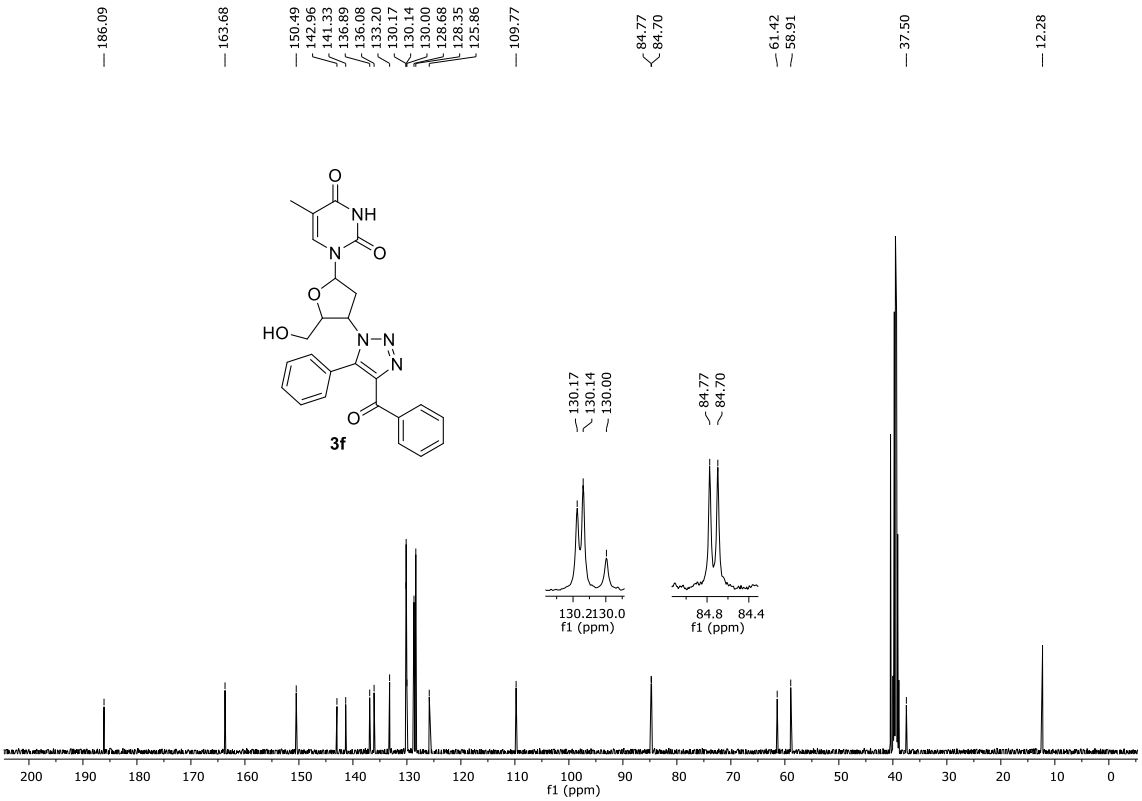
^{1}H NMR spectrum of compound **3e** (400 MHz, DMSO-d_6).



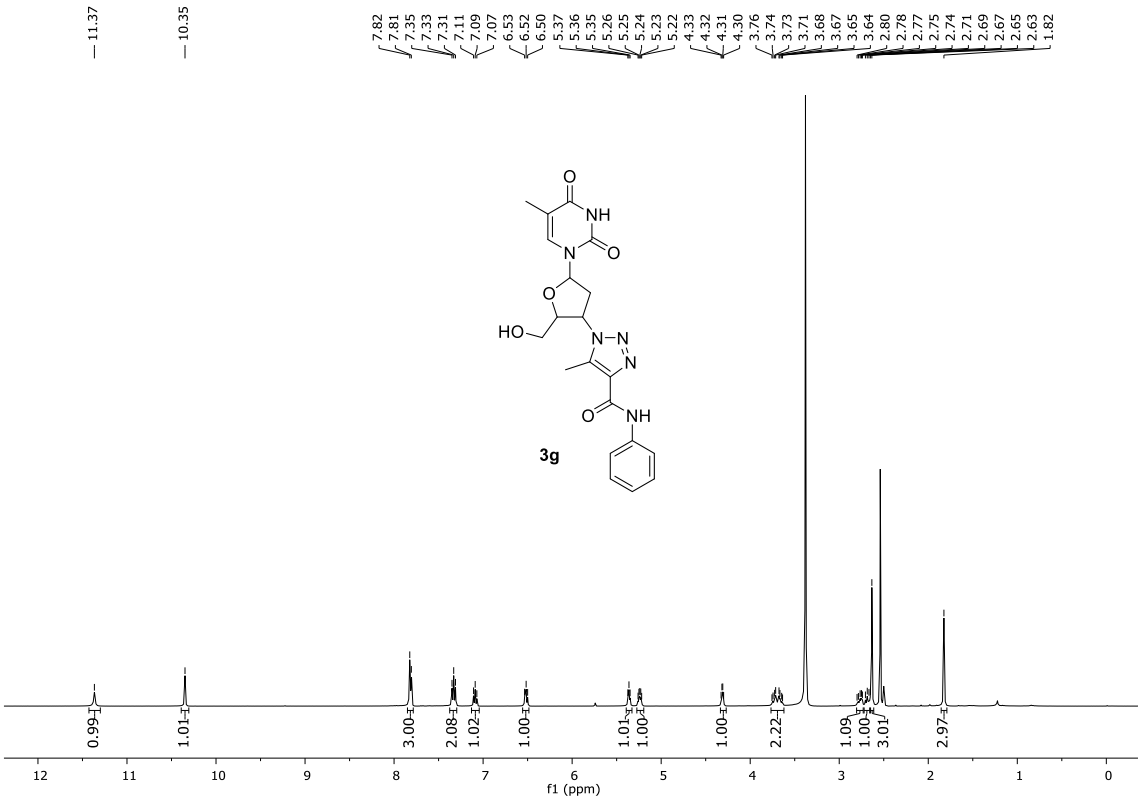
^{13}C NMR spectrum of compound **3e** (100 MHz, DMSO-d_6).



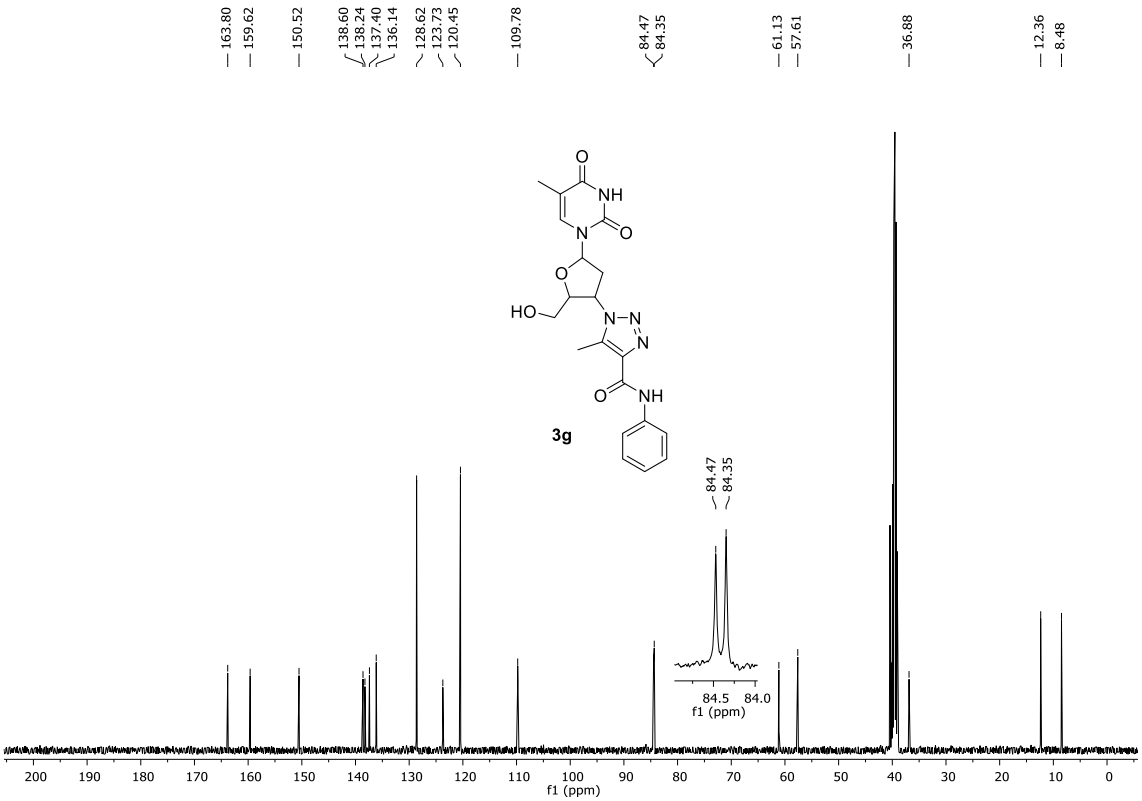
^{1}H NMR spectrum of compound **3f** (400 MHz, DMSO-d_6).



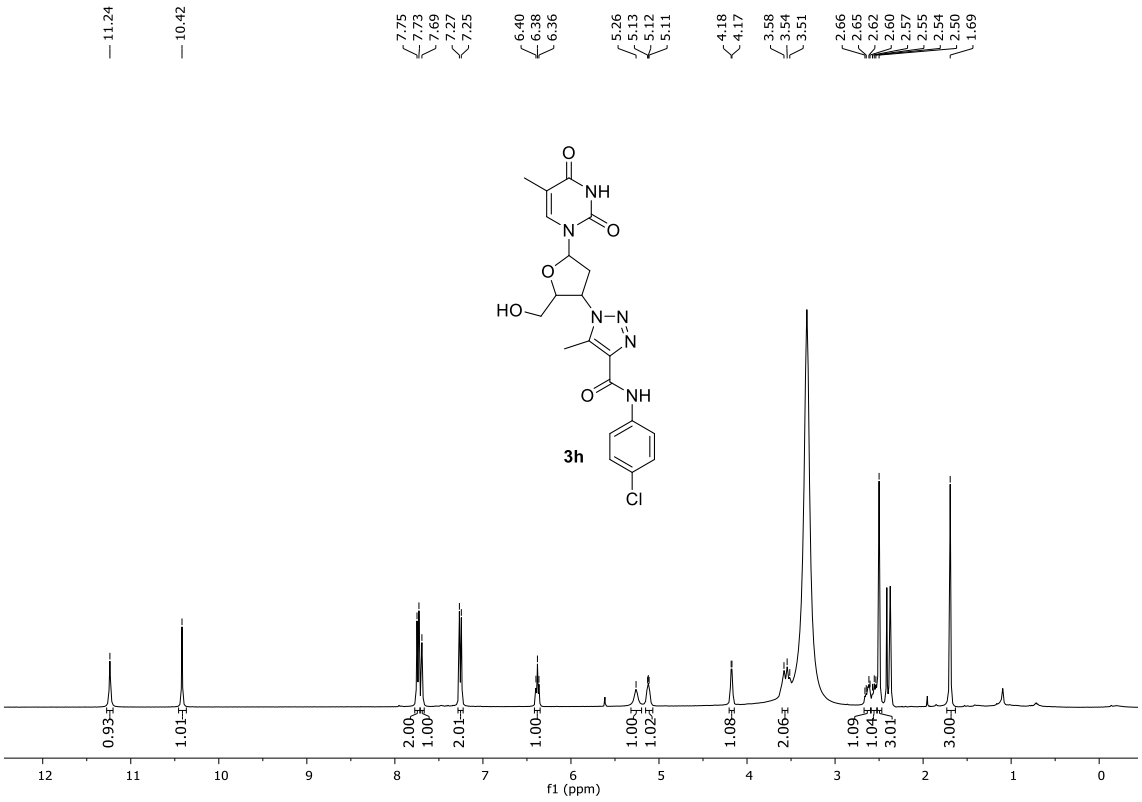
^{13}C NMR spectrum of compound **3f** (100 MHz, DMSO-d_6).



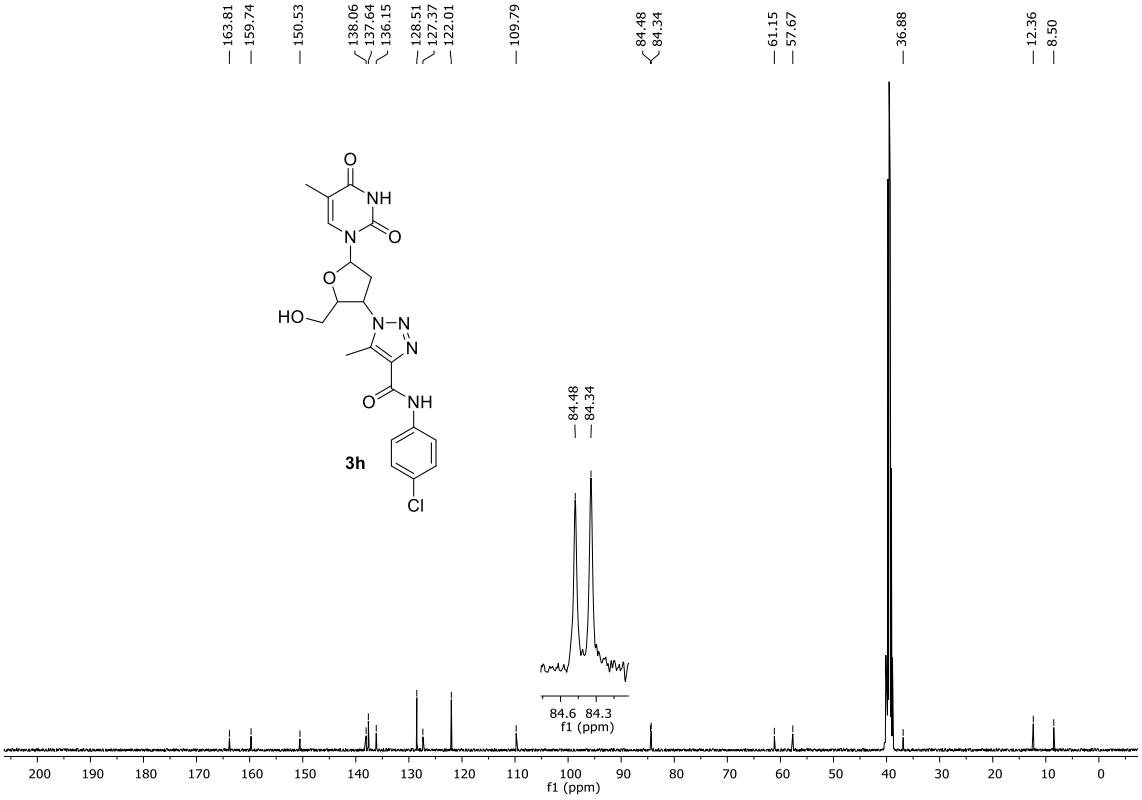
^{1}H NMR spectrum of compound **3g** (400 MHz, DMSO-d_6).



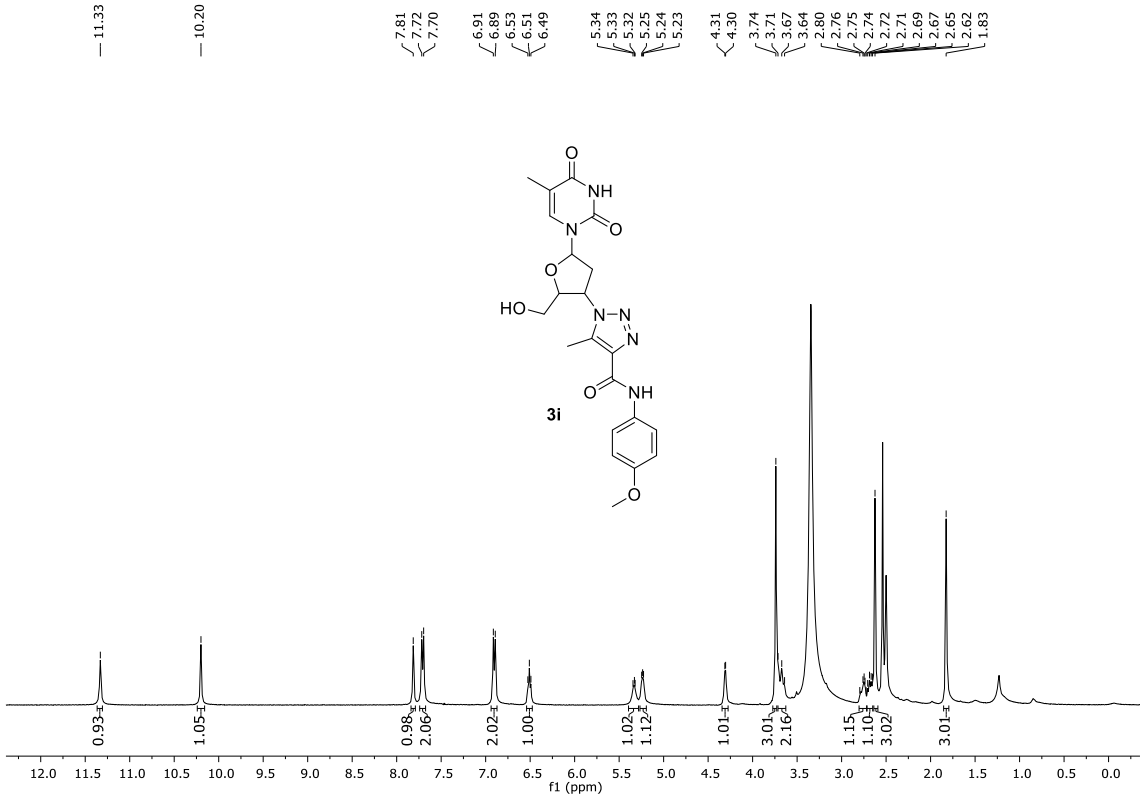
^{13}C NMR spectrum of compound **3g** (100 MHz, DMSO-d_6).



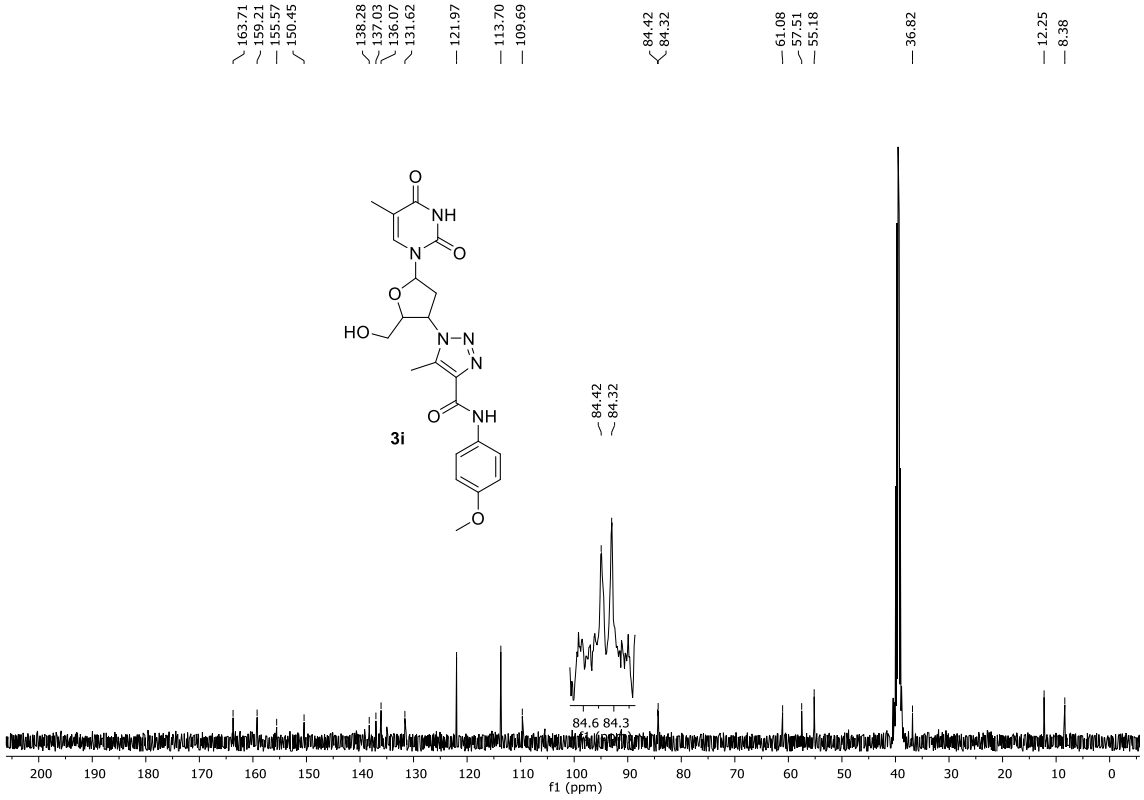
^{1}H NMR spectrum of compound **3h** (400 MHz, DMSO-d_6).



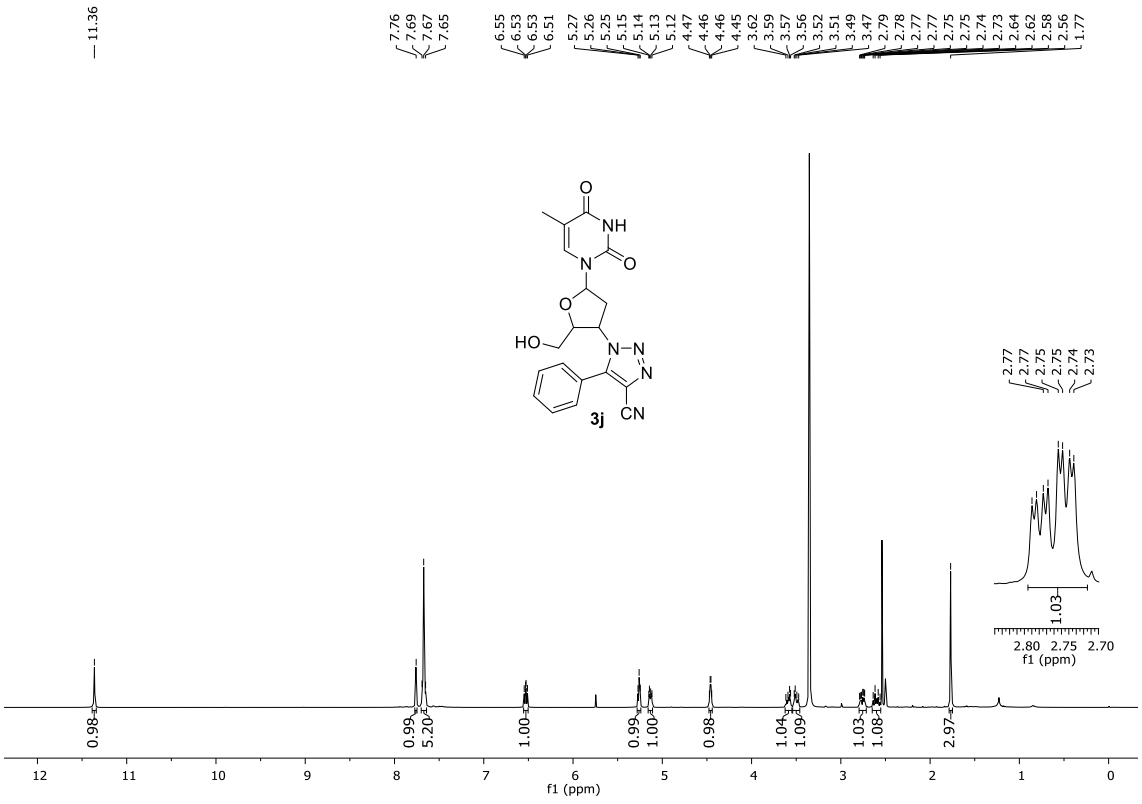
^{13}C NMR spectrum of compound **3h** (100 MHz, DMSO-d_6).



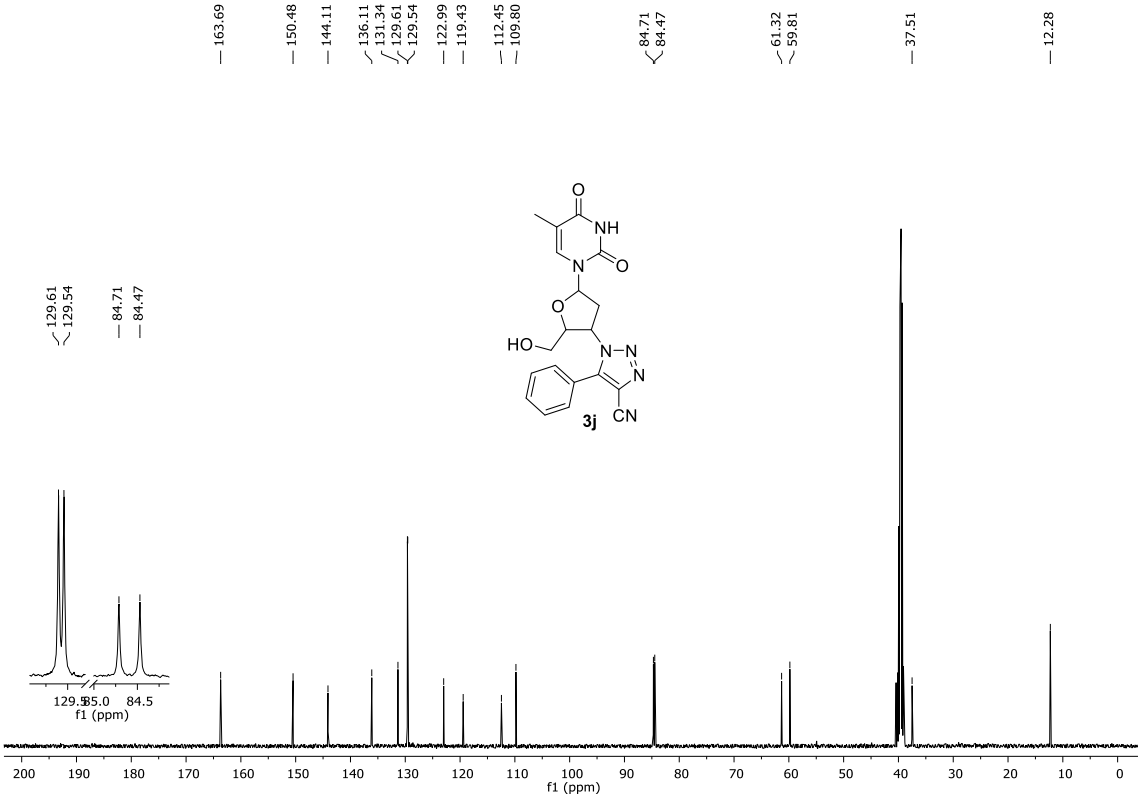
^{1}H NMR spectrum of compound **3i** (400 MHz, DMSO-d_6).



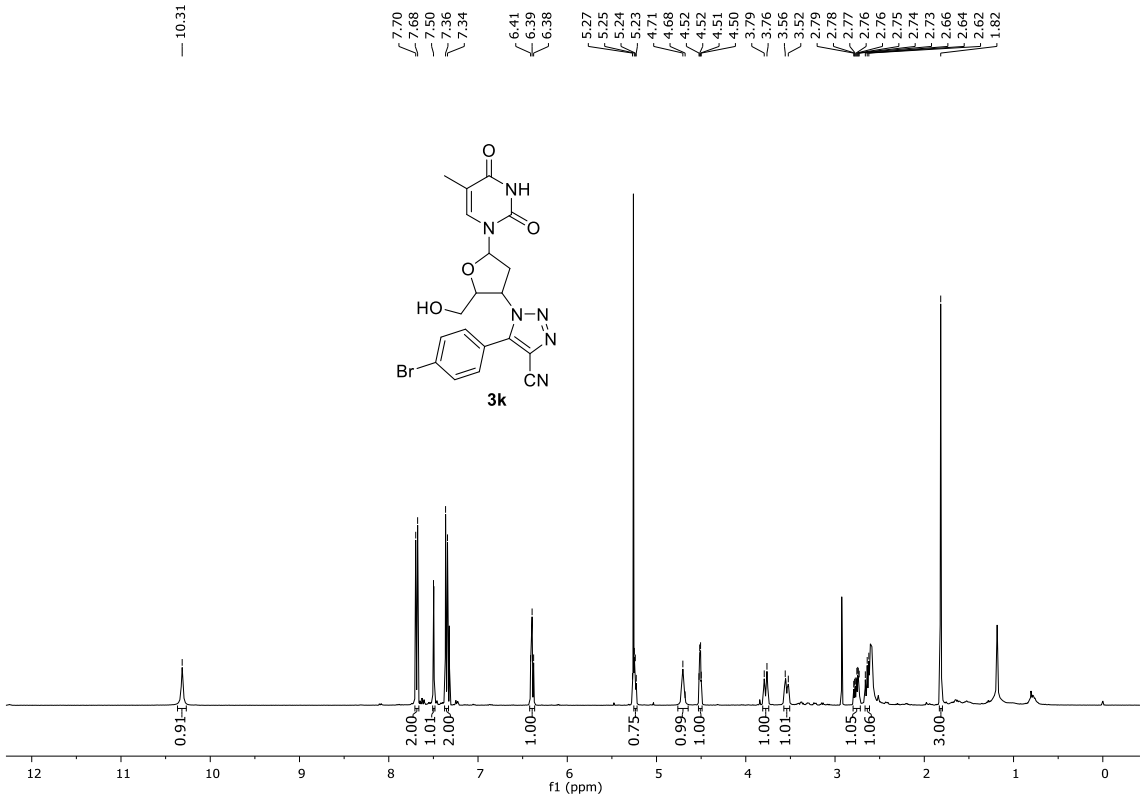
^{13}C NMR spectrum of compound **3i** (100 MHz, DMSO-d_6).



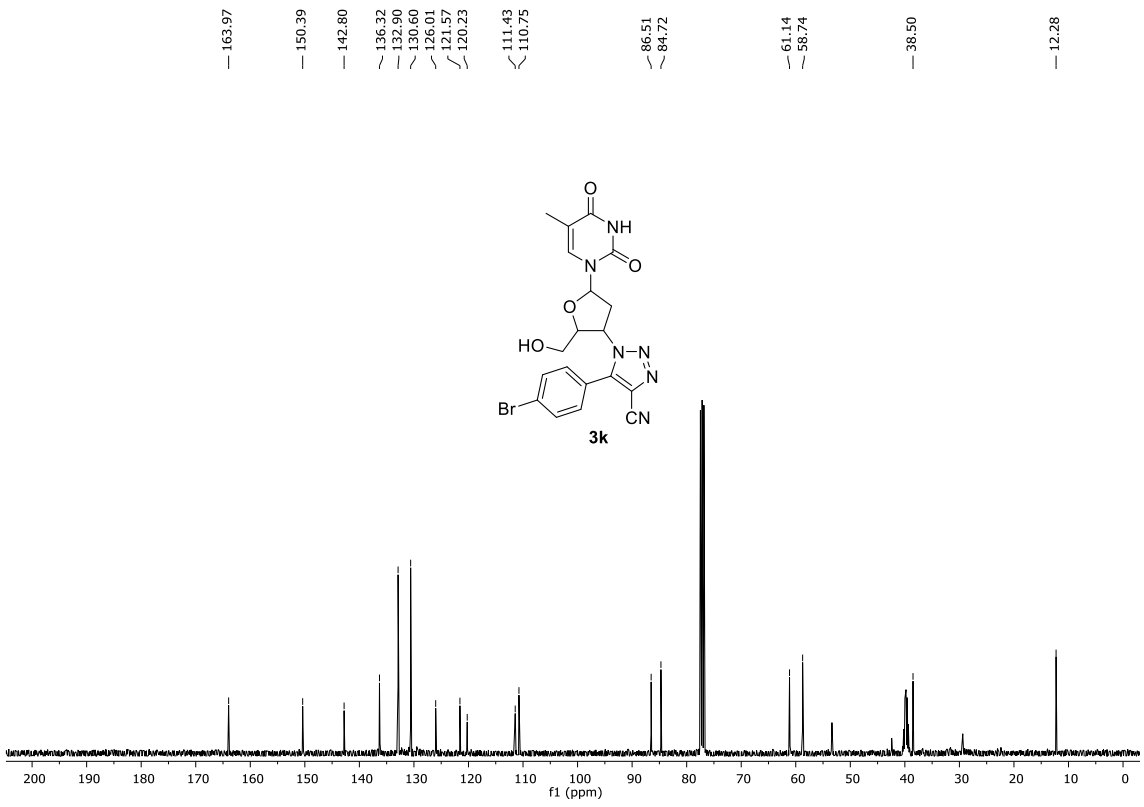
^{1}H NMR spectrum of compound **3j** (400 MHz, DMSO-d_6).



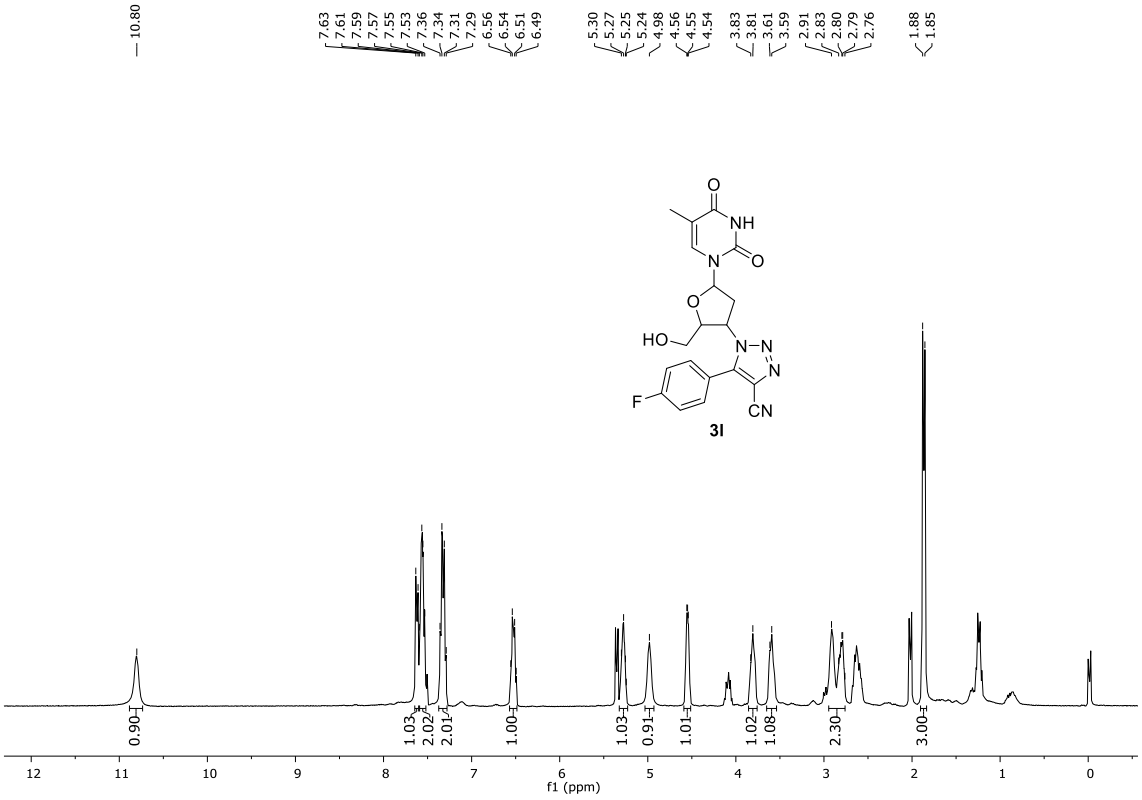
^{13}C NMR spectrum of compound **3j** (100 MHz, DMSO-d_6).



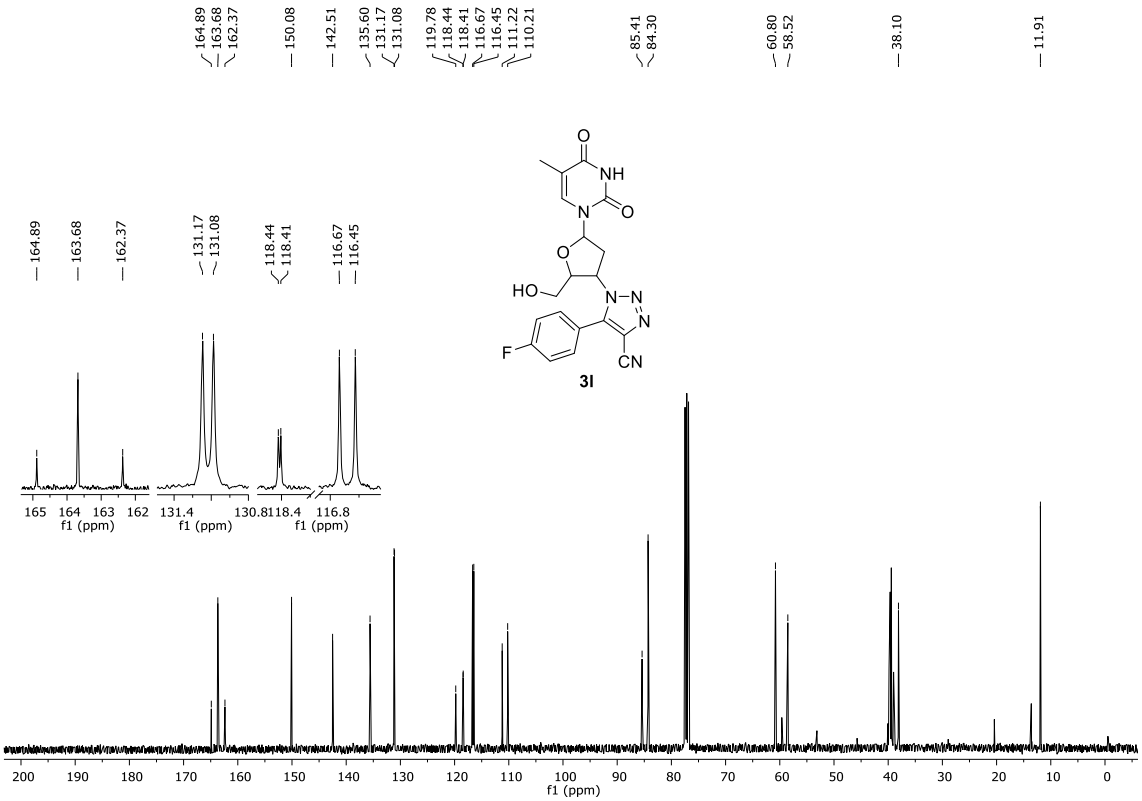
^{1}H NMR spectrum of compound **3k** (400 MHz, $CDCl_3$).



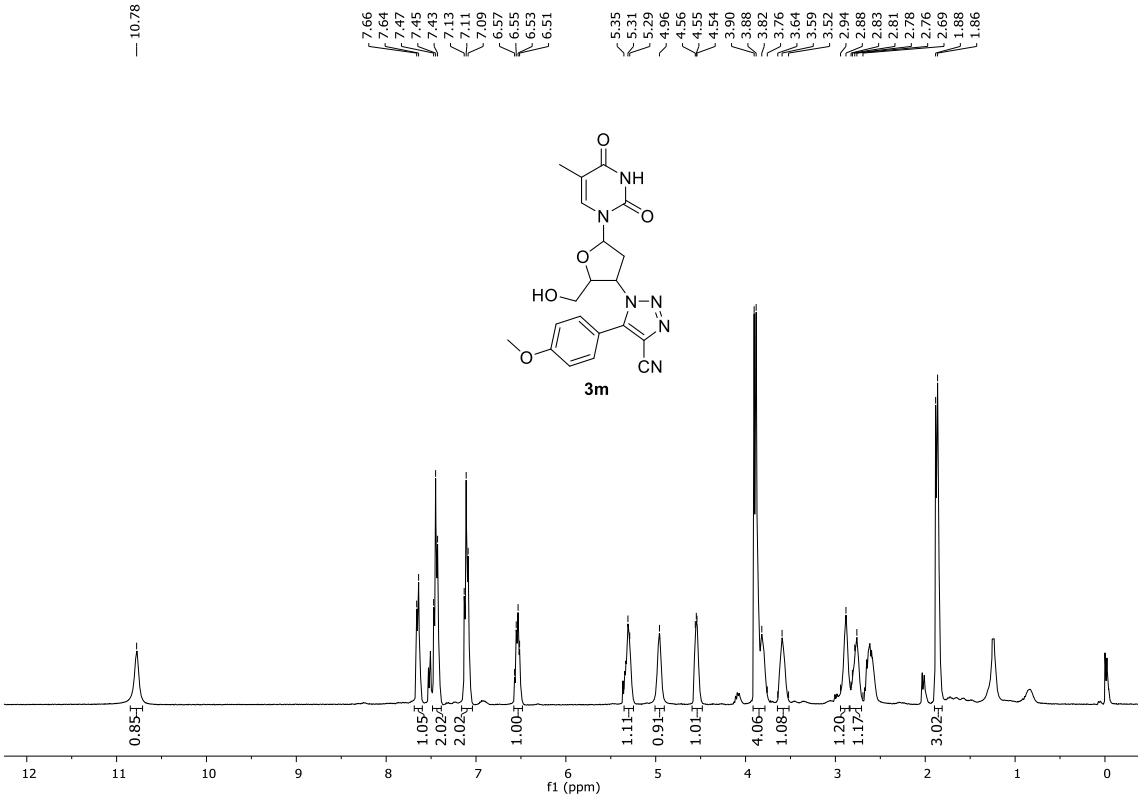
^{13}C NMR spectrum of compound **3k** (100 MHz, $CDCl_3$).



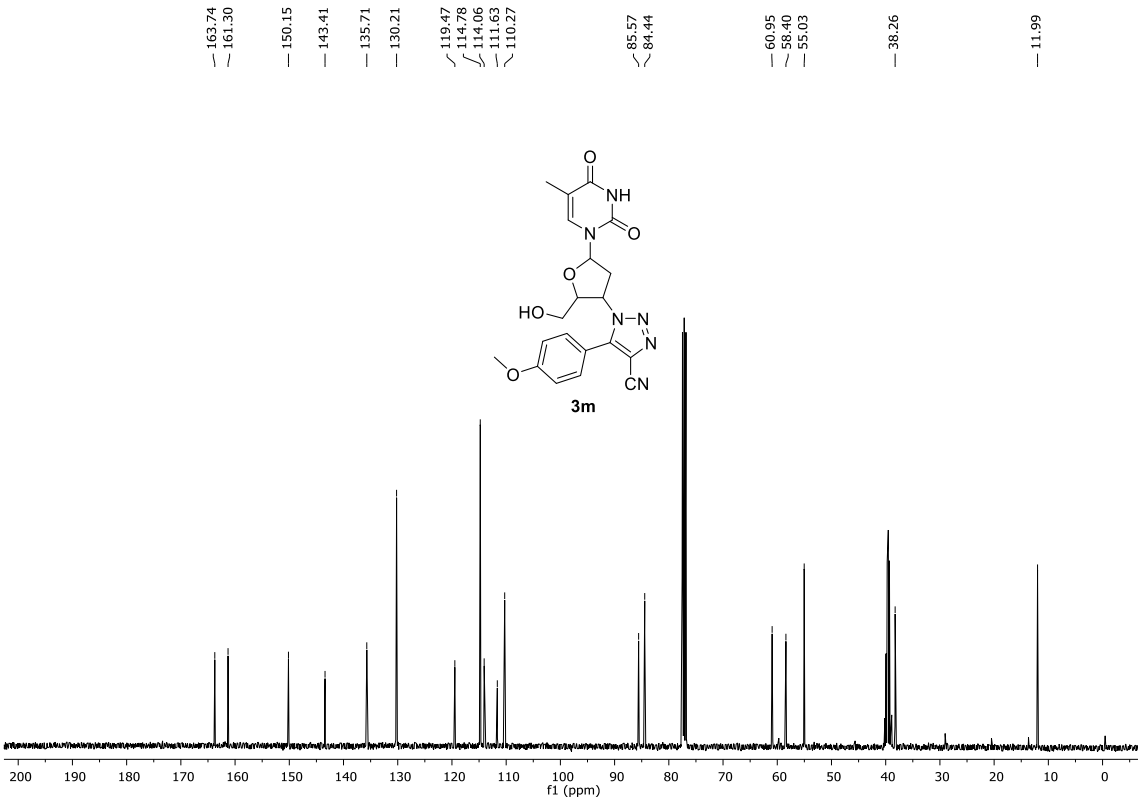
^{1}H NMR spectrum of compound **3l** (400 MHz, $CDCl_3$).



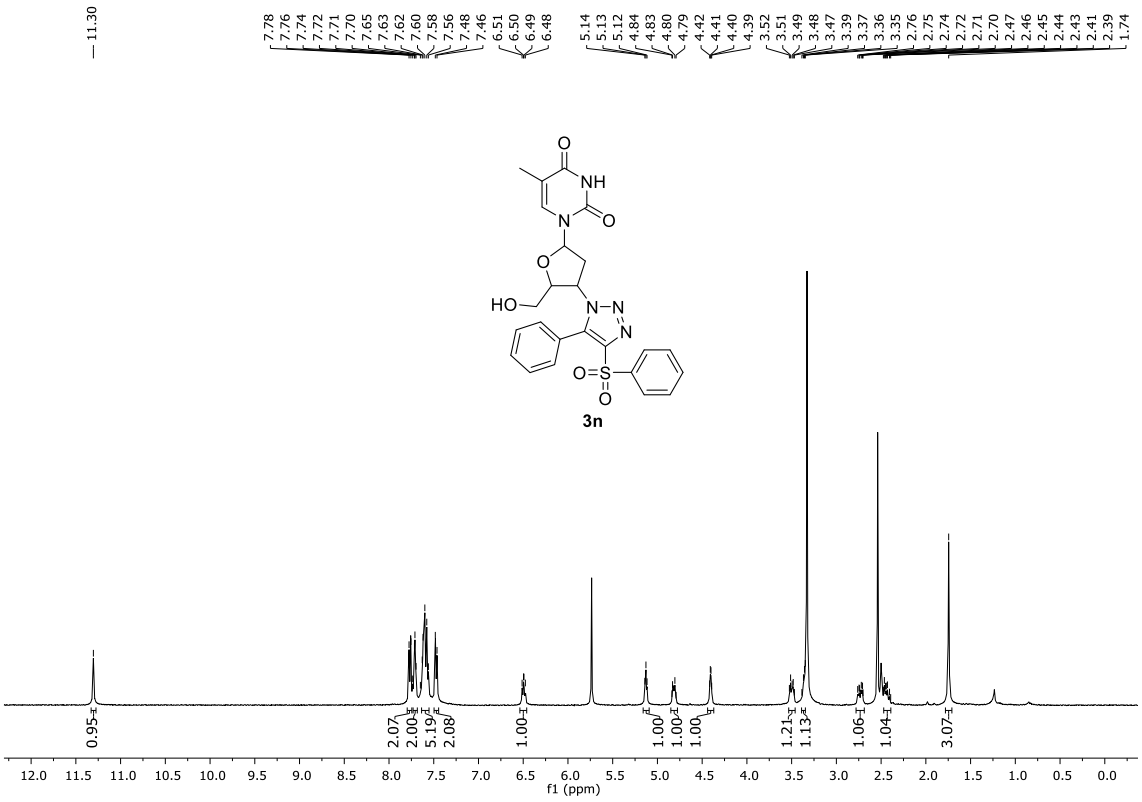
^{13}C NMR spectrum of compound **3l** (100 MHz, $CDCl_3$).



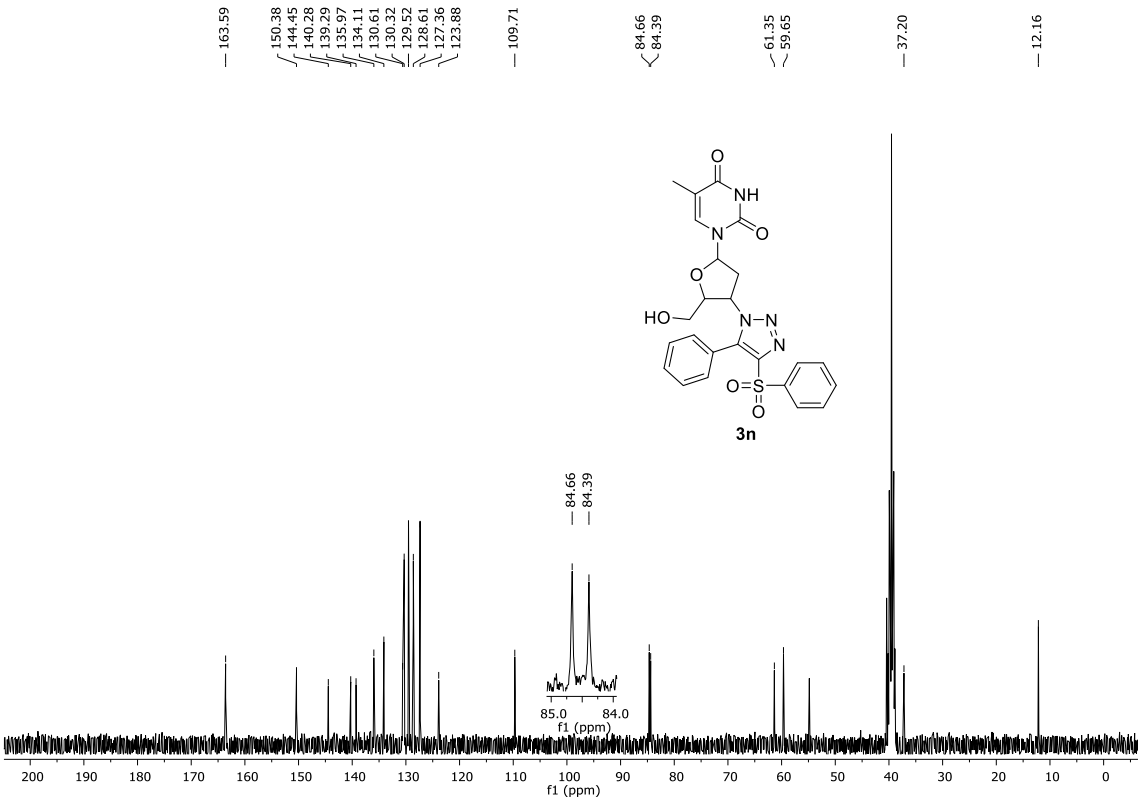
^{1}H NMR spectrum of compound **3m** (400 MHz, $CDCl_3$).



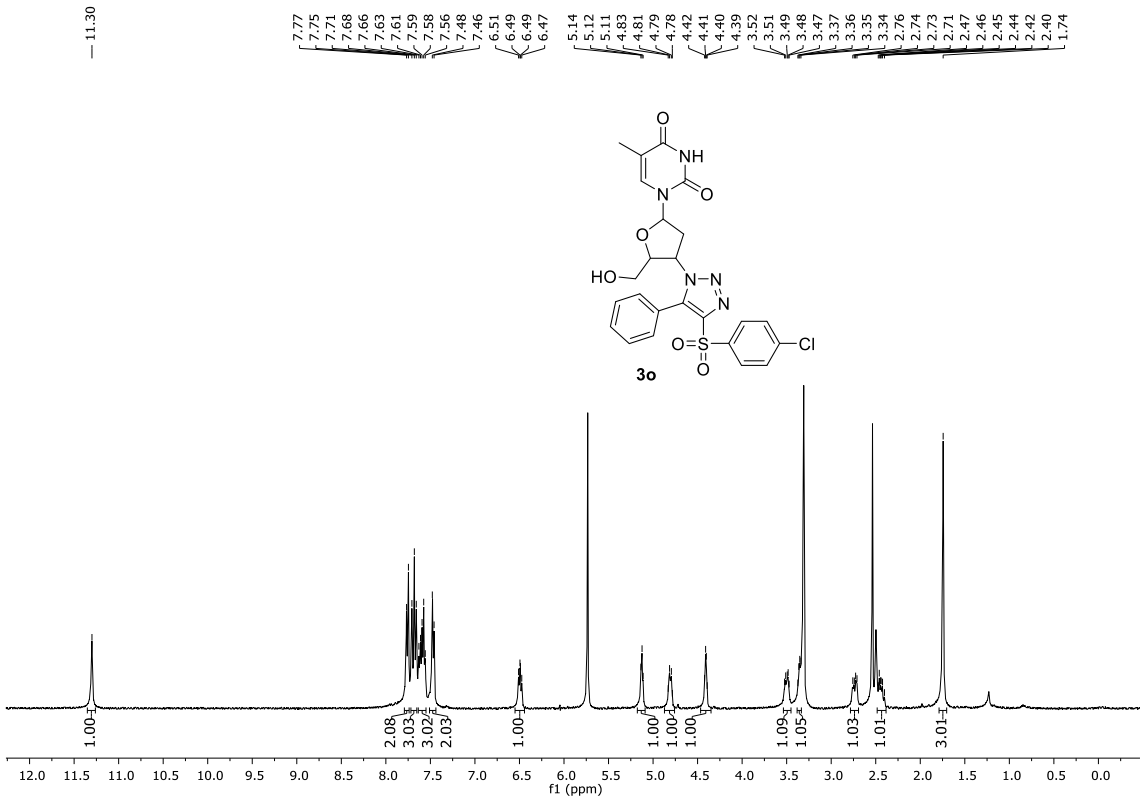
^{13}C NMR spectrum of compound **3m** (100 MHz, $CDCl_3$).



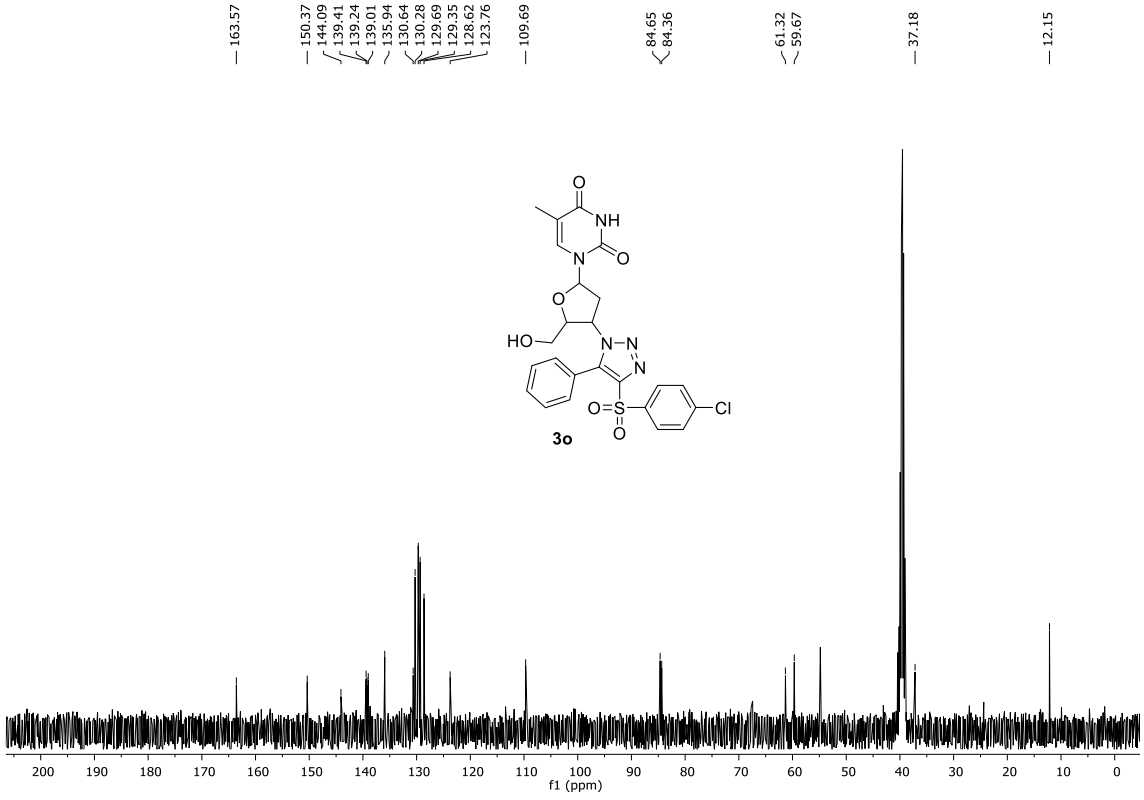
^{1}H NMR spectrum of compound **3n** (400 MHz, DMSO-d_6).



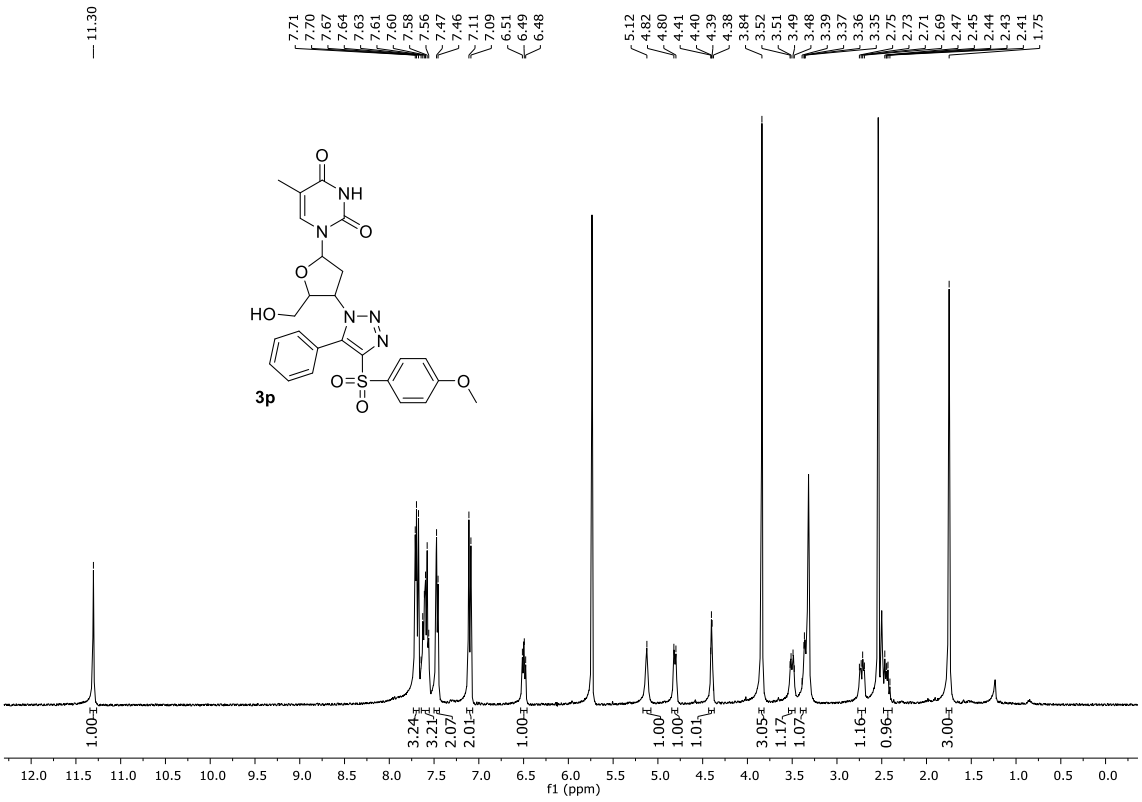
^{13}C NMR spectrum of compound **3n** (100 MHz, DMSO-d_6).



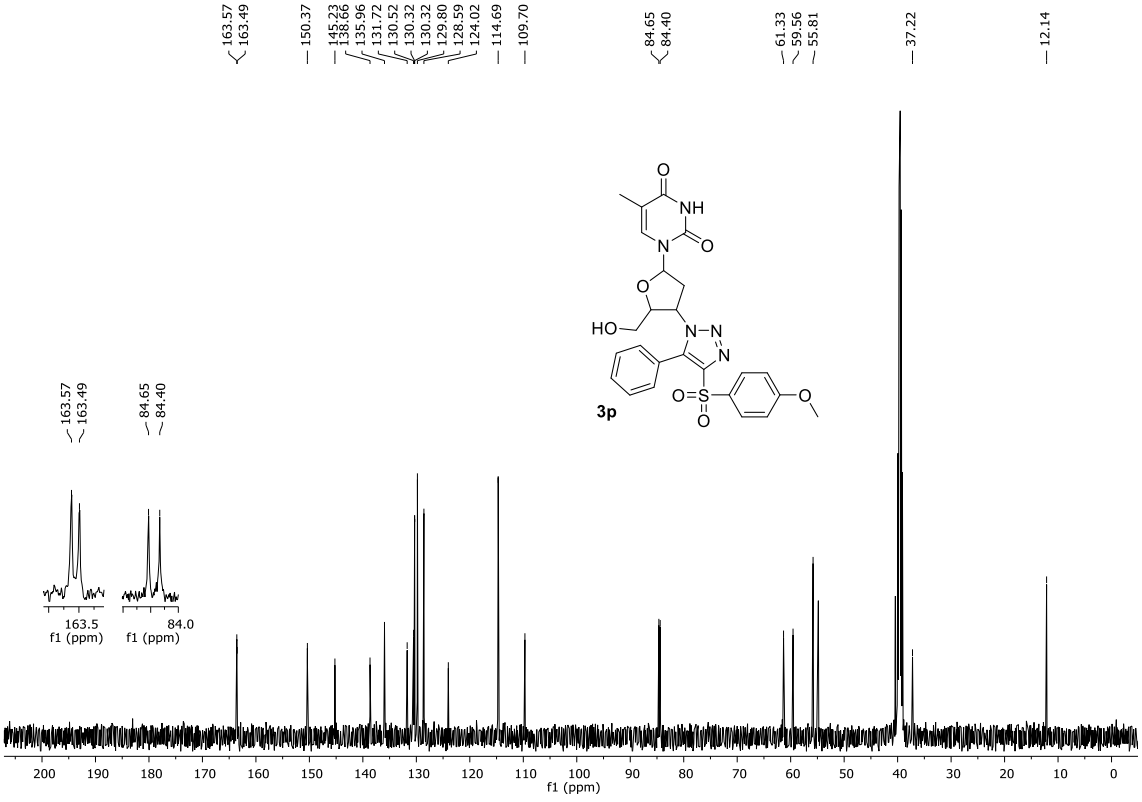
^{1}H NMR spectrum of compound **3o** (400 MHz, DMSO-d_6).



^{13}C NMR spectrum of compound **3o** (100 MHz, DMSO-d_6).



^{1}H NMR spectrum of compound **3p** (400 MHz, DMSO-d_6).



^{13}C NMR spectrum of compound **3p** (100 MHz, DMSO-d_6).

4.2 Manuscrito 2 – Organocatalytic synthesis and antitumor activity of novel 1,2,3-triazoles derived from fatty β-ketoesters

Manuscrito submetido à revista *ChemMedChem*

Organocatalytic synthesis and antitumor activity of novel 1,2,3-triazoles derived from fatty β-ketoesters

Carolina B. Gomes,[a] Caroline L. Corrêa,[a] Diego C. Cabrera,[b] Marcelo G. M. D'Oca,[b] Martha L. R. Benitez,[c] Tiago Collares,[c] Lucielli Savegnago,[d] Fabiana K. Seixas,[c]* Diego Alves[a]*

Abstract: We describe here the organocatalyzed synthesis and preliminary results of antitumor and cytotoxic activity of a range of 1,2,3-triazoles derived from fatty esters. Through enolate-mediated organocatalysis, these compounds were synthesized in moderate to excellent yields by the reaction of fatty esters **1** with aryl azides **2**, in the presence of a catalytic amount of DBU (5 mol%). All the compounds derived from palmitic acetoacetate **1a** were evaluated for the induces cytotoxicity *in vitro* in a human bladder cancer cell line and compounds **3a**, **3d**, **3e** and **3g** were identified as promising and presenting the lowest inhibitory concentration of IC50.

Introduction

Highly substituted 1,2,3-triazoles have inspired great interest in organic chemistry in the development of new compounds due to their variety of applications in pharmaceutical area and materials science.[1] The great interest to develop synthetic methodologies to obtain 1,2,3-triazoles emerged when Huisgen proposed in 1963, the cycloaddition reaction [3 + 2] employing an organic azide and a terminal alkyne.[2] Inspired in this work, a number of catalytic strategies employing transition metals (e.g. Cu, Ru, Ag and Ir) have been used to address the reactivity and selectivity issues inherent to the seminal strategy.[3]

Meantime, the use of transition metals as catalysts has restricted the biological evaluation of many 1,2,3-triazoles because of their eco-adverse effects, e.g. degradation induction of oligonucleotides[4] and polysaccharides.[5] To circunvent this drawback, 1,2,3-trizoles can be prepared by organocatalyzed [3+2] cycloadditions reactions through the generation of enamines or enolates, also known as organocatalytic azide-ketone [3+2]-cycloaddition (OrgAKC).[6] In the OrgAKC reactions enamines or enolates act as the dipolarophile partner in the 1,3-dipolar cycloadditions with organic azides. Therefore, significant efforts have been directed toward the development of more efficient catalytic systems for the synthesis of highly functionalized and complex 1,2,3-triazoles from various combinations of substrates.

Numerous reports have been developed describing that long chain compounds, such as fatty acid derivatives, present various biological activities,[7] including neuroprotective activity[7c] (Figure 1-A) and antioxidant activity (Figure 1- B).[7d] Fatty acids are the carboxylic acids, usually derived from triacylglycerols or phospholipids, formed from the cleavage of fats and oils. Most naturally occurring fatty acids have an un-branched chain of an even number of carbon atoms, from 4 to 28.[7a] The introduction of fatty chains into organic molecules can produce important changes in their chemical and physical properties, such as the increased permeability of these fatty compounds in the cell wall which is basically composed of lipids.[8]

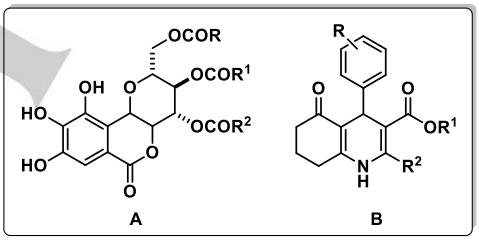


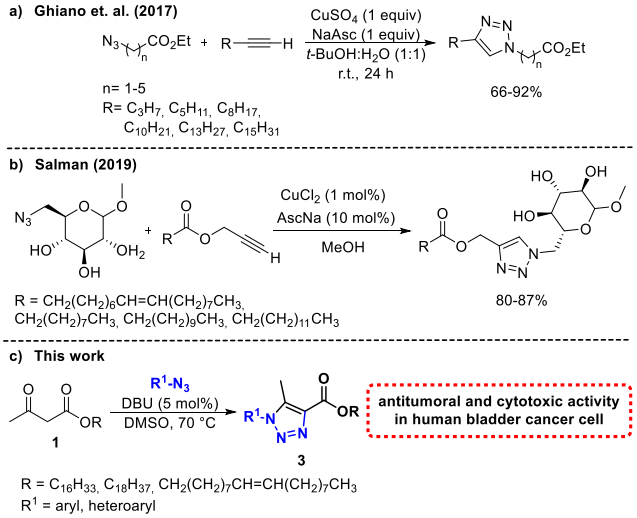
Figure 1. Selected examples of biologically active fatty esters.

In this sense, Ghiano and co-workers in 2017 reported the synthesis and antitubercular activity of 1,2,3-triazoles containing fatty esters.[9] Synthesized compounds were obtained in moderate to excellent yields and were tested against *Mycobacterium tuberculosis*, being most of them active with some of the analogs displaying activity at micromolar concentration (Scheme 1, eq. a). Salman in 2019 described the synthesis of four new functionalized 1,2,3-triazoles from multi hydroxyl compounds containing fatty esters as a potential biological compounds (Scheme 1, eq. B).[10] The synthesized compounds shown good antibacterial and antifungal proprierties against some selected gram-positive and fungi.

However, to the best of our knowledge, an organocatalytic approach to synthesize 1,2,3-triazoles derived from fatty acids have not been explored. In view of the exposed above and due to our interest correlated to the preparation of functionalized 1,2,3-triazoles, we report herein the organocatalyzed synthesis and preliminary results of antitumoral activity of a range of 1,2,3-triazoles derived from fatty β-ketoesters (Scheme 1, eq. c).

[a] Ms. C. B. Gomes, Ms. C. L. Corrêa, Prof. Dr. D. Alves*
LASOL-CCQFA, Universidade Federal de Pelotas - UFPel
P.O. Box 354 - 96010-900, Pelotas, RS, Brazil.
E-mail: diego.alves@ufpel.edu.br
[b] Mr. D. C. Cabrera, Prof. Dr. M. M. D'Oca
Laboratory Organic Synthesis Kolbe- Federal University of Rio Grande - FURG. Rio Grande, RS, Brazil.
[c] Dr. M. L. R. Benitez, Prof. Dr. T. Collares, Prof. Dr. F. K. Seixas
Grupo de Pesquisa em Oncologia Celular e Molecular - GPO, CDTec, Universidade Federal de Pelotas, UFPel, Pelotas, RS, Brazil.
E-mail: seixas.fk@gmail.com
[c] Prof. Dr. L. Savegnago
Grupo de Pesquisa em Neurobiotecnologia - GPN, CDTec, Universidade Federal de Pelotas, UFPel, Pelotas, RS, Brazil.

Supporting information for this article is given via a link at the end of the document.



Scheme 1. Examples of 1,2,3-triazoles derived from fatty long chains and this work.

Results and Discussion

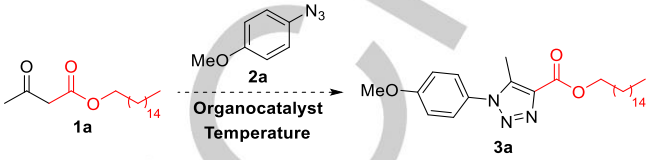
Synthesis

Initial experiments to optimize the reaction conditions were carried out using palmitic acetoacetate **1a** and *p*-methoxy phenylazide **2a** as standard reaction substrates (Table 1). We started the reaction screening reacting palmitic acetoacetate **1a** (0.2 mmol) and *p*-methoxy phenylazide **2a** (0.3 mmol) in DMSO (0.6 mL), using 10 mol% of diethylamine as the organocatalyst in reaction at room temperature (Table 1, Entry 1). Unfortunately, under this reaction conditions the desired product **3a** was not obtained and the respective start materials **1a** and **2a** were recovered. Satisfactorily, increasing the reaction temperature to 70 °C provide the desired product **3a** in 59% yield (Table 1, entry 2). Similar result was obtained under identical reaction conditions, however using 20 mol% of Et_2NH as the organocatalyst (Table 1, Entry 3).

When we changed the organocatalyst to other amines, such as pyrrolidine, triethylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), we achieved different results of the formation of product **3a** (Table 1, Entries 4-8). Reactions performed with 20 mol% of pyrrolidine and triethylamine furnished 59% and 23% of product **3a**, respectively (Table 1, Entries 4-5). To our delight, an improvement in the chemical yield of **3a** (86%) was achieved when the reaction was carried out at 70 °C using DBU as the organocatalyst (Table 1, Entry 6). Furthermore, reducing the organocatalyst charge from 20 to 10 and 5 mol %, a slight decrease in the yield of compound **3a** was observed (Table 1, Entries 7-8).

From the results shown in Table 1, it can be inferred that the best reaction conditions to obtain hexadecyl 1-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate **3a** is the stirring of a solution of palmitic acetoacetate **1a** (0.2 mmol), *p*-methoxy phenylazide **2a** (0.3 mmol) and DBU (5 mol%) as organocatalyst in DMSO (0.6 mL) at 70 °C under air atmosphere for 24 h (Table 1, entry 8).

Table 1 Optimization of the reaction conditions.[a]



Entry	Organocatalyst (mol%)	Temperature (°C)	Time (h)	Yield (%)[b]
1	Diethylamine (10)	25	48	-
2	Diethylamine (10)	70	24	59
3	Diethylamine (20)	70	24	63
4	Pyrrolidine (20)	70	24	59
5	Triethylamine (20)	70	24	23
6	DBU (20)	70	24	86
7	DBU (10)	70	24	85
8	**DBU (5)**	**70**	**24**	**83**

[a] Reactions were performed with palmitic acetoacetate **1a** (0.2 mmol) and *p*-methoxy phenylazide **2a** (0.3 mmol) in DMSO (0.6 mL) under an air atmosphere for 24 h**.** [b] Yields are given for isolated products.

Therefore, with the best reaction condition established for this OrgAKC reaction, we focused our attention to extend the scope of this methodology by reacting palmitic acetoacetate **1a** with a range of arylazides **2**. The results depicted in Figure 2 disclose that our protocol worked well in most cases and the desired 1,2,3-triazoles derived from palmitic ester **3a-j** could be obtained in moderated to excellent yields. A series of *p*-substituted arylazides bearing electron-donating **2a-b** and electron-withdrawing groups **2d-e** on the aromatic ring were tested to give the corresponding products **3a,3b, 3d** and **3e** in good isolated yields. 3-Nitrophenyl azide **2h** was efficiently reacted with palmitic acetoacetate **1a** giving the product **3h** in excellent yield. However, an interesting steric effect was observed when the reactions were performed with *o*-substituted arylazides. In these reactions, lower yields of products were obtained if compared to *p*-substituted arylazides. For example, 2-tolyl azide **2c**, 1-azido-2-fluorobenzene **2f** and 2-nitrophenyl azide **2g** furnishing the corresponding products **3c**, **3f** and **3g** in 44%, 63% and 75% yield, respectively. Finally, reactions performed with phenyl azide **2i** and 4-azido-7-chloroquinoline **2j** furnished the respective products **3i** and **3j** in satisfactory yields.

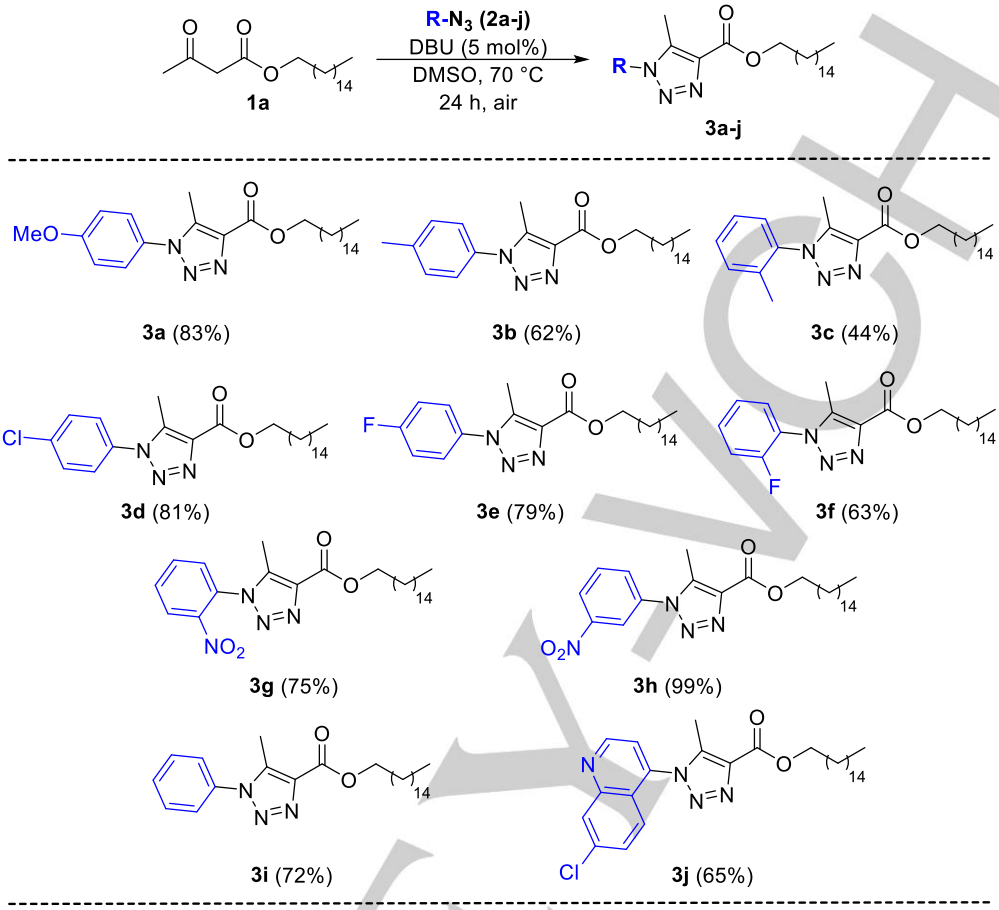
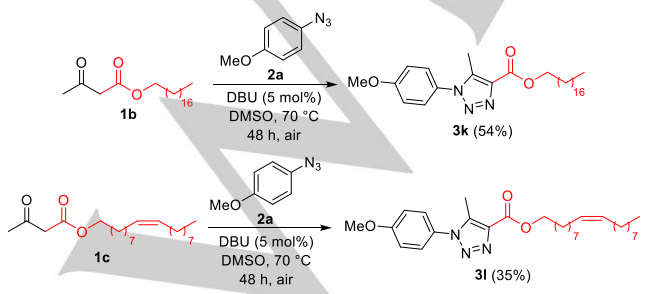


Figure 2. Generality in the synthesis of 1,2,3-triazoles derived from palmitic acetoacetate **3a-j**. Reactions were performed with palmitic acetoacetate **1a** (0.2 mmol) and arylazides **2** (0.3 mmol), using DBU (5 mol%) as a catalyst in DMSO (0.6 mL) under an air atmosphere at 70 °C for 24 h. Yields are given for isolated products.

In the next series of experiments, we extend the applicability of the optimized reaction conditions reacting *p*-methoxy phenylazide **2a** with stearic acetoacetate **1b** and oleyl acetoacetate **1c** as illustrated in Scheme 2. When stearic acetoacetate **1b** was used as a starting material, the corresponding 1,2,3-triazole **3k** was obtained moderately with 54% yield. Lower yield (35%) of 1,2,3-triazole **3l** was obtained when we carried out the reaction with oleyl acetoacetate **1c**. The reaction progress was followed by TLC and no total consumption of starting materials was observed even after 48 h.



Scheme 2. Reaction scope with stearic and oleyl acetoacetates **1b** and **1c,** respectively.

Anticancer Activity Assay

Studies showed that a variety of modified fatty acid are promising molecules to cancer treatment.[11] Cancer is a heterogeneous disease and one the most prevalent disease worldwide, and exist different treatments, such as surgical, radiation therapy, chemotherapy and immunotherapy.[12] The bladder cancer is the ninth most common malignancy, being the second urothelial cancer and the transitional cell carcinoma (TCC) represent the non-muscle invasive bladder cancer (NMIBC) about 70% of all cases.[13] Currently new chemotherapeutic compounds or drugs are required to treat this cancer, and nowadays are finding news compounds with antitumoral activities can help to decrease the risk of recurrence.

As example, Li *et al.* in 2016[14] reported the synthesis of novel 3-oxo-oleanolic acid coupled 1,2,3-triazole derivatives, and the cytotoxicity of these compounds was evaluated against five

different tumor cell lines. The obtained results shown that most of synthesized compounds presented potent activity and inhibitory activity against A375-S2 and HT1080 cells.

Therefore, the obtained 1,2,3-triazoles derived from palmitic β-ketoester **3a-j** were subjected to antitumoral and cytotoxic activity *in vitro* on human bladder cancer cell line. The results from MTT assay showed that most of the 1,2,3-triazoles derived from palmitic ester induced cytotoxicity on 5637 human bladder cancer cells in 48h (Figures 3 and 4). Besides, it was observed a decrease in cellular viability. The IC_{50} values (inhibitory concentration) were showed as mean ± SEM (Table 2).

After 48 h of incubation, compounds **3a**, **3c-e** (Figure 3) and **3g-j** (Figure 4) inhibited cell growth by 50% in concentrations ranging from 8.72 μM to 63.46 μM. In addition, compound **3d** inhibited cell growth more than 50% at three of the tested concentrations (12.5 μM, 50 μM and 100 μM) (Figure 3). The analogues **3i** and **3j** inhibited cell growth more than 50% only at higher concentration (Figure 4), showed antitumoral activity at concentrations of 62.78 μM and 63.46 μM respectively, in comparison to other compounds that presented low inhibitory concentration as **3d** (8.72 μM), **3g** (12.74 μM), **3e** (18.65 μM) and **3a** (22.50 μM). Also could be concluded that the electron-withdrawing group at the *para*-position in compounds **3d** (8.72 μM) and **3e** (18.65 μM) are able to increase the activity, while just the phenyl ring in compound **3i** (63.46 μM) lead to the decrease in the activity.

On the other hand, the compounds **3b** and **3f** did not show antitumoral activity because did not reach of 50% of the cellular growth inhibition at maximum concentration tested (100 μM).

Table 2. Inhibitory concentration (IC_{50}) values of 1,2,3-triazoles derived from palmitic chains **3a-j** against human bladder cancer cell line (5637) in 48 h of treatment. Data were represented as mean ± SEM.

Compounds	IC_{50} μM	Compounds	IC_{50} μM
3a	22.50 ± 6.28	**3f**	N/A
3b	N/A	**3g**	12.74 ± 3.99
3c	26.87 ± 11.07	**3h**	26.88 ± 8.93
3d	8.72 ± 1.19	**3i**	62.78 ± 14.63
3e	18.65 ± 7.57	**3j**	63.46 ± 7.32

IC_{50} Concentration required to inhibit growth by 50% compared to controls. N/A (not applicable). It was not inhibit 50% of the cellular growth in the higher concentration tested.

WILEY-VCH

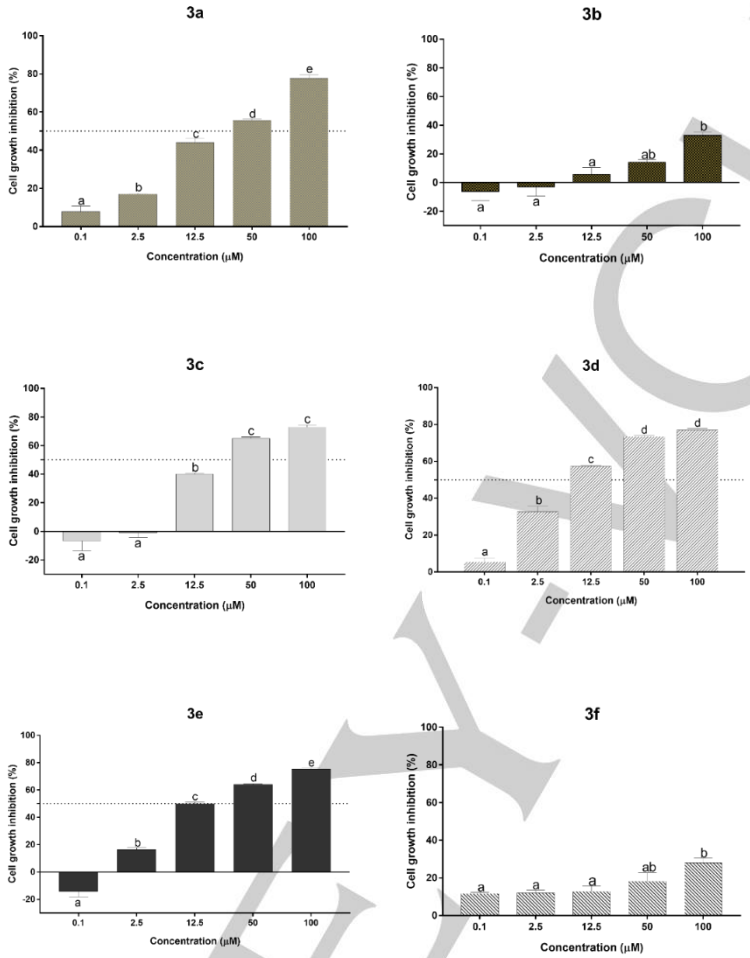


Figure 3. Cell growth inhibition by MTT in 5637 cells. Cells were treated with 1,2,3-triazoles **3a-f** at different concentrations of 0.1-100 μM for 48h. Data were obtained from three independent experiments. Different letters represent significant differences between the means of concentrations. $p < 0.05$ was considered significant.

WILEY-VCH

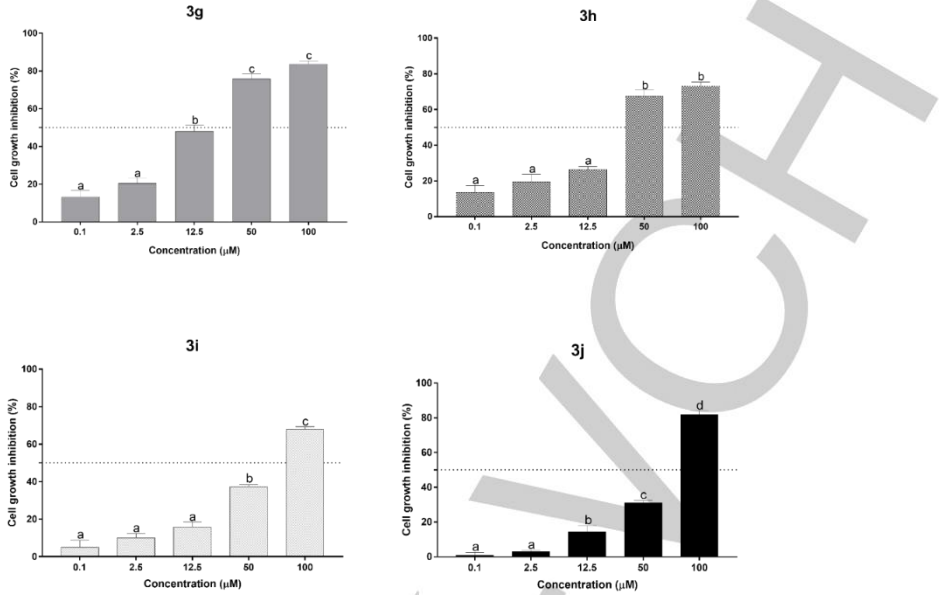


Figure 4. Cell growth inhibition by MTT in 5637 cells. Cells were treated with 1,2,3-triazoles **3g-j** at different concentrations of 0.1-100 μM for 48h. Data were obtained from three independent experiments. Different letters represent significant differences between the means of concentrations. p <0.05 was considered significant.

Conclusion

In summary, we describe a synthetic procedure for the preparation of 1,2,3-triazoles derived from fatty β-ketoesters by DBU-catalyzed 1,3-dipolar cycloaddition reactions of fatty esters with different aryl azides. These reactions tolerate a range of substituents on aryl azides and have proved to be an efficient methodology for the synthesis of new 1,2,3-triazoles containing fatty esters that were obtained in moderate to excellent yields. Compounds derived from palmitic acetoacetate were screened for the antitumor and cytotoxic activity *in vitro* on human bladder cancer cell line and compounds **3a**, **3d**, **3e** and **3g** were identified as promising for the bladder cancer treatment.

Experimental Section

General Information

The reactions were monitored by TLC carried out on Merck silica gel (60 F254) by using UV light as visualizing agent and 5% vanillin in 10% H_2SO_4 and heat as developing agents. Hydrogen nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 400 MHz on Bruker Avance III HD 400 spectrometer. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm, referenced to tetramethylsilane (TMS) as the external reference. Coupling constants (*J*) are reported in Hertz. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of double doublets), t (triplet), q (quartet), quint (quintet) and m (multiplet). Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 100 MHz on Bruker Avance III HD 400 spectrometer. Chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$. Low-resolution mass spectra were obtained with a Shimadzu GC-MS-QP2010 mass spectrometer. High resolution mass spectra (HRMS) were recorded on a Bruker Micro TOF-QII spectrometer 10416. The solvents and reagents were used as received or purified using standard procedures.

General procedure for the synthesis of 1,2,3-triazoles derived from fatty β-ketoesters 3a-l

The appropriate arylazide **2a-j** (0.3 mmol) was first added to a solution of fatty β-ketoesters **1a-c** (0.2 mmol) in DMSO (0.6 mL), followed by DBU (5 mol %) as catalyst. The reaction mixture was stirred in an open flask at 70 °C for 24 hours (48h for fatty esters **1b-c**). After completion of the reaction, the crude product was purified by column chromatography on silica gel with a mixture of hexane/ethyl acetate (90:10) as eluent to afford the desired product **3a-l**. Spectral data for the products prepared are listed below.

Spectral data of the products

Hexadecyl 1-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (3a). Yield: 0.076 g (83%); yellow solid, mp: 63-65 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.34 (d, *J* = 8.9 Hz, 2H), 7.04 (d, *J* = 8.9 Hz, 2H), 4.38 (t, *J* = 7.0 Hz, 2H), 3.88 (s, 3H), 2.54 (s, 3H), 1.81 (quint, *J* = 7.0, 2H), 1.44 (quint, *J* = 7.0 Hz, 2H), 1.34-1.25 (m, 24H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 162.1, 160.8, 139.0, 136.7, 128.4, 126.9 (2C), 114.9 (2C), 65.3, 55.8, 32.1, 29.82 (2C), 29.80 (2C), 29.78 (2C), 29.72, 29.66, 29.5, 29.4, 28.9, 26.1, 22.8, 14.3, 10.1. MS (relative intensity) m/z: 457 (M^+ 7), 205 (100), 187 (29), 161 (42), 83 (20).

Hexadecyl 5-methyl-1-(*p*-tolyl)-1*H*-1,2,3-triazole-4-carboxylate (3b). Yield: 0.055 g (62%); yellow solid, mp: 76-78 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.36 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 4.38 (t, *J* = 6.9 Hz, 2H), 2.56 (s, 3H), 2.45 (s, 3H), 1.81 (quint, *J* = 6.9 Hz, 2H), 1.44 (quint,

J = 6.9 Hz, 2H), 1.29-1.25 (m, 24H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 162.4, 140.8, 139.2, 137.1, 133.5, 130.7 (2C), 125.6 (2C), 65.7, 32.4, 30.14 (2C), 30.12 (2C), 30.10 (2C), 30.04, 29.97, 29.8, 29.7, 29.2, 26.4, 23.1, 21.7, 14.6, 10.5. MS (relative intensity) m/z: 441 (M^+ 7), 342 (6), 189 (100), 173 (30), 146 (32).

Hexadecyl 5-methyl-1-(*o*-tolyl)-1*H*-1,2,3-triazole-4-carboxylate (3c). Yield: 0.039 g (44%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.50-7.46 (m, 1H), 7.42-7.36 (m, 2H), 7.22 (d, *J* = 7.6 Hz, 1H), 4.40 (t, *J* = 7.0 Hz, 2H), 2.41 (s, 3H), 2.05 (s, 3H), 1.83 (quint, *J* = 7.0 Hz, 2H), 1.46 (quint, *J* = 7.0 Hz, 2H), 1.30-1.26 (m, 24H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 162.0, 139.7, 136.4, 135.6, 134.4, 131.5, 130.9, 127.3, 127.2, 65.4, 32.0, 29.79 (2C), 29.77 (2C), 29.75 (2C), 29.7, 29.6, 29.5, 29.4, 28.9, 26.1, 22.8, 17.3, 14.2, 9.5. MS (relative intensity) m/z: 441 (M^+ 3), 189 (86), 144 (100), 118 (68), 91 (42).

Hexadecyl 1-(4-chlorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (3d). Yield: 0.075 g (81%); yellow solid, mp: 82-84 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.55 (d, *J* = 8.7 Hz, 2H), 7.41 (d, *J* = 8.7 Hz, 2H), 4.39 (t, *J* = 6.9 Hz, 2H), 2.58 (s, 3H), 1.81 (quint, *J* = 6.9 Hz, 2H), 1.44 (quint, *J* = 6.9 Hz, 2H), 1.29-1.25 (m, 24H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 162.2, 139.2, 137.4, 136.7, 134.4, 130.4 (2C), 127.0 (2C), 65.8, 32.4, 30.15 (2C), 30.12 (2C), 30.11 (2C), 30.04, 29.97, 29.8, 29.7, 29.2, 26.4, 23.1, 14.6, 10.5. MS (relative intensity) m/z: 461 (M^+ 6), 362 (9), 306 (5), 209 (100), 111 (37).

Hexadecyl 1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (3e). Yield: 0.070 g (79%); white solid, mp: 68-70 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.47-7.43 (m, 2H), 7.29-7.25 (m, 2H), 4.39 (t, *J* = 6.9 Hz, 2H), 2.58 (s, 3H), 1.82 (quint, *J* = 6.9 Hz, 2H), 1.44 (quint, *J* = 6.9 Hz, 2H), 1.33-1.26 (m, 24H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 163.4 (d, *J* = 251.4 Hz), 161.9, 139.0, 137.0, 131.7 (d, *J* = 3.4 Hz), 127.6 (d, *J* = 9.0 Hz) (2C), 117.0 (d, *J* = 23.2 Hz) (2C), 65.5, 32.1, 29.83 (2C), 29.80(2C), 29.79(2C), 29.72, 29.66, 29.5, 29.4, 28.9, 26.1, 22.8, 14.3, 10.1. MS (relative intensity) m/z: 445 (M^+ 3), 222 (29), 204 (30), 193 (100), 95 (33).

Hexadecyl 1-(2-fluorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (3f). Yield: 0.056 g (63%); yellow solid, mp: 44-46 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.62-7.57 (m, 1H), 7.53-7.49 (m, 1H), 7.39-7.31 (m, 2H), 4.40 (t, *J* = 6.7 Hz, 2H), 2.52 (s, 3H), 1.83 (quint, *J* = 6.7 Hz, 2H), 1.46 (quint, *J* = 6.7 Hz, 2H), 1.32-1.26 (m, 24H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 161.7, 156.2 (d, *J* = 254.1 Hz), 140.5, 136.5, 132.5 (d, *J* = 7.8 Hz), 128.8, 125.3 (d, *J* = 3.9 Hz), 123.4 (d, *J* = 12.5 Hz), 117.0 (d, *J* = 19.2 Hz), 65.3, 32.0, 29.74 (2C), 29.72 (2C), 29.70 (2C), 29.64, 29.57, 29.4, 29.3, 28.8, 26.0, 22.7, 14.2, 9.4. MS (relative intensity) m/z: 445 (M^+ 6), 204 (50), 177 (51), 122 (100), 95 (32).

Hexadecyl 5-methyl-1-(2-nitrophenyl)-1*H*-1,2,3-triazole-4-carboxylate (3g). Yield: 0.071 g (75%); yellow solid, mp: 78-80 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.25 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.90-7.86 (m, 1H), 7.84-7.80 (m, 1H), 7.52 (dd, *J* = 7.7, 1.6 Hz, 1H), 4.40 (t, *J* = 6.9 Hz, 2H), 2.50 (s, 3H), 1.83 (quint, *J* = 7.0 Hz, 2H), 1.45 (quint, *J* = 6.7 Hz, 2H), 1.34-1.26 (m, 24H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 161.7, 145.5, 140.9, 136.7, 134.5, 132.1, 130.0, 128.9, 126.2, 65.6, 32.1, 29.82 (2C), 29.80 (2C), 29.79 (2C), 29.7, 29.6, 29.5, 29.4, 28.8, 26.1, 22.8, 14.3, 9.6. MS (relative intensity) m/z: 473 (M^+ 4), 249 (44), 231 (58), 179 (100), 163 (81).

Hexadecyl 5-methyl-1-(3-nitrophenyl)-1*H*-1,2,3-triazole-4-carboxylate (3h). Yield: 0.093 g (99%); yellow solid, mp: 76-78 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.43 (ddd, *J* = 8.1, 2.2, 1.2 Hz, 1H), 8.38-8.37 (m, 1H), 7.87 (ddd, *J* = 8.0, 2.1, 1.2 Hz, 1H), 7.83-7.79 (m, 1H), 4.39 (t, *J* = 6.8 Hz, 2H), 2.66 (s, 3H), 1.84-1.77 (m, 6H), 1.44 (quint, *J* = 7.2 Hz, 2H), 1.30-1.24 (m, 20H), 0.86 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 161.6, 148.9, 138.9, 137.5, 136.5, 131.10, 131.06, 124.8, 120.5, 65.6, 32.0, 29.80 (2C), 29.78 (2C), 29.76 (2C), 29.7, 29.6, 29.5, 29.4, 28.8, 26.1, 22.8, 14.2, 10.2. MS (relative intensity) m/z: 472 (M^+ 1), 249 (78), 231 (89), 163 (72), 83 (100).

Hexadecyl 5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxylate (3i). Yield: 0.059 g (72%); yellow solid, mp: 54-56 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.61-7.54 (m, 3H), 7.47-7.44 (m, 2H), 4.40 (t, *J* = 6.9 Hz, 2H), 2.59 (s, 3H), 1.82 (quint, *J* = 6.9 Hz, 2H), 1.45 (quint, *J* = 6.9 Hz, 2H), 1.31-1.26 (m, 24H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 162.0, 138.9, 136.9, 135.6, 130.2, 129.8 (2C), 125.5 (2C), 65.4, 32.0, 29.81 (2C), 29.79 (2C), 29.77 (2C), 29.7, 29.6, 29.5, 29.4, 28.9, 26.1, 22.8, 14.2, 10.2. MS (relative intensity) m/z: 412 (M^+ 0.3), 186 (34), 175 (100), 130 (82), 118 (41).

Hexadecyl 1-(7-chloroquinolin-4-yl)-5-methyl-1H-1,2,3-triazole-4-carboxylate (3j). Yield: 0.066 g (65%); beige solid, mp: 59-61 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 9.14 (d, *J* = 4.5 Hz, 1H), 8.29 (d, *J* = 2.1 Hz, 1H), 7.58 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.43 (d, *J* = 4.5 Hz, 1H), 7.33 (d, *J* = 9.0 Hz, 1H), 4.44 (t, *J* = 6.9 Hz, 2H), 2.48 (s, 3H), 1.85 (quint, *J* = 7.0 Hz, 2H), 1.47 (quint, *J* = 7.0 Hz, 2H), 1.30-1.26 (m, 24H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 161.6, 151.5, 150.2, 140.4, 139.7, 137.4, 137.1, 130.1, 129.3, 123.9, 122.4, 119.0, 65.7, 32.0, 29.81 (2C), 29.80 (2C), 29.77 (2C), 29.7, 29.6, 29.5, 29.4, 28.8, 26.1, 22.8, 14.2, 9.8. MS (relative intensity) m/z: 512 (M^+ 9), 483 (32), 243 (39), 216 (100), 99 (20).

Octadecyl 1-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (3k). Yield: 0.052 g (54%); yellow solid, mp: 74-76 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.35 (d, *J* = 8.9 Hz, 2H), 7.05 (d, *J* = 8.9 Hz, 2H), 4.39 (t, *J* = 6.9 Hz, 2H), 3.89 (s, 3H), 2.55 (s, 3H), 1.82 (quint, *J* = 6.9 Hz, 2H), 1.44 (quint, *J* = 6.9 Hz, 2H), 1.30-1.26 (m, 28H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 162.1, 160.8, 139.0, 136.7, 128.4, 126.9 (2C), 114.9 (2C), 65.3, 55.8, 32.1, 29.83 (4C), 29.80 (2C), 29.78 (2C), 29.72, 29.66, 29.5, 29.4, 28.9, 26.1, 22.8, 14.2, 10.1. MS (relative intensity) m/z: 485 (M^+ 3), 457 (21), 205 (100), 188 (29), 161 (32).

(*Z*)-Octadec-9-en-1-yl 1-(4-methoxyphenyl)-5-methyl-1H-1,2,3-triazole-4-carboxylate (3l). Yield: 0.034 g (35%); yellow solid, mp: 84-86 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.35 (d, *J* = 8.9 Hz, 2H), 7.05 (d, *J* = 8.9 Hz, 2H), 5.36-5.33 (m, 2H), 4.39 (t, *J* = 6.8 Hz, 2H), 3.89 (s, 3H), 2.55 (s, 3H), 2.04-1.99 (m, 4H), 1.82 (quint, *J* = 7.0 Hz, 2H), 1.45 (quint, *J* = 8.0 Hz, 2H), 1.29-1.26 (m, 20H), 0.88 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 162.1, 160.8, 139.1, 136.7, 130.1, 129.9, 128.4, 126.9 (2C), 114.9 (2C), 65.3, 55.8, 32.0, 29.91, 29.88, 29.8, 29.7, 29.6, 29.5 (2C), 29.41, 29.37, 28.9, 27.4, 26.1, 22.8, 14.2, 10.1. MS (relative intensity) m/z: 482 (M^+ 2), 205 (53), 188 (31), 134 (31), 97 (19), 83 (100).

Anticancer Activity Assay

Cell culture: The human bladder carcinoma cell line (5637) was obtained from the Rio de Janeiro Cell Bank (PABCAM, Federal University of Rio de Janeiro, RJ, Brazil). The carcinoma cells were cultured in RPMI1640 (Vitrocell Embriolife, Campinas, Brazil), supplemented with 10% of fetal bovine serum (FBS) Gibco (New York, USA), 1% L-glutamine, and 1% penicillin/streptomycin. Cells were grown at 37 ºC and 5% CO_2 in a humidified incubator and were used cells in the logarithmic growth phase.

Determination of cytotoxicity: The viability of 5637 cells were determined by measuring the reduction of soluble MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] to water insoluble formazan.[15] Cells line 5636 were seeded at a density of 2× 10^4 cells/well into a 96-well plate in a volume of 100 µL and grown for 24 hours at 37 ºC. Then, cells were incubated with 1,2,3-triazoles derived from palmitic ester **3a-j** diluted in DMSO (vehicle, with concentration less than 0.5%) with different concentrations (0.1, 2.5, 12.5, 50 and 100 µM) for 48 hours. Next, 5 mg/mL of MTT solution was added to each plate and remained in contact with cells for 3 hours at 37 °C. After this period, the medium was removed and was added to each well 200 µL of DMSO and the formazan crystals were dissolved on a shaker for 20 min at 150 rpm. Then, the absorbance

of each well was read on a microplate reader (MR-96A-Microplate Reader) at a wavelength of 492 nm. The inhibition (%) of cell proliferation was determined by the formula: cell growth inhibition = [1-(Abs_{492} treated cells/Abs_{492} control cells)] x 100%.[16] Control cells were considered the cells that were not submitted to any treatment. The IC_{50} (concentration that inhibits 50% of cell growth) and the results were obtained by at least three independent experiments in triplicate for each experiment.

Statistical analysis

The IC_{50} values were calculated by a non-linear regression method using GraphPad Prism 7.0 software. Differences in the mean values between concentrations were evaluated by analysis of variance (ANOVA) followed by a Tukey test for all pairwise multiple comparisons in Statistic version 10.0 (Analytical Software, Tallahassee, FL). Data were expressed as mean ± SEM at least three independent experiments and $p < 0.05$ was considered statistically significant.

Acknowledgements

The authors are grateful for the financial support and scholarships from the Brazilian agencies CNPq and FAPERGS (PRONEM 16/2551-0000240-1). CNPq is also acknowledged for the fellowship for M.M.D., L.S., T.C., F.S. and D.A.. This study was partially financed by the Coordenação de Aperfeiçoamento de Pessoal de Nivel Superior-Brasil (CAPES)-Finance Code 001. We are grateful to Prof. Thiago Barcellos from University of Caxias do Sul (UCS) for providing the HRMS analysis.

Author information

Corresponding Author

*E-mail: diego.alves@ufpel.edu.br. Tel/Fax: +55 5332757533 (D.A.).

Notes

The authors declare no competing financial interest.

Keywords: Fatty acids; 1,2,3-Triazoles; organocatalysis; antitumoral; bladder cancer.

[1] (a) W. Dehaen, V. A. Bakulev, *Chemistry of 1,2,3-triazoles*, Springer International Publishing, New York, 1st ed., **2014**. For a recent set of reviews in this area, see themed issues: (b) *Chem. Soc. Rev.* 2010, **39**, 1221. (c) *Acc. Chem. Res.* 2011, **44**, 651.

[2] R. Huisgen, *Angew. Chem., Int. Ed.* **1963**, *2*, 565.

[3] (a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596. (b) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057. (c) A. Krasinski, Z. Radic, R. Manetsch, J. Raushel, P. Taylor, K. B. Sharpless, H. C. Kolb, *J. Am. Chem. Soc.* **2005**, *127*, 6686. (d) L. V. Lee, M. L. Mitchell, S. Huang, V. V. Fokin, K. B. Sharpless, C. Wong, *J. Am. Chem. Soc.* **2003**, *125*, 9588. (e) J. E. Hein, J. P. Tripp, L. B. Krasnova, K. B. Sharpless, V. V. Fokin, *Angew. Chem. Int. Ed.* **2009**, *48*, 8018. (f) L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. Jia, *J. Am. Chem. Soc.* **2005**, *127*, 15998. (g) B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia, V. V. Fokin, *J. Am. Chem. Soc.* **2008**, *130*, 8923. (h) J. McNulty, K. Keskar, R. Vemula, *Chem. Eur. J.* **2011**, *17*, 14727. (i) J. McNulty, K. Keskar, *Eur. J. Org. Chem.* **2012**, 5462. (j) S. Ding, G. Jia, J. Sun, *Angew. Chem. Int. Ed.* **2014**, *53*, 1877.

[4] (a) K. Jomova, M. Valko, *Toxicology* **2011**, *283*, 65. (b) J. Gierlich, G. A. Burley, P. M. E. Gramlich, D. M. Hammond, T. Carell, *Org. Lett.* **2006**, *8*, 3639.

[5] (a) E. Lallana, E. Fernandez-Megia, R. Riguera, *J. Am. Chem. Soc.* **2009**, *131*, 5748. (b) A. J. Link, M. K. S. Vink, D. A. Tirrell, *J. Am. Chem. Soc.* **2004**, *126*, 1098. (c) L. M. Gaetke, C. K. Chow, *Toxicology* **2003**, *189*, 147.

[6] (a) D. B. Ramachary, K. Ramakumar, V. V. Narayana, *Chem. Eur. J.* **2008**, *14*, 9143. (b) L. J. T. Danence, Y. Gao, M. Li, Y. Huang, J. Wang, *Chem. Eur. J.* **2011**, *17*, 3584. (c) M. Belkheira, D. E. Abed, J. -M. Pons, C. Bressy, C. *Chem. Eur. J.* **2011**, *17*, 12917. (d) L. Wang, S. Peng, L. J. T. Danence, Y. Gao, J. Wang, *Chem. Eur. J.* **2012**, *18*, 6088. (e) D. K. J. Yeung, T. Gao, J. Huang, S. Sun, H. Guo, J. Wang, J. *Green Chem.* **2013**, *15*, 2384. (f) D. B. Ramachary, A. B. Shashank, *Chem. Eur. J.* **2013**, *19*, 13175. (g) W. Li, Z. Du, J. Huang, Q. Jia, K. Zhang, J. Wang, *Green Chem.* **2014**, *16*, 3003. (h) M. T. Saraiva, G. P. Costa, N. Seus, R. F. Schumacher, G. Perin, M. W. Paixão, R. Luque, D. Alves, D. *Org. Lett.* **2015**, *17*, 6206. (i) N. Seus, B. Goldani, E. J. Lenardão, L. Savegnago, M. W. Paixão, D. Alves, D. *Eur. J. Org. Chem.* **2014**, 5, 1059. (j) N. Seus, L. C. Gonçalves, A. M. Deobald, L. Savegnago, D. Alves, M. W. Paixão, *Tetrahedron* **2012**, *68*, 10456. (k) D. Alves, B. Goldani, E. J. Lenardão, G. Perin, R. F. Schumacher, M. W. Paixão, *Chem. Rec.* **2018**, *18*, 527. (l) A. Ali, A. G. Corrêa, D. Alves, J. Zukerman-Schpector, B. Westermann, M. A. B. Ferreira, M. W. Paixão, *Chem. Commun.* **2014**, *50*, 11926. (m) A. B. Shashank, S. Karthik, R. Madhavachary, D. B. Ramachary *Chem. Eur. J.* **2014**, *20*, 16877. (n) D. B. Ramachary, A. B. Shashank, S. Karthik, *Angew. Chem., Int. Ed.* **2014**, *126*, 10588.

[7] (a) V. Venepally, R. C. R. Jala, *Eur. J. Med. Chem.* **2017**, *141*, 113. (b) V. P. M. Rahman, S. Mukhtar, W. H. Ansari, G. Lemiere, *Eur. J. Med. Chem.* **2005**, *40*, 173. (c) H. Takahashi, M. Kosaka, Y. Watanabe, K. Nakade, Y. Fukuyama, *Bioorg. Med. Chem.* **2003**, *11*, 1781. (d) R. C. Brinkerhoff, E. Santa-Helena, P. C. Amaral, D. C. Cabrera, R. F. Ongaratto, P. M. Oliveira, C. M. D'Oca, C. A. Gonçalves, L. E. M. Nery, M. G. M. D'Oca, *RSC Adv.* **2019**, *9*, 24688.

[8] (a) D. Richard, K. Kefi, U. Barbe, P. Bausero, F. Visioli, *Pharmacol. Res.* **2008**, *57*, 451. (b) P. Beck, J. M. Sandos,B. L. Kuhn, D. N. Moreira, A. F. C. Flores, M. A. P. Martins, M. G. M. D'Oca, L. A. Piovesan, *J. Braz. Chem. Soc.* **2012**, *23*, 2122.

[9] D. G. Ghiano, A. Iglesia, N. Liu, P. J. Tonge, H. R. Morbidoni, G. R. Labadie, *Eur. J. Med. Chem.* **2017**, *125*, 842.

[10] S. M. Salman, *Int. J. Res. Pharm. Sci.* **2019**, *10*, 2334.

[11] (a) V. P. Mujeebur-Rahman, S. Mukhtar, W. H. Ansari, G. Lemiere, *Eur. J. Med. Chem.* **2005**, *40*, 173. (b) Y. Nagao, J. Mustafa, S. Sano, M. Ochiai, T. Tazuko, T. Shigeru, *Med. Chem. Res.* **1991**, *1*, 295. (c) M. S. F. L. K. Jie, J. Mustafa, M. K. Pasha, *Chem. Phys. Lipids* **1999**, *100*, 165.

[12] K. D. Miller, R. L. Siegel, C. C. Lin, A. B. Mariotto, J. L. Kramer, J. H. Rowland, *CA Cancer J. Clin.* **2016**, *66*, 271.

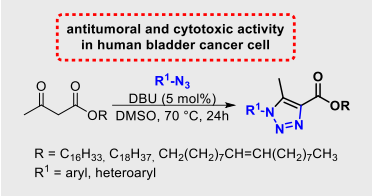
[13] (a) A. Naselli, R. Hurle, S. Paparella, N. M. Buffi, G. Lughezzani, G. Lista, *Eur. Urol. Focus* **2017**, *4*, 558. (b) O. Sanli, J. Dobruch, M. A. Knowles, M. Burger, *Nat. Publ. Gr.* **2017**, *3*, 1. (c) R. L. Siegel, K. D. Miller, A. Jemal, *CA Cancer J. Clin.* **2017**, *67*, 7.

[14] F. Li, Y. Liu, S. Wang, G. Wei, M. Cheng, *Chem. Res. Chin. Univ.* **2016**, *32*, 938.

[15] (a) T. Mosmann, *J. Immunol. Methods* **1983**, *65*, 55. (b) J. W. Tessmann, J. Buss, K. R. Begnini, L. M. Berneira, F. R. Paula, C. M. P. Pereira, T. Collares, F. K. Seixas, *Biomed. Pharmacother.* **2017**, *94*, 37.

[16] F. Nedel, V. F. Campos, D. Alves, A. J. A. McBride, O. A. Dellagostin, T. Collares, L. Savegnago, F. K. Seixas, *Life Sci.* **2012**, *91*, 345.

WILEY-VCH



A range of 1,2,3-triazoles derived from fatty β-ketoesters was synthesized and preliminary results of antitumor and cytotoxic activity were described. These compounds were synthesized in moderate to excellent yields by the reaction of fatty β-ketoesters with aryl azides using 5 mol% of DBU as a catalyst. All the compounds derived from palmitic acetoacetate were evaluated for the antitumor and cytotoxic activity *in vitro* on human bladder cancer cell line few of them were identified as promising and presenting the lowest inhibitory concentration of IC50.

Carolina B. Gomes, Caroline L. Corrêa, Diego C. Cabrera, Marcelo G. M. D'Oca, Martha L. R. Benitez, Tiago Collares, Lucielli Savegnago, Fabiana K. Seixas, Diego Alves**

Page No. – Page No.

Organocatalytic synthesis and antitumor activity of novel 1,2,3-triazoles derived from fatty β-ketoesters

Organocatalytic synthesis and antitumor activity of novel 1,2,3-triazoles derived from fatty β-ketoesters

Carolina B. Gomes,[a] Caroline L. Corrêa,[a] Diego C. Cabrera,[b] Marcelo G. M. D'Oca,[b] Martha L. R. Benitez,[c] Tiago Collares,[c] Lucielli Savegnago,[d] Fabiana K. Seixas,[c]* Diego Alves[a]*

[a] *Laboratório de Síntese Orgânica Limpa, Universidade Federal de Pelotas, UFPel. PO Box 354 - CEP 96010-900, Pelotas, RS, Brazil.*

[b] *Laboratory Organic Synthesis Kolbe- Federal University of Rio Grande - FURG. Rio Grande, RS, Brazil.*

[c] *Grupo de Pesquisa em Oncologia Celular e Molecular - GPO, CDTec, Universidade Federal de Pelotas, UFPel, Pelotas, RS, Brazil.*

[d] *Grupo de Pesquisa em Neurobiotecnologia - GPN, CDTec, Universidade Federal de Pelotas, UFPel, Pelotas, RS, Brazil.*

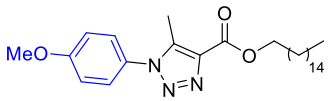
***Corresponding author:** E-mail: diego.alves@ufpel.edu.br, Phone / Fax: (+) 55 53 32757533.

Contents

General Information: The reactions were monitored by TLC carried out on Merck silica gel (60 F254) by using UV light as visualizing agent and 5% vanillin in 10% H_2SO_4 and heat as developing agents. Hydrogen nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 400 MHz on Bruker Avance III HD 400 spectrometer. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm, referenced to tetramethylsilane (TMS) as the external reference. Coupling constants (*J*) are reported in Hertz. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of double doublets), t (triplet), q (quartet), quint (quintet) and m (multiplet). Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 100 MHz on Bruker Avance III HD 400 spectrometer. Chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$. Low-resolution mass spectra were obtained with a Shimadzu GC-MS-QP2010 mass spectrometer. High resolution mass spectra (HRMS) were recorded on a Bruker Micro TOF-QII spectrometer 10416. The solvents and reagents were used as received or purified using standard procedures.

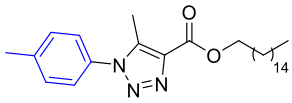
***General procedure for the synthesis of 1,2,3-triazoles derived from fatty β-ketoesters 3a-l*:** The appropriate arylazide **2a-j** (0.3 mmol) was first added to a solution of fatty β-ketoesters **1a-c** (0.2 mmol) in DMSO (0.6 mL), followed by DBU (5 mol %) as catalyst. The reaction mixture was stirred in an open flask at 70 °C for 24 hours (48h for fatty esters **1b-c**). After completion of the reaction, the crude product was purified by column chromatography on silica gel with a mixture of hexane/ethyl acetate (90:10) as eluent to afford the desired product **3a-l**. Spectral data for the products prepared are listed below.

Spectral data of the products:

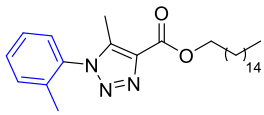


Hexadecyl 1-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (3a). Yield: 0.076 g (83%); yellow solid, mp: 63-65 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.34 (d, *J* = 8.9 Hz, 2H), 7.04 (d, *J* = 8.9 Hz, 2H), 4.38 (t, *J* = 7.0 Hz, 2H), 3.88 (s, 3H), 2.54 (s, 3H), 1.81 (quint, *J* = 7.0, 2H), 1.44 (quint, *J* = 7.0 Hz, 2H), 1.34-1.25 (m, 24H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 162.1, 160.8, 139.0, 136.7, 128.4, 126.9 (2C), 114.9 (2C), 65.3, 55.8, 32.1, 29.82 (2C), 29.80 (2C), 29.78 (2C), 29.72, 29.66,

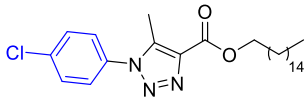
29.5, 29.4, 28.9, 26.1, 22.8, 14.3, 10.1. MS (relative intensity) m/z: 457 (M^+ 7), 205 (100), 187 (29), 161 (42), 83 (20).



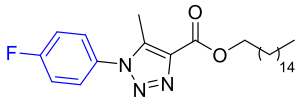
Hexadecyl 5-methyl-1-(*p*-tolyl)-1*H*-1,2,3-triazole-4-carboxylate (3b). Yield: 0.055 g (62%); yellow solid, mp: 76-78 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.36 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 4.38 (t, J = 6.9 Hz, 2H), 2.56 (s, 3H), 2.45 (s, 3H), 1.81 (quint, J = 6.9 Hz, 2H), 1.44 (quint, J = 6.9 Hz, 2H), 1.29-1.25 (m, 24H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 162.4, 140.8, 139.2, 137.1, 133.5, 130.7 (2C), 125.6 (2C), 65.7, 32.4, 30.14 (2C), 30.12 (2C), 30.10 (2C), 30.04, 29.97, 29.8, 29.7, 29.2, 26.4, 23.1, 21.7, 14.6, 10.5. MS (relative intensity) m/z: 441 (M^+ 7), 342 (6), 189 (100), 173 (30), 146 (32).



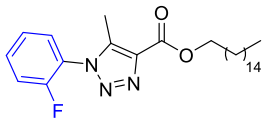
Hexadecyl 5-methyl-1-(*o*-tolyl)-1*H*-1,2,3-triazole-4-carboxylate (3c). Yield: 0.039 g (44%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.50-7.46 (m, 1H), 7.42-7.36 (m, 2H), 7.22 (d, J = 7.6 Hz, 1H), 4.40 (t, J = 7.0 Hz, 2H), 2.41 (s, 3H), 2.05 (s, 3H), 1.83 (quint, J = 7.0 Hz, 2H), 1.46 (quint, J = 7.0 Hz, 2H), 1.30-1.26 (m, 24H), 0.88 (t, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 162.0, 139.7, 136.4, 135.6, 134.4, 131.5, 130.9, 127.3, 127.2, 65.4, 32.0, 29.79 (2C), 29.77 (2C), 29.75 (2C), 29.7, 29.6, 29.5, 29.4, 28.9, 26.1, 22.8, 17.3, 14.2, 9.5. MS (relative intensity) m/z: 441 (M^+ 3), 189 (86), 144 (100), 118 (68), 91 (42).



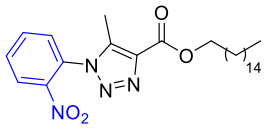
Hexadecyl 1-(4-chlorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (3d). Yield: 0.075 g (81%); yellow solid, mp: 82-84 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.55 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.7 Hz, 2H), 4.39 (t, J = 6.9 Hz, 2H), 2.58 (s, 3H), 1.81 (quint, J = 6.9 Hz, 2H), 1.44 (quint, J = 6.9 Hz, 2H), 1.29-1.25 (m, 24H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 162.2, 139.2, 137.4, 136.7, 134.4, 130.4 (2C), 127.0 (2C), 65.8, 32.4, 30.15 (2C), 30.12 (2C), 30.11 (2C), 30.04, 29.97, 29.8, 29.7, 29.2, 26.4, 23.1, 14.6, 10.5. MS (relative intensity) m/z: 461 (M^+ 6), 362 (9), 306 (5), 209 (100), 111 (37).



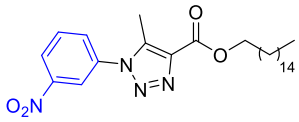
Hexadecyl 1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (3e). Yield: 0.070 g (79%); white solid, mp: 68-70 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.47-7.43 (m, 2H), 7.29-7.25 (m, 2H), 4.39 (t, *J* = 6.9 Hz, 2H), 2.58 (s, 3H), 1.82 (quint, *J* = 6.9 Hz, 2H), 1.44 (quint, *J* = 6.9 Hz, 2H), 1.33-1.26 (m, 24H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 163.4 (d, *J* = 251.4 Hz), 161.9, 139.0, 137.0, 131.7 (d, *J* = 3.4 Hz), 127.6 (d, *J* = 9.0 Hz) (2C), 117.0 (d, *J* = 23.2 Hz) (2C), 65.5, 32.1, 29.83 (2C), 29.80(2C), 29.79(2C), 29.72, 29.66, 29.5, 29.4, 28.9, 26.1, 22.8, 14.3, 10.1. MS (relative intensity) m/z: 445 (M^+ 3), 222 (29), 204 (30), 193 (100), 95 (33).



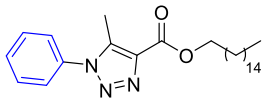
Hexadecyl 1-(2-fluorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (3f). Yield: 0.056 g (63%); yellow solid, mp: 44-46 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.62-7.57 (m, 1H), 7.53-7.49 (m, 1H), 7.39-7.31 (m, 2H), 4.40 (t, *J* = 6.7 Hz, 2H), 2.52 (s, 3H), 1.83 (quint, *J* = 6.7 Hz, 2H), 1.46 (quint, *J* = 6.7 Hz, 2H), 1.32-1.26 (m, 24H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 161.7, 156.2 (d, *J* = 254.1 Hz), 140.5, 136.5, 132.5 (d, *J* = 7.8 Hz), 128.8, 125.3 (d, *J* = 3.9 Hz), 123.4 (d, *J* = 12.5 Hz), 117.0 (d, *J* = 19.2 Hz), 65.3, 32.0, 29.74 (2C), 29.72 (2C), 29.70 (2C), 29.64, 29.57, 29.4, 29.3, 28.8, 26.0, 22.7, 14.2, 9.4. MS (relative intensity) m/z: 445 (M^+ 6), 204 (50), 177 (51), 122 (100), 95 (32).



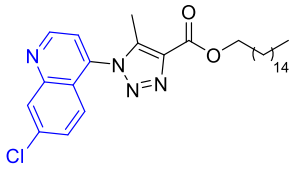
Hexadecyl 5-methyl-1-(2-nitrophenyl)-1*H*-1,2,3-triazole-4-carboxylate (3g). Yield: 0.071 g (75%); yellow solid, mp: 78-80 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.25 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.90-7.86 (m, 1H), 7.84-7.80 (m, 1H), 7.52 (dd, *J* = 7.7, 1.6 Hz, 1H), 4.40 (t, *J* = 6.9 Hz, 2H), 2.50 (s, 3H), 1.83 (quint, *J* = 7.0 Hz, 2H), 1.45 (quint, *J* = 6.7 Hz, 2H), 1.34-1.26 (m, 24H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 161.7, 145.5, 140.9, 136.7, 134.5, 132.1, 130.0, 128.9, 126.2, 65.6, 32.1, 29.82 (2C), 29.80 (2C), 29.79 (2C), 29.7, 29.6, 29.5, 29.4, 28.8, 26.1, 22.8, 14.3, 9.6. MS (relative intensity) m/z: 473 (M^+ 4), 249 (44), 231 (58), 179 (100), 163 (81).



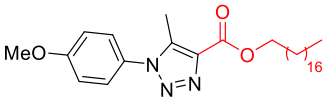
Hexadecyl 5-methyl-1-(3-nitrophenyl)-1*H*-1,2,3-triazole-4-carboxylate (3h). Yield: 0.093 g (99%); yellow solid, mp: 76-78 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.43 (ddd, J = 8.1, 2.2, 1.2 Hz, 1H), 8.38-8.37 (m, 1H), 7.87 (ddd, J = 8.0, 2.1, 1.2 Hz, 1H), 7.83-7.79 (m, 1H), 4.39 (t, J = 6.8 Hz, 2H), 2.66 (s, 3H), 1.84-1.77 (m, 6H), 1.44 (quint, J = 7.2 Hz, 2H), 1.30-1.24 (m, 20H), 0.86 (t, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 161.6, 148.9, 138.9, 137.5, 136.5, 131.10, 131.06, 124.8, 120.5, 65.6, 32.0, 29.80 (2C), 29.78 (2C), 29.76 (2C), 29.7, 29.6, 29.5, 29.4, 28.8, 26.1, 22.8, 14.2, 10.2. MS (relative intensity) m/z: 472 (M^+ 1), 249 (78), 231 (89), 163 (72), 83 (100).



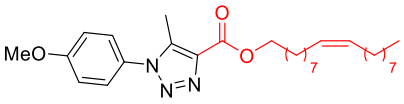
Hexadecyl 5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxylate (3i). Yield: 0.059 g (72%); yellow solid, mp: 54-56 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.61-7.54 (m, 3H), 7.47-7.44 (m, 2H), 4.40 (t, J = 6.9 Hz, 2H), 2.59 (s, 3H), 1.82 (quint, J = 6.9 Hz, 2H), 1.45 (quint, J = 6.9 Hz, 2H), 1.31-1.26 (m, 24H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 162.0, 138.9, 136.9, 135.6, 130.2, 129.8 (2C), 125.5 (2C), 65.4, 32.0, 29.81 (2C), 29.79 (2C), 29.77 (2C), 29.7, 29.6, 29.5, 29.4, 28.9, 26.1, 22.8, 14.2, 10.2. MS (relative intensity) m/z: 412 (M^+ 0.3), 186 (34), 175 (100), 130 (82), 118 (41).



Hexadecyl 1-(7-chloroquinolin-4-yl)-5-methyl-1H-1,2,3-triazole-4-carboxylate (3j). Yield: 0.066 g (65%); beige solid, mp: 59-61 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 9.14 (d, J = 4.5 Hz, 1H), 8.29 (d, J = 2.1 Hz, 1H), 7.58 (dd, J = 9.0, 2.1 Hz, 1H), 7.43 (d, J = 4.5 Hz, 1H), 7.33 (d, J = 9.0 Hz, 1H), 4.44 (t, J = 6.9 Hz, 2H), 2.48 (s, 3H), 1.85 (quint, J = 7.0 Hz, 2H), 1.47 (quint, J = 7.0 Hz, 2H), 1.30-1.26 (m, 24H), 0.88 (t, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 161.6, 151.5, 150.2, 140.4, 139.7, 137.4, 137.1, 130.1, 129.3, 123.9, 122.4, 119.0, 65.7, 32.0, 29.81 (2C), 29.80 (2C), 29.77 (2C), 29.7, 29.6, 29.5, 29.4, 28.8, 26.1, 22.8, 14.2, 9.8. MS (relative intensity) m/z: 512 (M^+ 9), 483 (32), 243 (39), 216 (100), 99 (20).



Octadecyl 1-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (3k). Yield: 0.052 g (54%); yellow solid, mp: 74-76 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.35 (d, J = 8.9 Hz, 2H), 7.05 (d, J = 8.9 Hz, 2H), 4.39 (t, J = 6.9 Hz, 2H), 3.89 (s, 3H), 2.55 (s, 3H), 1.82 (quint, J = 6.9 Hz, 2H), 1.44 (quint, J = 6.9 Hz, 2H), 1.30-1.26 (m, 28H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 162.1, 160.8, 139.0, 136.7, 128.4, 126.9 (2C), 114.9 (2C), 65.3, 55.8, 32.1, 29.83 (4C), 29.80 (2C), 29.78 (2C), 29.72, 29.66, 29.5, 29.4, 28.9, 26.1, 22.8, 14.2, 10.1. MS (relative intensity) m/z: 485 (M^+ 3), 457 (21), 205 (100), 188 (29), 161 (32).



(*Z*)-Octadec-9-en-1-yl 1-(4-methoxyphenyl)-5-methyl-1H-1,2,3-triazole-4-carboxylate (3l). Yield: 0.034 g (35%); yellow solid, mp: 84-86 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.35 (d, J = 8.9 Hz, 2H), 7.05 (d, J = 8.9 Hz, 2H), 5.36-5.33 (m, 2H), 4.39 (t, J = 6.8 Hz, 2H), 3.89 (s, 3H), 2.55 (s, 3H), 2.04-1.99 (m, 4H), 1.82 (quint, J = 7.0 Hz, 2H), 1.45 (quint, J = 8.0 Hz, 2H), 1.29-1.26 (m, 20H), 0.88 (t, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 162.1, 160.8, 139.1, 136.7, 130.1, 129.9, 128.4, 126.9 (2C), 114.9 (2C), 65.3, 55.8, 32.0, 29.91, 29.88, 29.8, 29.7, 29.6, 29.5 (2C), 29.41, 29.37, 28.9, 27.4, 26.1, 22.8, 14.2, 10.1. MS (relative intensity) m/z: 482 (M^+ 2), 205 (53), 188 (31), 134 (31), 97 (19), 83 (100).

Anticancer Activity Assay:

Cell culture: The human bladder carcinoma cell line (5637) was obtained from the Rio de Janeiro Cell Bank (PABCAM, Federal University of Rio de Janeiro, RJ, Brazil). The carcinoma cells were cultured in RPMI1640 (Vitrocell Embriolife, Campinas, Brazil), supplemented with 10% of fetal bovine serum (FBS) Gibco (New York, USA), 1% L-glutamine, and 1% penicillin/streptomycin. Cells were grown at 37 ºC and 5% CO_2 in a humidified incubator and were used cells in the logarithmic growth phase.

Determination of cytotoxicity: The viability of 5637 cells were determined by measuring the reduction of soluble MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium

bromide] to water insoluble formazan.[1] Cells line 5636 were seeded at a density of 2×10^4 cells/well into a 96-well plate in a volume of 100 µL and grown for 24 hours at 37 ºC. Then, cells were incubated with 1,2,3-triazoles derived from palmitic ester **3a-j** diluted in DMSO (vehicle, with concentration less than 0.5%) with different concentrations (0.1, 2.5, 12.5, 50 and 100 µM) for 48 hours. Next, 5 mg/mL of MTT solution was added to each plate and remained in contact with cells for 3 hours at 37 °C. After this period, the medium was removed and was added to each well 200 µL of DMSO and the formazan crystals were dissolved on a shaker for 20 min at 150 rpm. Then, the absorbance of each well was read on a microplate reader (MR-96A-Microplate Reader) at a wavelength of 492 nm. The inhibition (%) of cell proliferation was determined by the formula: cell growth inhibition = [1-(Abs_{492} treated cells/Abs_{492} control cells)] x 100%.[2] Control cells were considered the cells that were not submitted to any treatment. The IC_{50} (concentration that inhibits 50% of cell growth) and the results were obtained by at least three independent experiments in triplicate for each experiment.

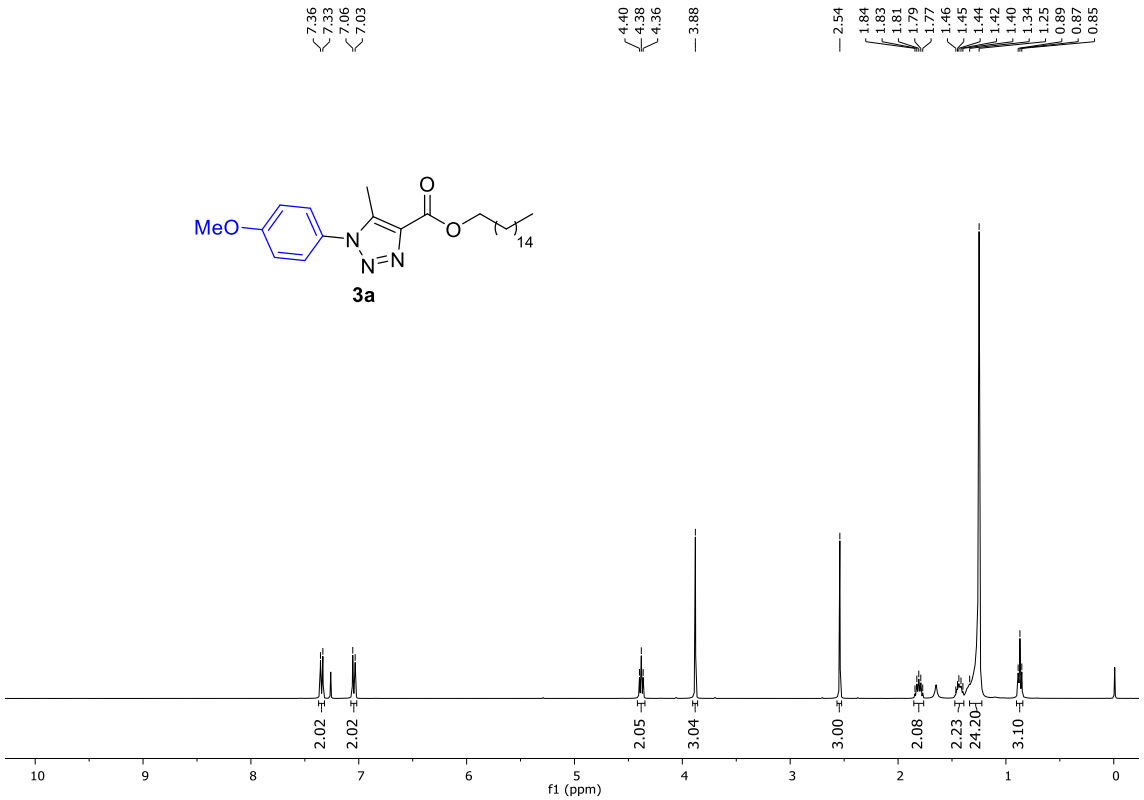
Statistical analysis

The IC_{50} values were calculated by a non-linear regression method using GraphPad Prism 7.0 software. Differences in the mean values between concentrations were evaluated by analysis of variance (ANOVA) followed by a Tukey test for all pairwise multiple comparisons in Statistic version 10.0 (Analytical Software, Tallahassee, FL). Data were expressed as mean ± SEM at least three independent experiments and $p < 0.05$ was considered statistically significant.

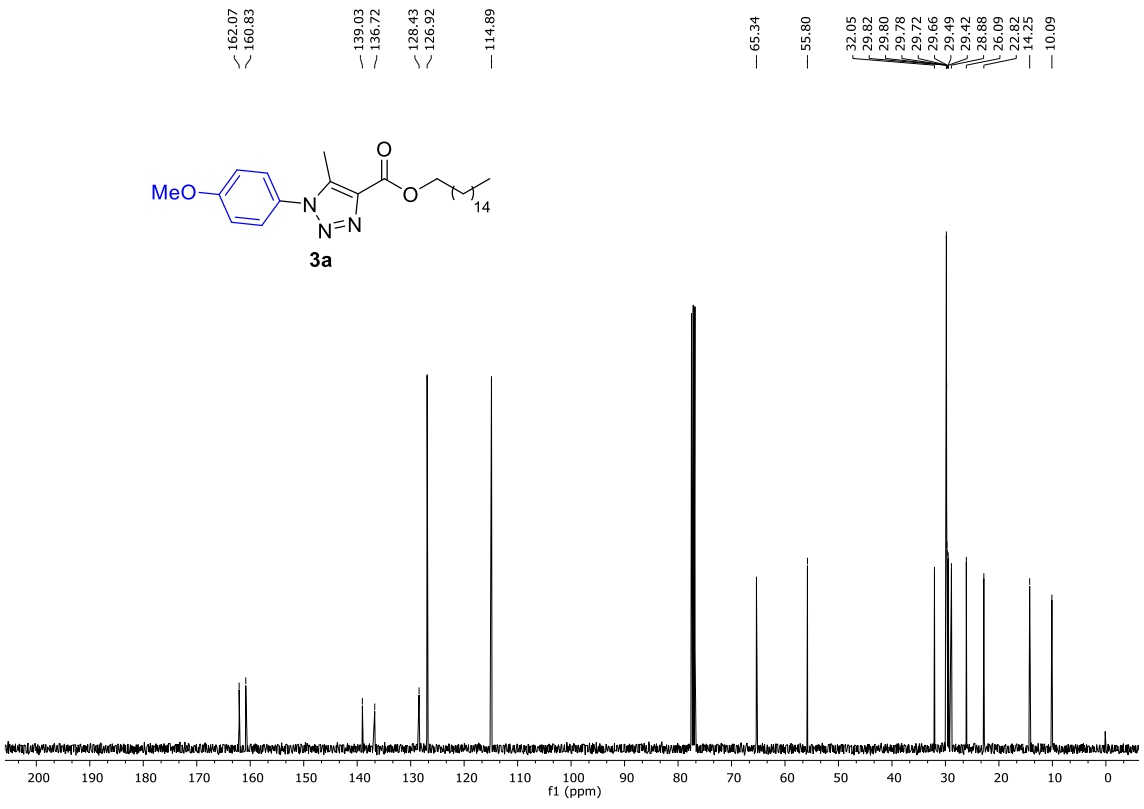
[1] (a) T. Mosmann, *J. Immunol. Methods* **1983**, *65*, 55. (b) J. W. Tessmann, J. Buss, K. R. Begnini, L. M. Berneira, F. R. Paula, C. M. P. Pereira, T. Collares, F. K. Seixas, *Biomed. Pharmacother.* **2017**, *94*, 37.

[2] F. Nedel, V. F. Campos, D. Alves, A. J. A. McBride, O. A. Dellagostin, T. Collares, L. Savegnago, F. K. Seixas, *Life Sci.* **2012**, *91*, 345.

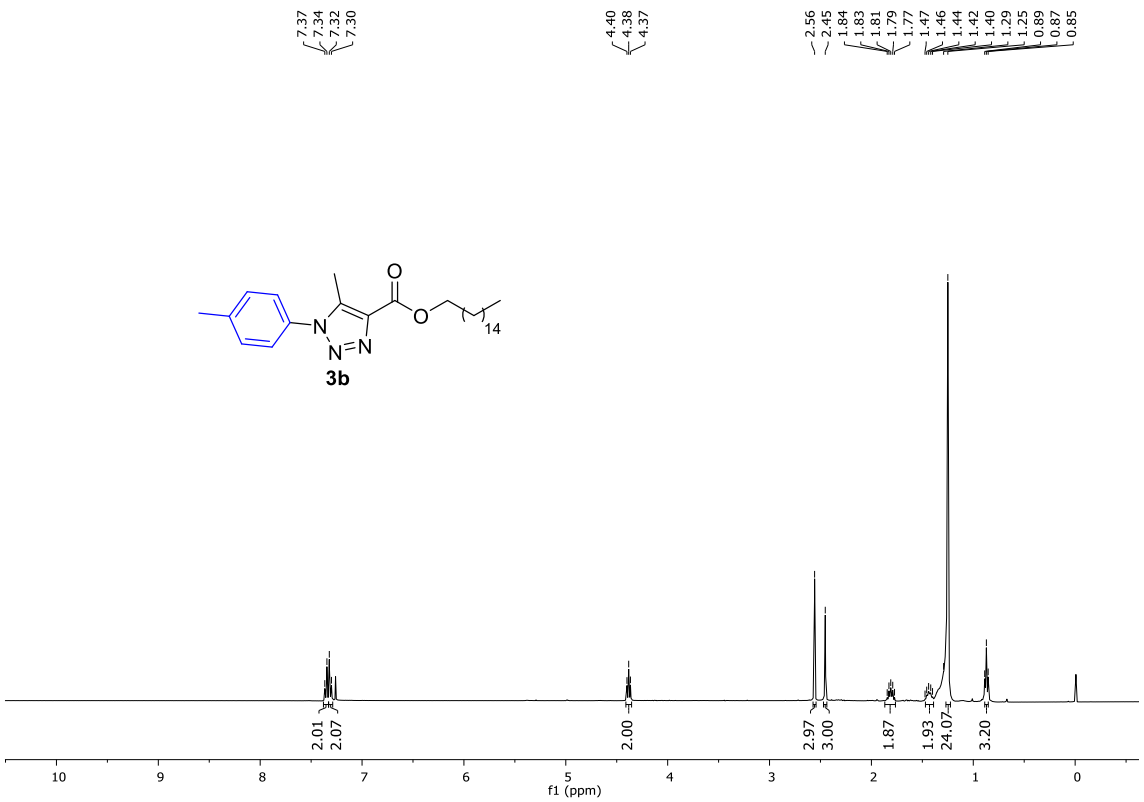
SELECTED SPECTRA



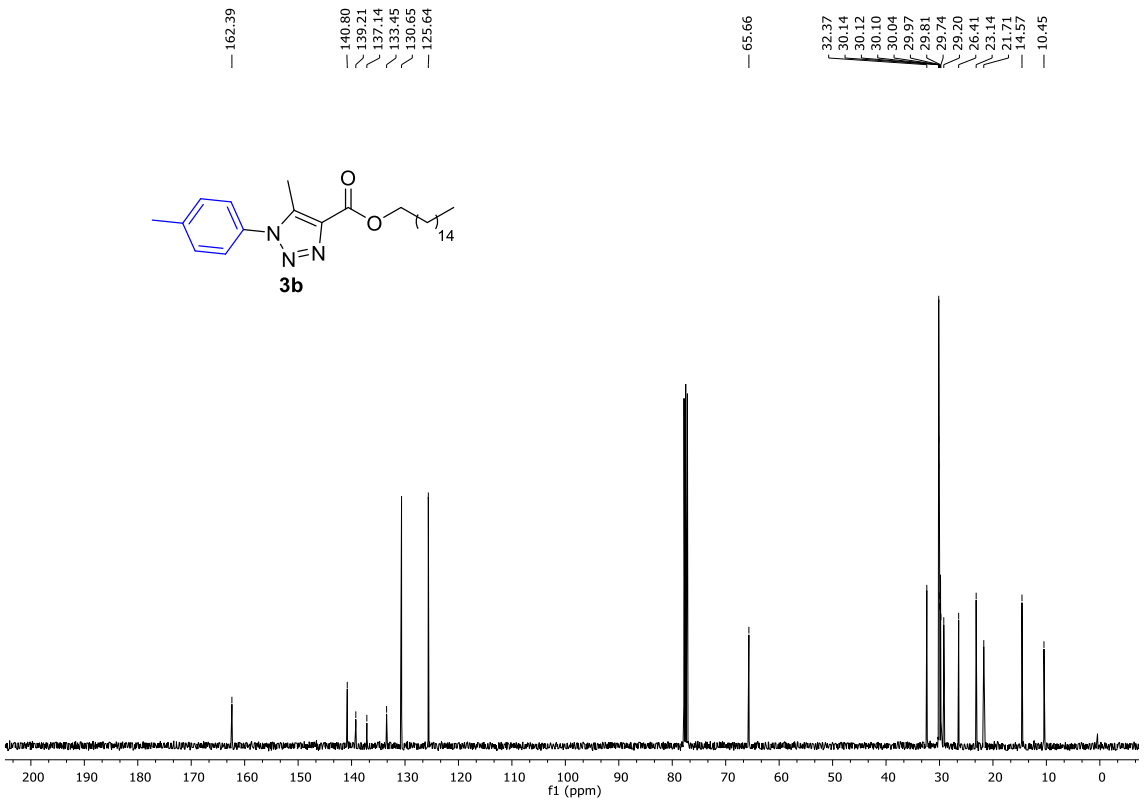
^{1}H NMR spectra of compound **3a** (400 MHz, $CDCl_3$)



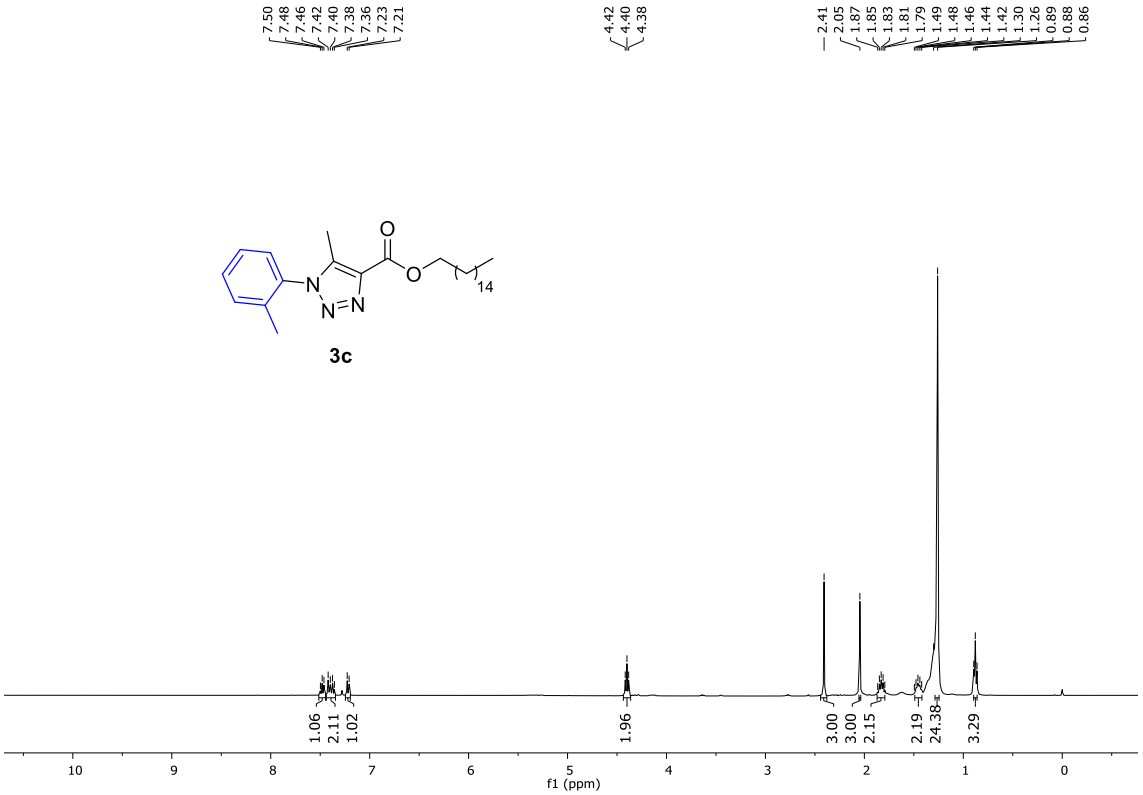
^{13}C NMR spectra of compound **3a** (100 MHz, $CDCl_3$)



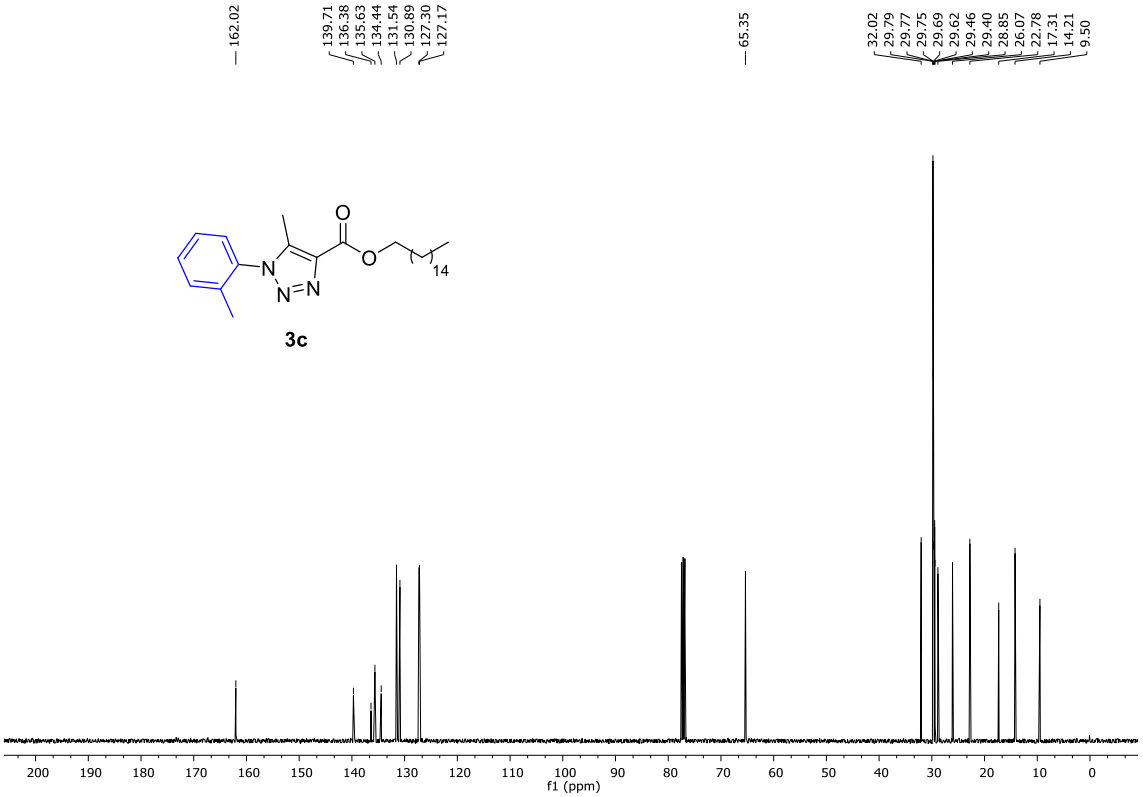
^{1}H NMR spectra of compound **3b** (400 MHz, $CDCl_3$)



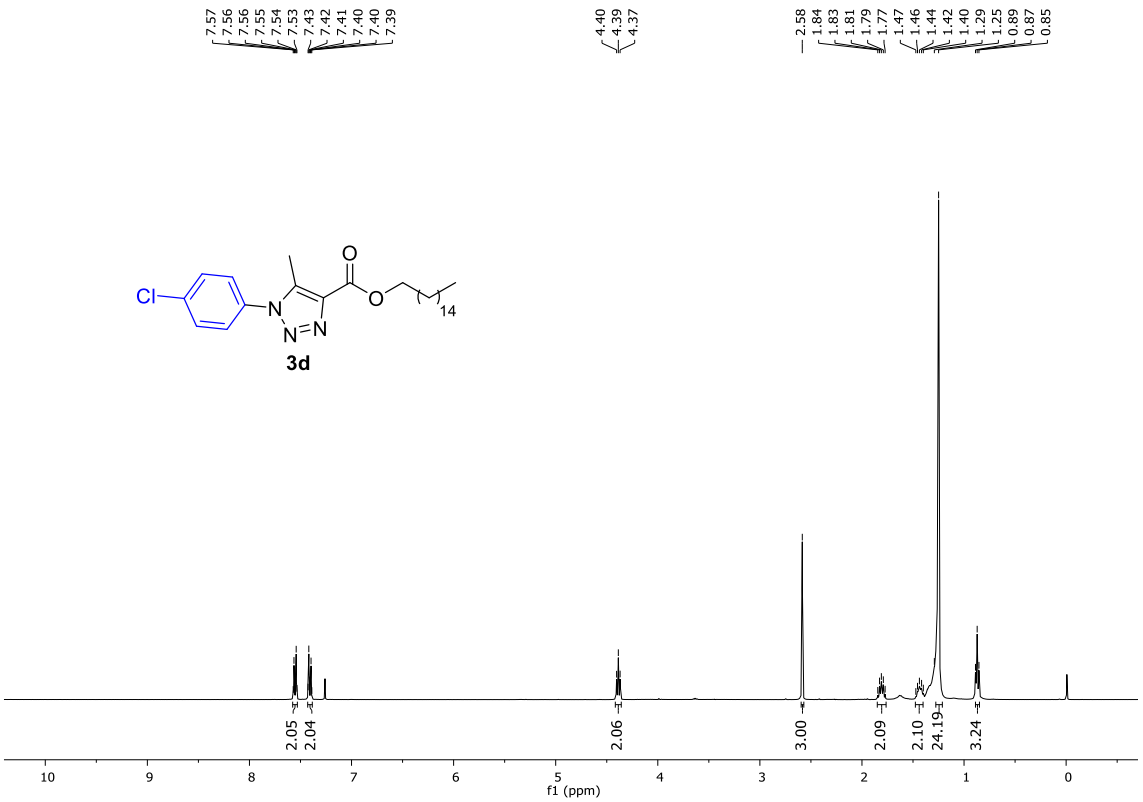
^{13}C NMR spectra of compound **3b** (100 MHz, $CDCl_3$)



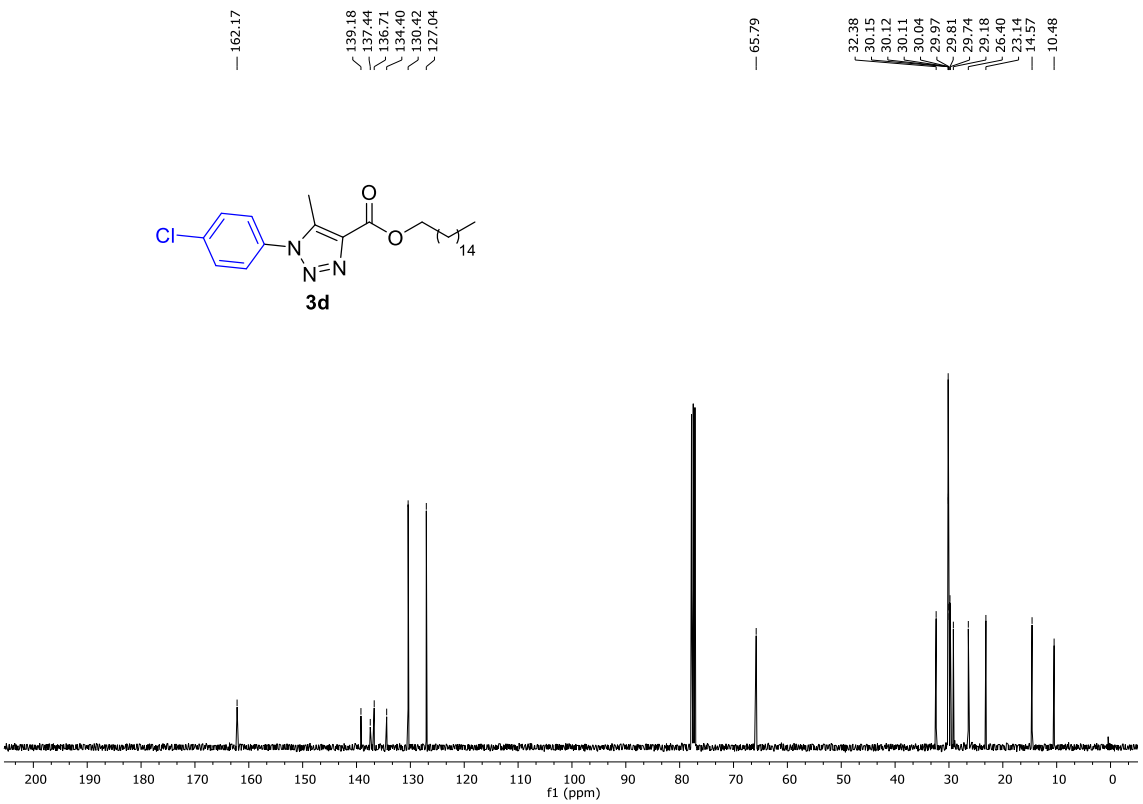
^{1}H NMR spectra of compound **3c** (400 MHz, $CDCl_3$)



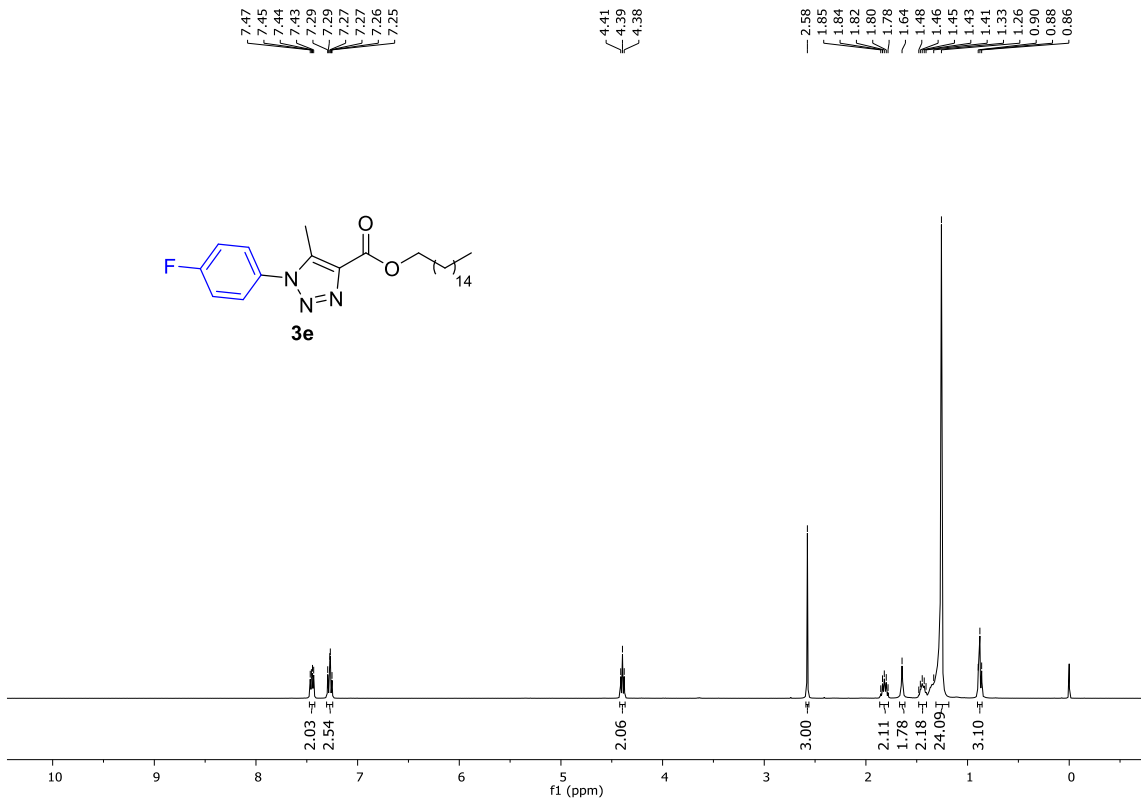
^{13}C NMR spectra of compound **3c** (100 MHz, $CDCl_3$)



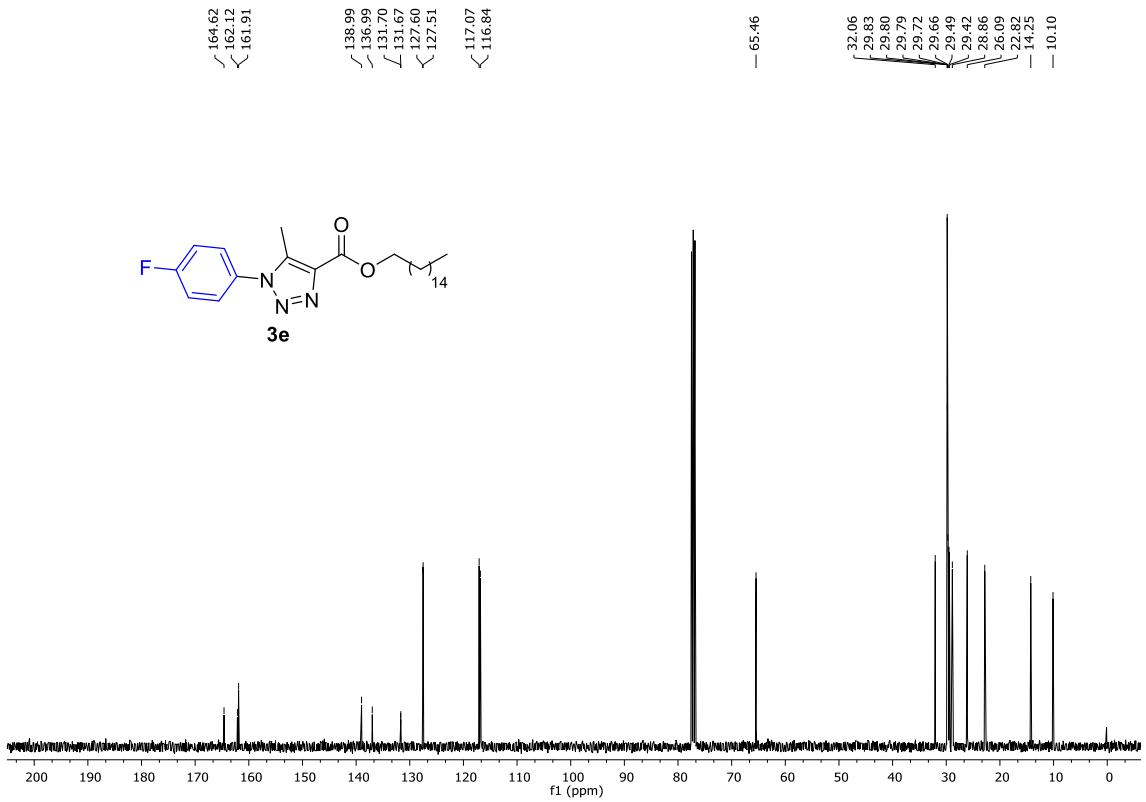
^{1}H NMR spectra of compound **3d** (400 MHz, $CDCl_3$)



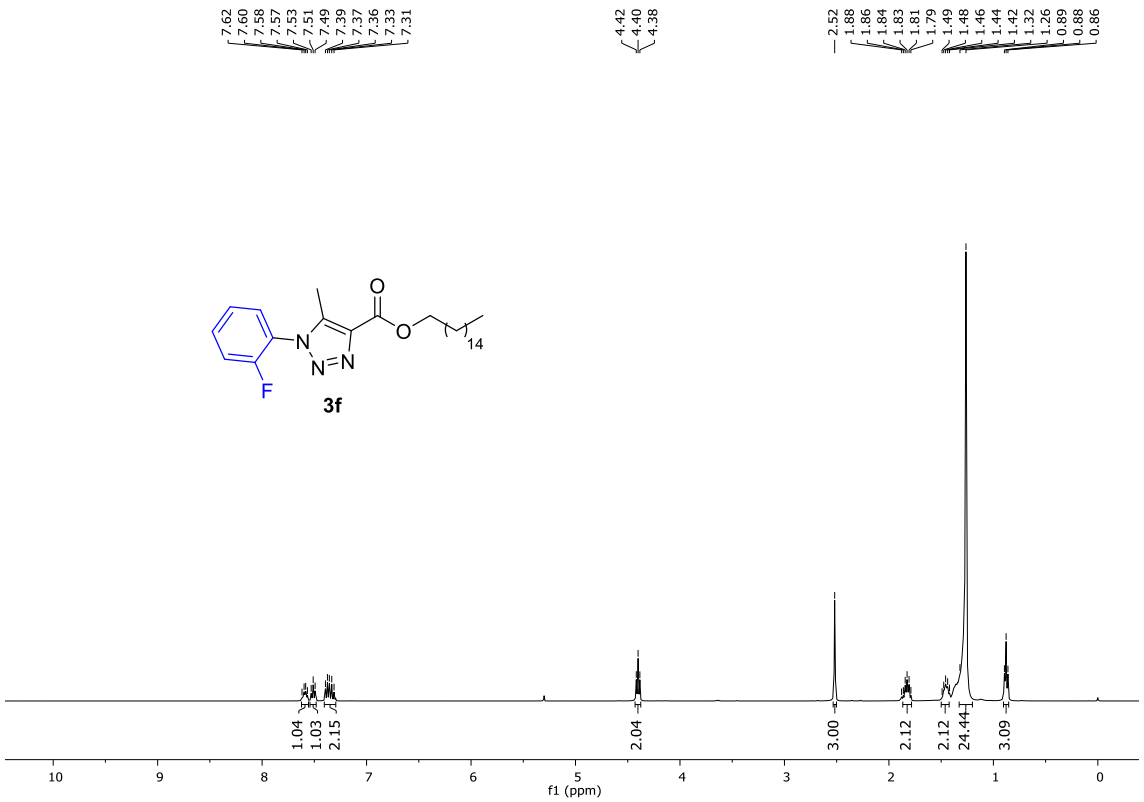
^{13}C NMR spectra of compound **3d** (100 MHz, $CDCl_3$)



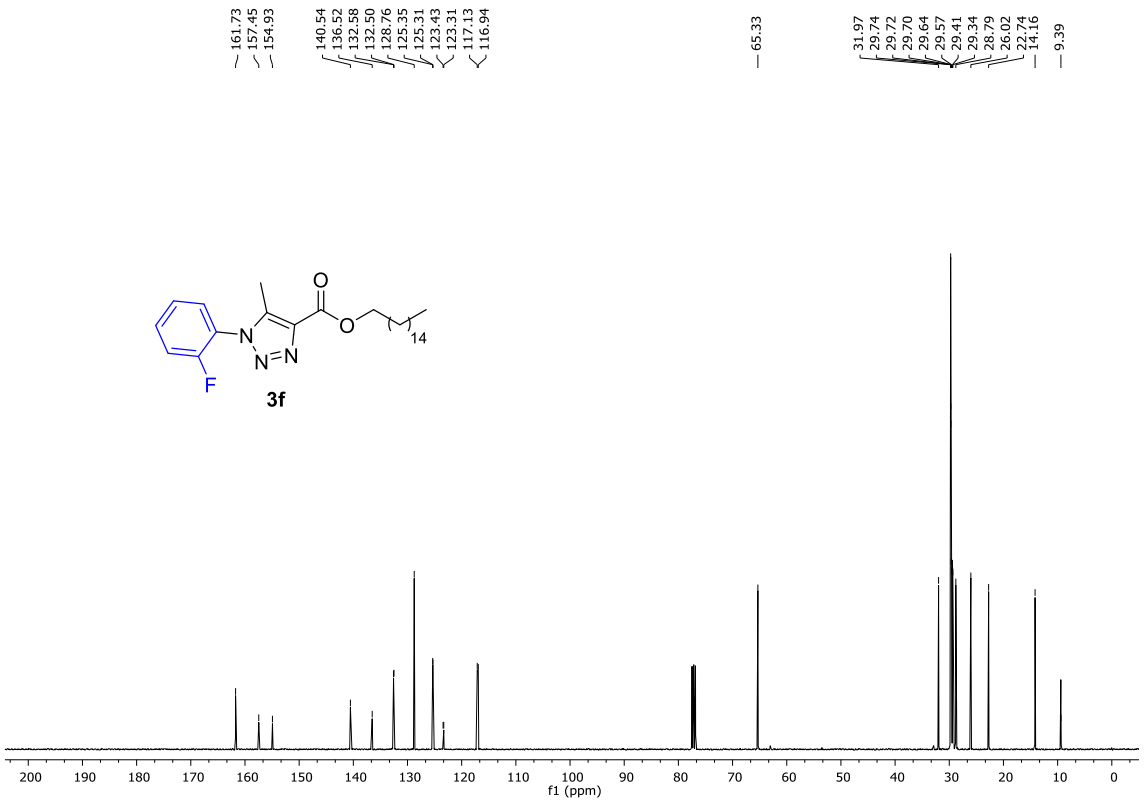
^{1}H NMR spectra of compound **3e** (400 MHz, $CDCl_3$)



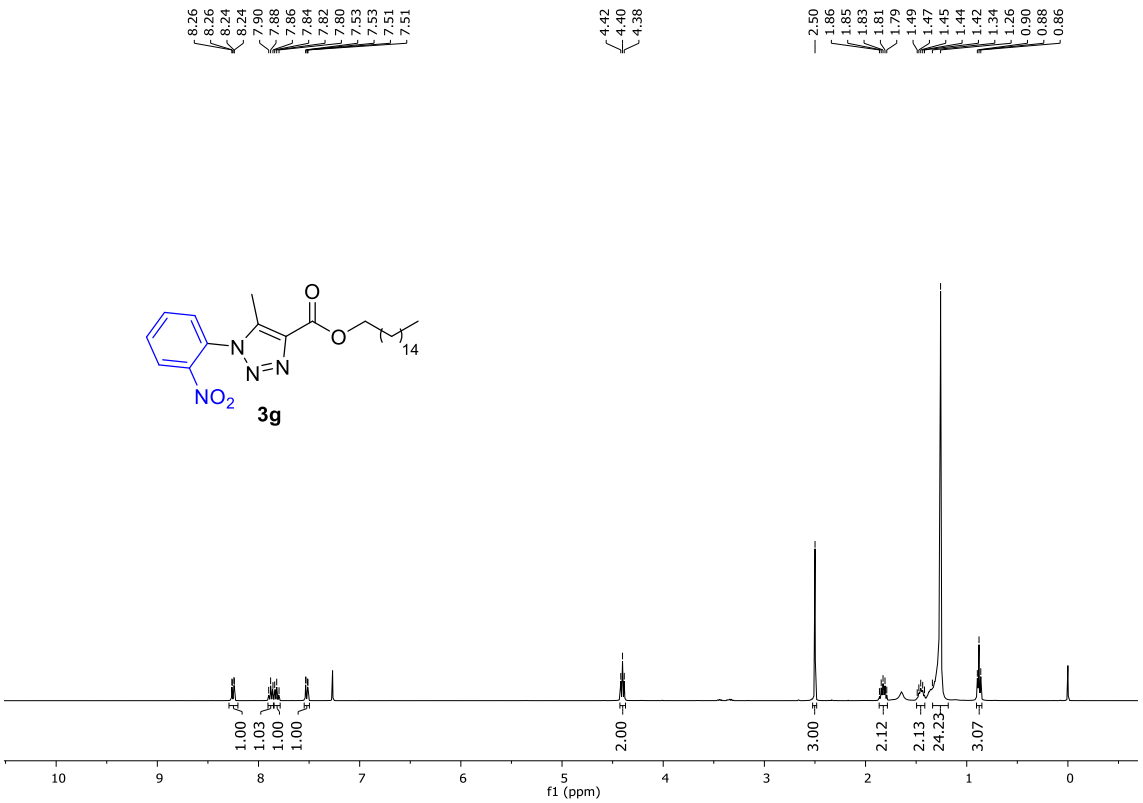
^{13}C NMR spectra of compound **3e** (100 MHz, $CDCl_3$)



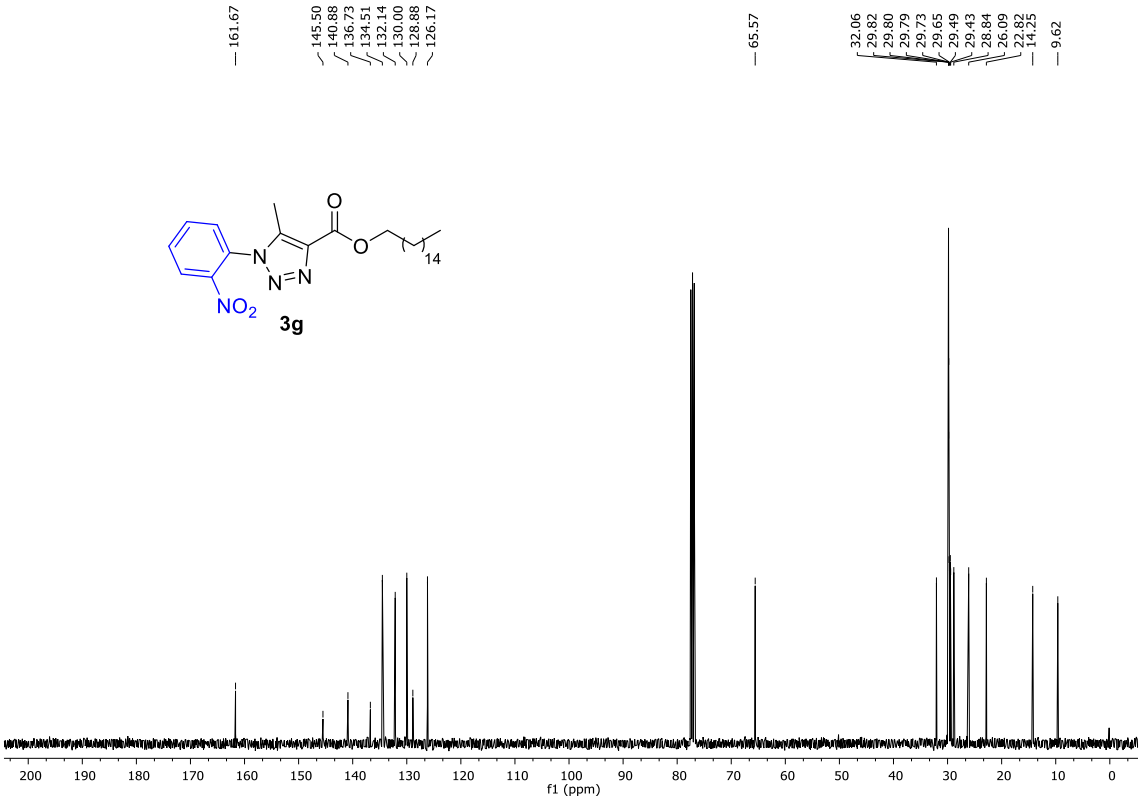
^{1}H NMR spectra of compound **3f** (400 MHz, $CDCl_3$)



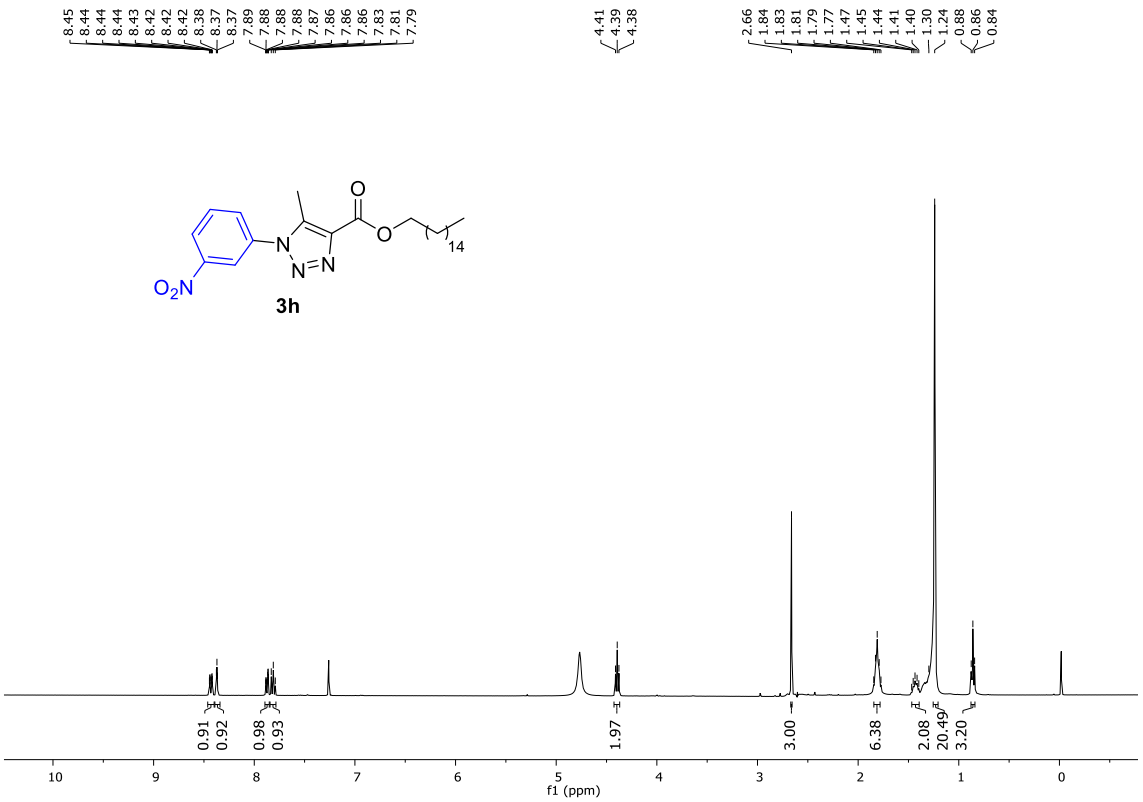
^{13}C NMR spectra of compound **3f** (100 MHz, $CDCl_3$)



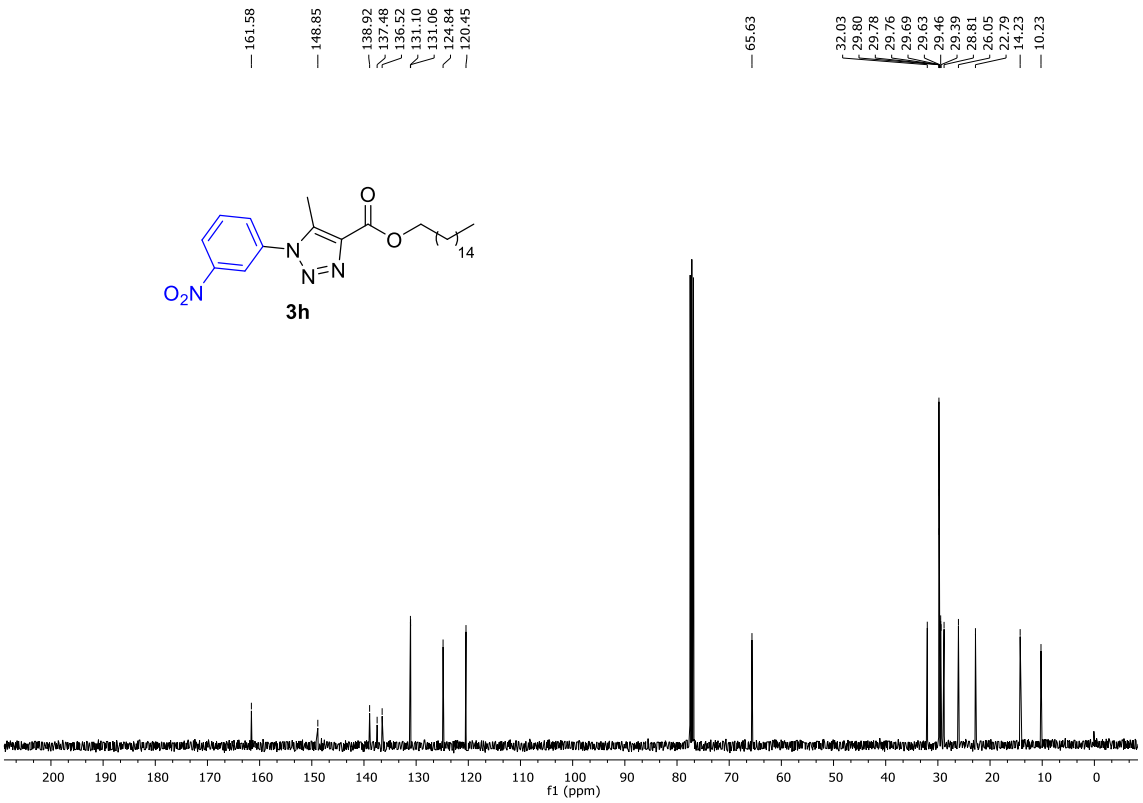
^{1}H NMR spectra of compound **3g** (400 MHz, $CDCl_3$)



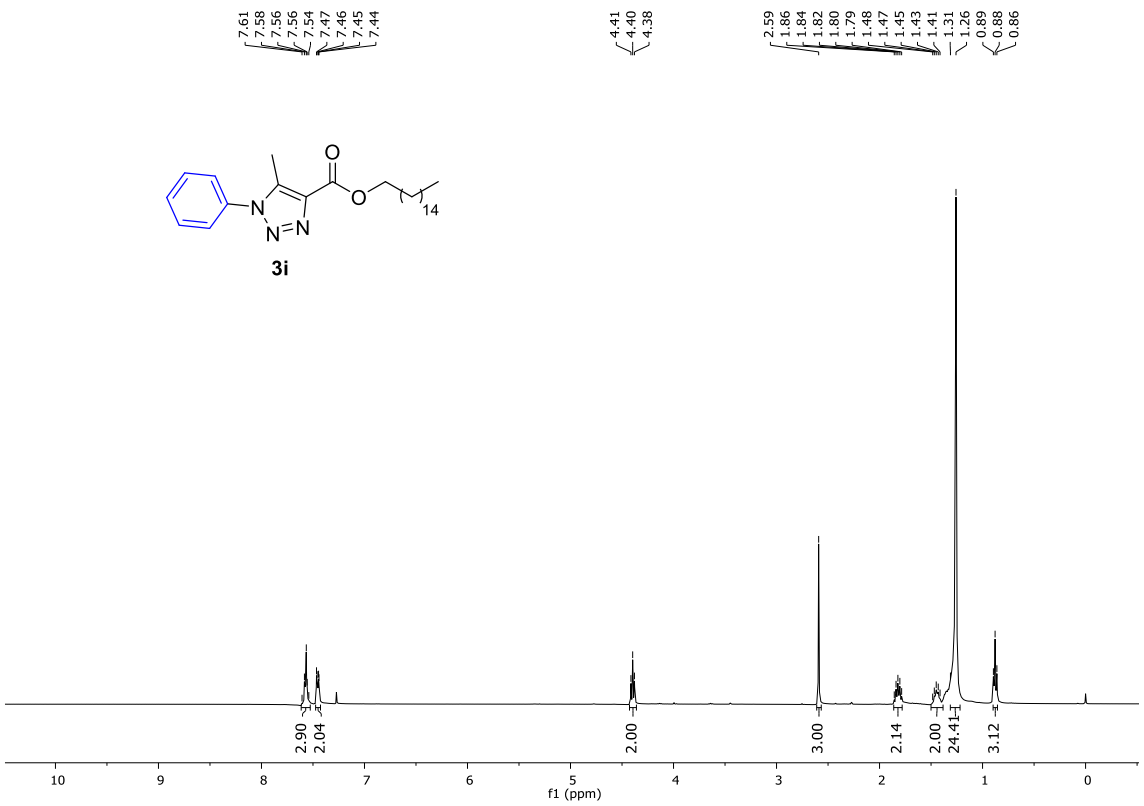
^{13}C NMR spectra of compound **3g** (100 MHz, $CDCl_3$)



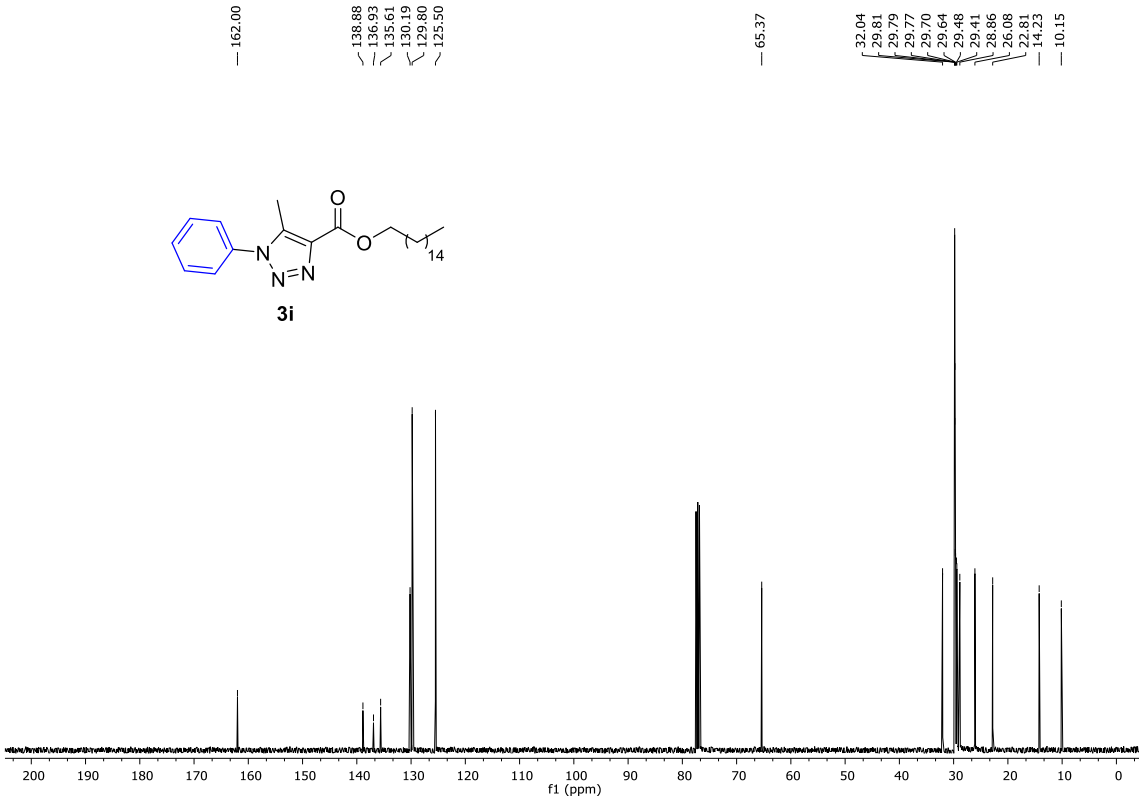
^{1}H NMR spectra of compound **3h** (400 MHz, $CDCl_3$)



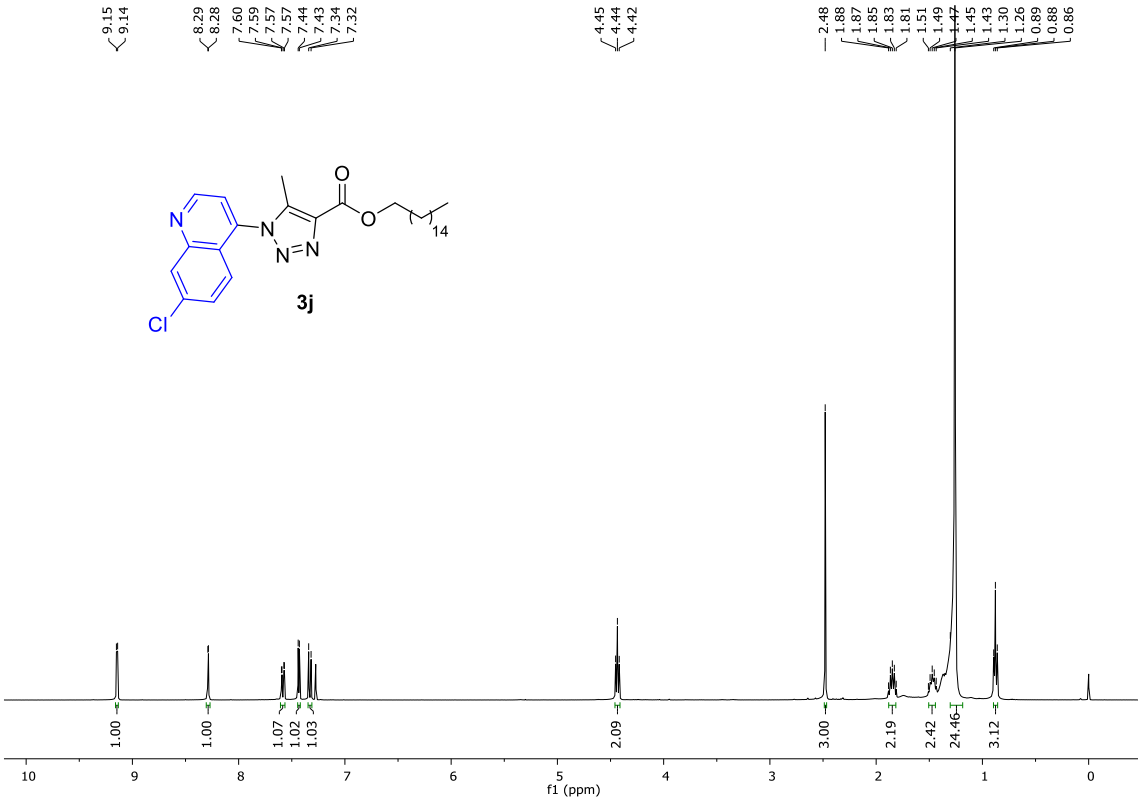
^{13}C NMR spectra of compound **3h** (100 MHz, $CDCl_3$)



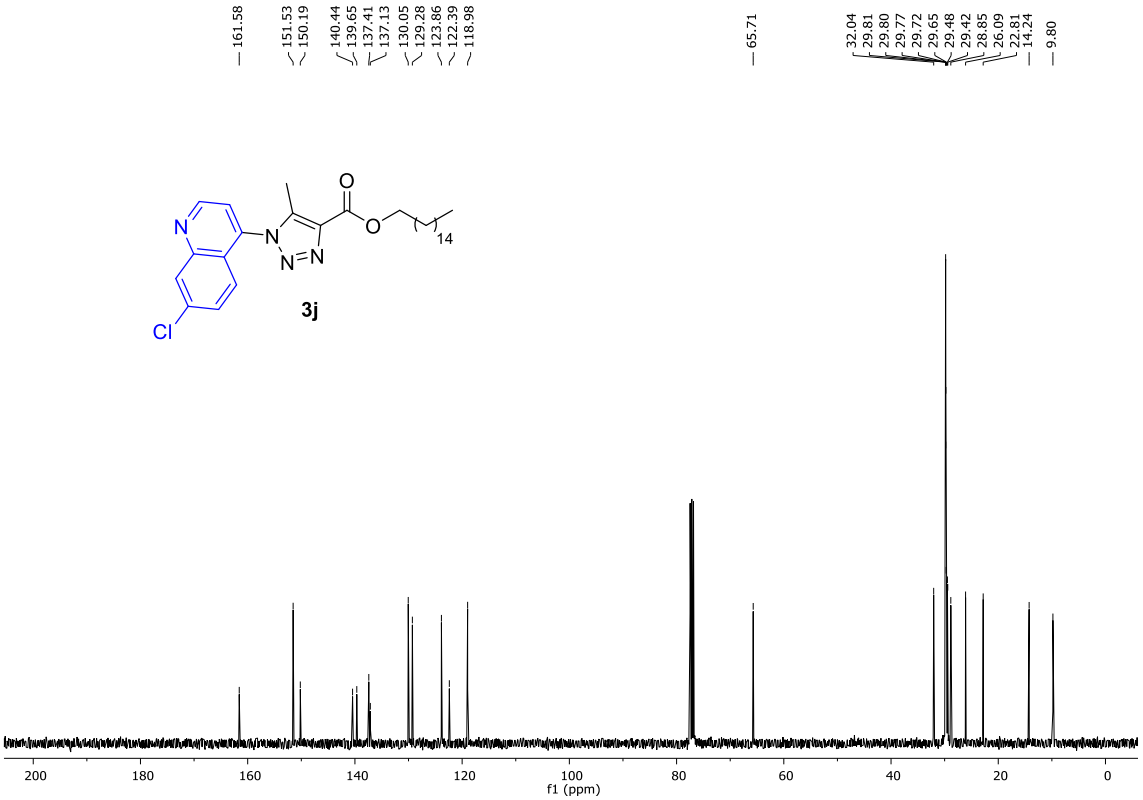
^{1}H NMR spectra of compound **3i** (400 MHz, $CDCl_3$)



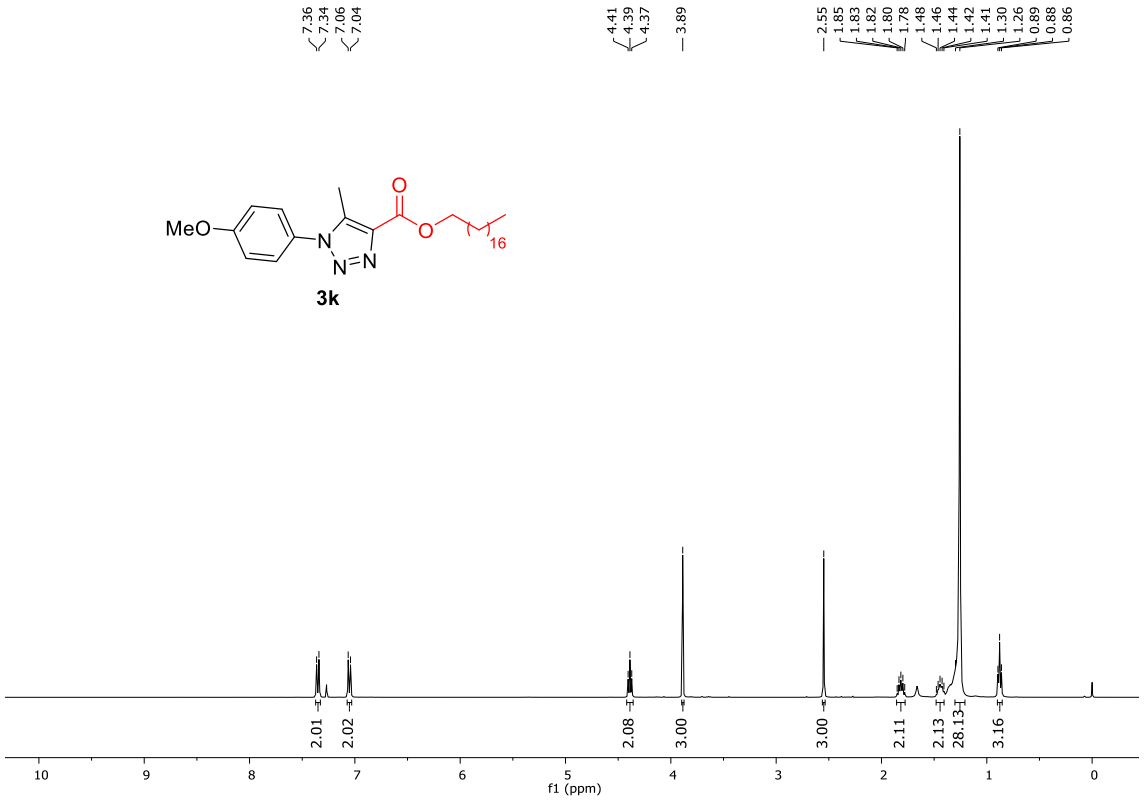
^{13}C NMR spectra of compound **3i** (100 MHz, $CDCl_3$)



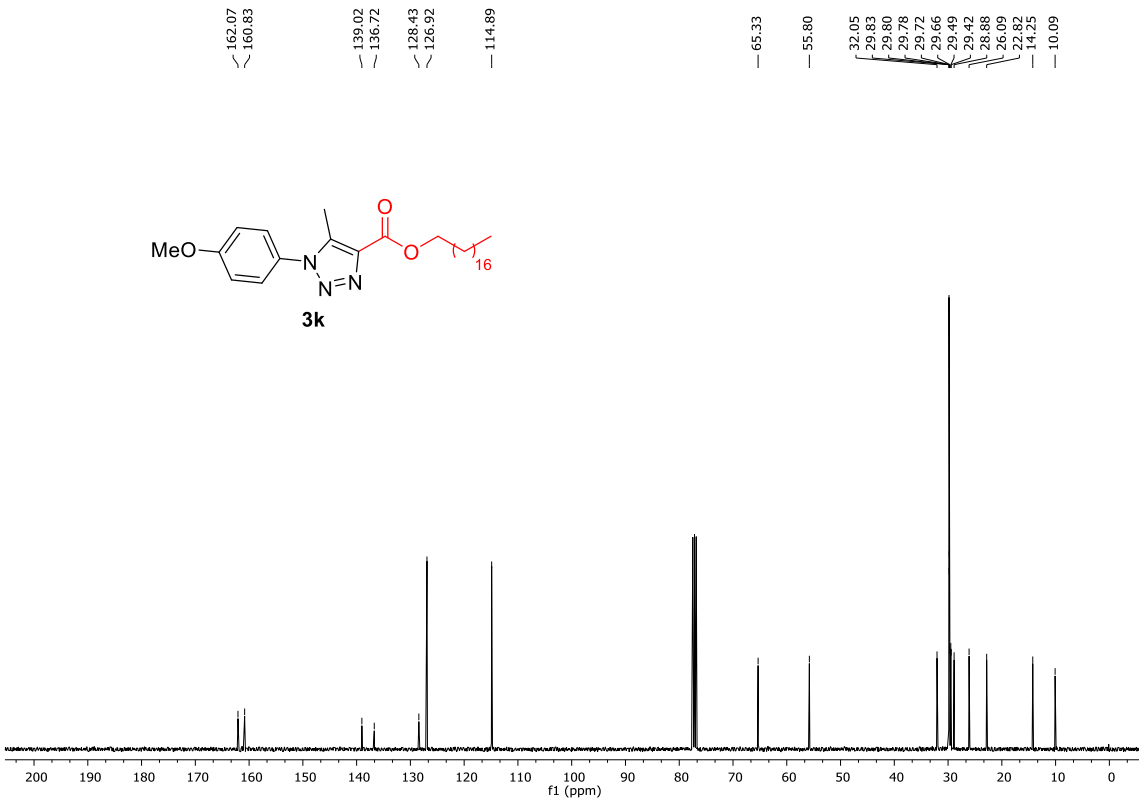
^{1}H NMR spectra of compound **3j** (400 MHz, $CDCl_3$)



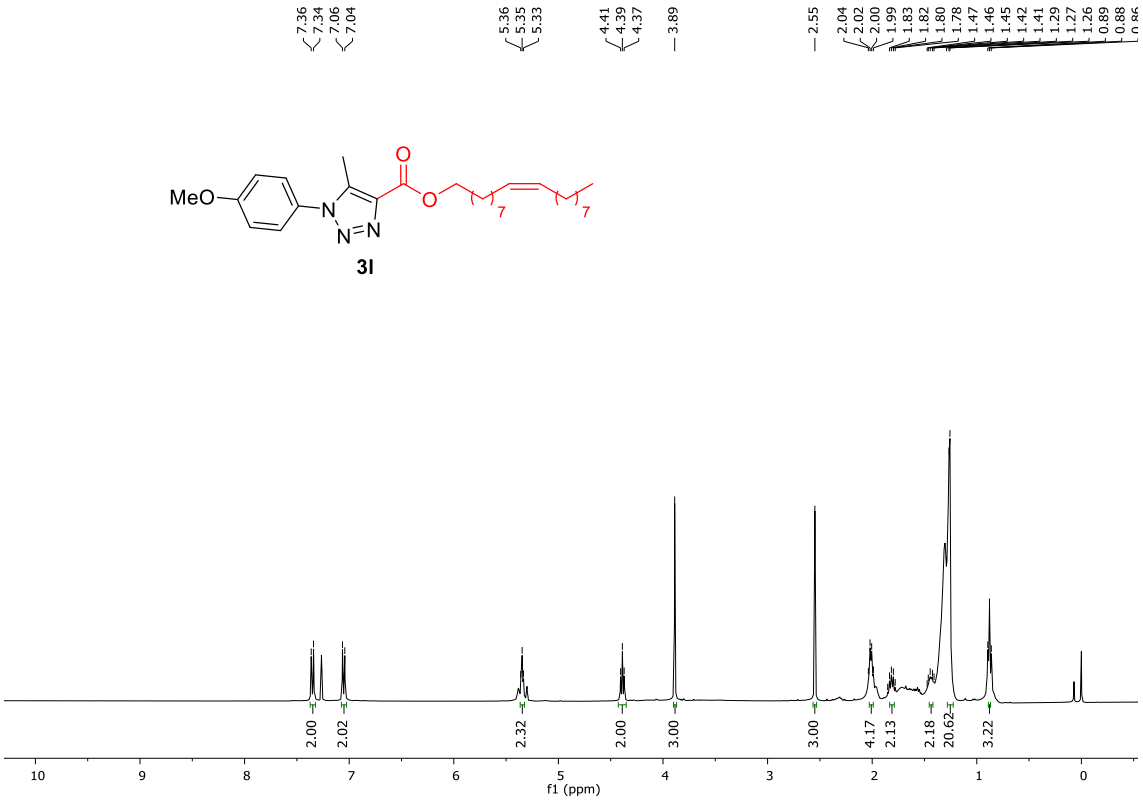
^{13}C NMR spectra of compound **3j** (100 MHz, $CDCl_3$)



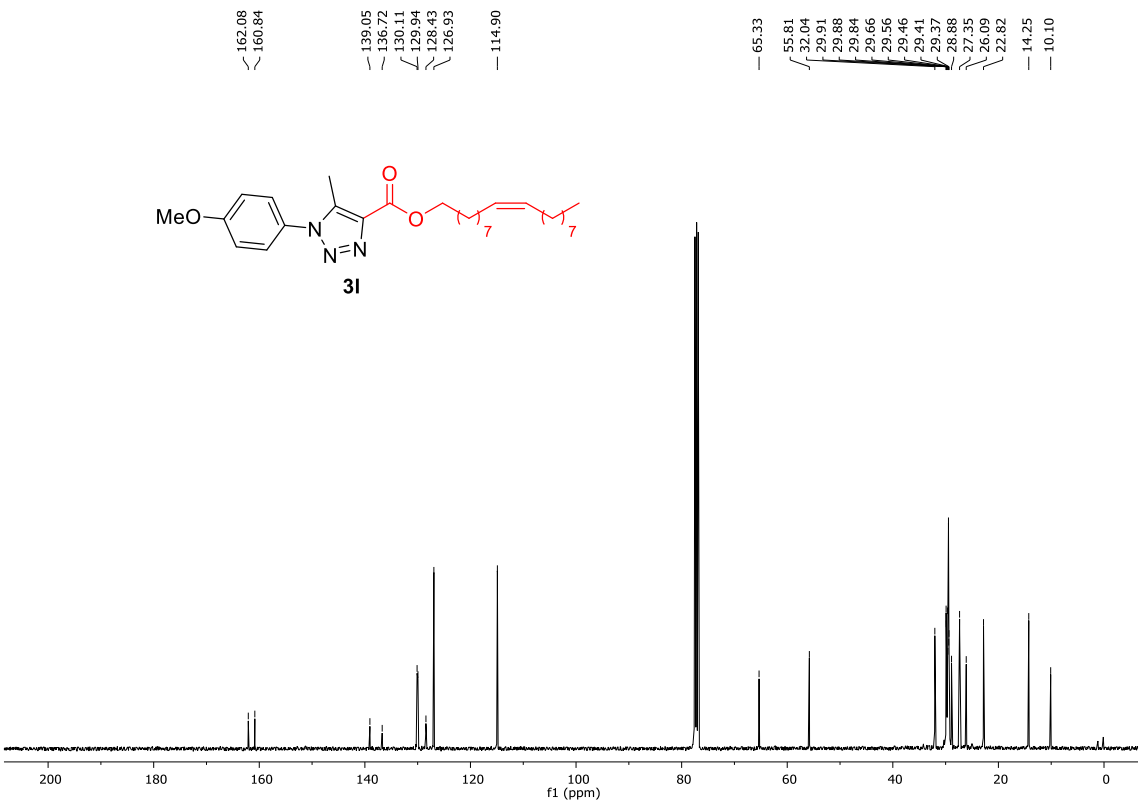
^{1}H NMR spectra of compound **3k** (400 MHz, $CDCl_3$)



^{13}C NMR spectra of compound **3k** (100 MHz, $CDCl_3$)



^{1}H NMR spectra of compound **3l** (400 MHz, $CDCl_3$)



^{13}C NMR spectra of compound **3l** (100 MHz, $CDCl_3$).

5 CONCLUSÃO GERAL

Em vista do que foi exposto, pode-se concluir que os 1,2,3-triazóis derivados de zidovudina e ésteres graxos foram obtidos a partir de uma metodologia simples e eficiente, utilizando baixas quantidades de organocatalisador e rendimentos variando de bons a excelentes, tendo em vista a complexidade de cada substrato. Nos trabalhos foi possível observar que a natureza eletrônica dos substituintes é um fator decisivo que afeta diretamente a taxa de reação, a formação dos produtos desejados e seus respectivos rendimentos.

Aliado a isso, cabe-se destacar que os compostos testados apresentaram resultados promissores quanto a sua capacidade antioxidante em 1,2,3-triazóis derivados de zidovudina, sendo uma série candidata a posteriores avaliações do potencial antioxidante. Como apresentado no **Capítulo 1**, foi desenvolvido um procedimento sintético para a preparação de dezesseis exemplos de 1,2,3-triazóis derivados de zidovudina pela reação de cicloadição 1,3-dipolar do AZT com diferentes compostos dicarbonílicos, incluindo ésteres, nitrilas, cetonas, amidas e sulfonas. Essas reações toleraram uma variedade de substituintes nos compostos dicarbonílicos e provaram ser uma metodologia eficiente com rendimentos de bons a excelentes (59% a 91%).

Adicionalmente, desenvolveu-se um procedimento sintético para 1,2,3-triazóis derivados de ésteres graxos que tolerou uma variedade de substituintes nas azidas arílicas com rendimentos de moderados a excelentes (35%- 99%). Os 1,2,3-triazóis derivados do acetoacetato palmítico sintetizados se destacaram quanto a sua capacidade citotóxica contra células tumorais de bexiga, se apresentando como moléculas promissoras frente aos resultados expostos no **Capítulo 2,** exceto os compostos **3b** e **3f**.

6 REFERÊNCIAS

AHER, N. G.; PORE, V. S.; MISHRA, N. N.; KUMAR, A.; SHUKLA, P. K.; SHARMA, A.; BHAT, M. K. Synthesis and antifungal activity of 1,2,3-triazole containing fluconazole analogues. *Bioorganic & Medicinal Chemistry Letters* 19 **(2009)** 759–763.

ANEBOUSELVY, K.; SHRUTHI, K. S.; RAMACHARY, D. B. Asymmetric Supramolecular Organocatalysis: a complementary upgrade to organocatalysis. *Eur. J. Org. Chem.* **(2017)** 5460–5483.

BARAN, R.; VEVERKOVA, E.; SKVORCOVA, A.; SEBESTA, R. Enantioselective Michael addition of 1,3-dicarbonyl compounds to nitroalkene catalyzed by chiral squaramides – a key step in the synthesis of pregabalin. *Org. Biomol. Chem.* **(2013)** DOI: 10.1039/C3OB41709C.

BARANIAK, D.; KACPRZAK, K.; CELEWICZ L. Synthesis of 30-azido-30-deoxythymidine (AZT)—Cinchona alkaloid conjugates via click chemistry: Toward novel fluorescent markers and cytostatic agents. *Bioorganic & Medicinal Chemistry Letters* 21 **(2011)** 723–726.

BASKIN, J. M.; BERTOZZI, C. R. Bioorthogonal Click Chemistry: Covalent Labeling in Living Systems. *QSAR Comb. Sci*. 26 **(2007)** 1211 – 1219.

BECK, P.; SANTOS, J. M. DOS; KUHN, B. L.; MOREIRA, D. N.; FLORES, A. F. C.; MARTINS, M. A. P.; M. G. D'OCA, M.; PIOVESAN, L. A. Regiospecific Synthesis of New Fatty N-Acyl Trihalomethylated Pyrazoline Derivatives from Fatty Acid Methyl Esters (FAMEs). *J. Braz. Chem. Soc.* 23 **(2012)** 2122-2127.

BEGNINI, K. R.; DUARTE, W. R.; SILVA, L. P. DA; BUSSA, J. H.; GOLDANI, B. S.; FRONZA, M.; SEGATTO, N. V.; ALVES, D.; SAVEGNAGO, L.; SEIXAS, F. K.; COLLARES, T. Apoptosis induction by 7-chloroquinoline-1,2,3-triazoyl carboxamides in triple negative breast cancer cells. *Biomedicine & Pharmacotherapy* 91 **(2017)** 510–516.

BODNÁR, B.; MERNYÁK, E.; WÖLFLING, J.; SCHNEIDER, G.; HERMAN, B. E.; SZÉCSI, M; SINKA, I.; ZUPKÓ, I.; KUPIHÁR, Z.; KOVÁCS, L. Synthesis and Biological Evaluation of Triazolyl 13 -Estrone–Nucleoside Bioconjugates. *Molecules* 21 **(2016)** 1212.

BRASE, S.; GIL, C.; KNEPPER, K.; ZIMMERMANN, V. Organic Azides: An Exploding Diversity of a Unique Class of Compounds *Angew. Chem. Int. Ed.* 44 **(2005)** 5188-5240.

BRINKERHOFF, R. C.; SANTA-HELENA, E.; AMARAL, P. C. DO; CABRERA, D. DA C.; ONGARATTO, R. F.; OLIVEIRA, P. M. DE; D'OCA, C. M.; GONÇALVES, C. A. N.; NERY, L. E. M.; D'OCA, M. G. M. Evaluation of the antioxidant activities of fatty polyhydroquinolines synthesized by Hantzsch multicomponent reactions. *RSC Adv.* 9 **(2019)** 24688.

CARY, FRANCIS. **Advanced Organic Chemistry**. 5 ed. Spring Verlag, 2007.

CASTRO, S. de; CAMARASA, M. Polypharmacology in HIV inhibition: can a drug with simultaneous action against two relevant targets be an alternative to

combination therapy? *European Journal of Medicinal Chemistry* 150 **(2018)** 206 - 227.

CHAVAN, S. R.; GAVALE, K. S.; KHAN, A.; JOSHI, R.; KUMBHAR N.; CHAKRAVARTY D.; DHAVALE, D. D. Iminosugars Spiro-Linked with Morpholine-Fused 1,2,3-Triazole: Synthesis, Conformational Analysis, Glycosidase Inhibitory Activity, Antifungal Assay, and Docking Studies. *ACS Omega* 2 **(2017)** 7203-7218.

CHEN, Y; SIT, S; CHEN, J; SWIDORSKI, J. J.; LIU, Z.; SIN, N; VENABLES, B. L.; PARKE, D. D.; NOWICKA-SANS, B; LIN, Z; LI, Z.; TERRY, B. J.; PROTACK, T.; RAHEMATPURA, S.; HANUMEGOWDA, U.; JENKINS, S.; KRYSTAL, M.; DICKER, I. D; MEANWELL, N. A.; REGUEIRO-REN, A. The design, synthesis and structure-activity relationships associated with C28 amine-based betulinic acid derivatives as inhibitors of HIV-1 maturation. *Bioorganic & Medicinal Chemistry Letters* 28 **(2018)** 1550–1557.

CUI, F.; CHEN, J.; MO, Z.; SU, S.; CHEN, Y.; MA, X.; TANG, H.; WANG, H.; PAN, Y.; XU, Y. Copper-Catalyzed Decarboxylative/Click Cascade Reaction: Regioselective Assembly of 5-Selenotriazole Anticancer Agents. *Org. Lett.* 20 **(2018)** 925−929.

DANENCE, L. J. T.; GAO, Y.; LI, M.; HUANG, Y.; WANG, J. Organocatalytic Enamide–Azide Cycloaddition Reactions: Regiospecific Synthesis of 1,4,5-Trisubstituted-1,2,3-Triazoles. *Chem. Eur. J.* 17 **(2011)** 3584 – 3587.

DAYAKAR, C.; KUMAR, B. S.; SNEHA, G.; SAGARIKA, G.; MEGHANA, K.; RAMAKRISHNA, S.; PRAKASHAM, R. S.; RAJU, B. C. Synthesis, pharmacological activities and molecular docking studies of pyrazolyltriazoles as anti-bacterial and anti-inflammatory agents. *Bioorganic & Medicinal Chemistry* 25 **(2017)** 5678–5691.

DEBETS, M. F.; VAN BERKEL, S. S.; DOMMERHOLT, J.; DIRKS, A. J.; RUTJES, F. P. J. T.; VAN DELFT, F. L. Bioconjugation with Strained Alkenes and Alkynes. *Acc. Chem. Res.* 44 **(2011)** 805- 815.

DEBIA, N. P.; SARAIVA, M. T.; MARTINS, B. S.; BEAL, R.; GONÇALVES, P. F.; RODEMBUSCH, F. S.; ALVES, D.; LÜDTKE, D. S. Synthesis of Amino Acid-Derived 1,2,3-Triazoles: Development of a Nontrivial Fluorescent Sensor in Solution for the Enantioselective Sensing of a Carbohydrate and Bovine Serum Albumin Interaction. *J. Org. Chem.* 83 **(2018)** 1348−1357.

DEMARAY, J. A.; THUENER J. E.; DAWSON M.N.; SUCHECK S. J. Synthesis of triazole-oxazolidinones via a one-pot reaction and evaluation of their antimicrobial activity. *Bioorg Med Chem Lett* 18 **(2008)** 4868–4871.

DHEER, D.; SINGH, V.; SHANKAR, R. Medicinal Attributes of 1,2,3-Triazoles: Current Developments. *Bioorganic Chemistry* **(2017)**.

DU, X.; SHI, Z.; PENG, Z.; ZHAO, C.; ZHANG, YUMING; WANG, Z.; LI, X.; LIU G.; LI, X. Acetoacetate induces hepatocytes apoptosis by the ROS-mediated MAPKs pathway in ketotic cows. *J Cell Physiol.* 232 **(2017)** 3296–3308.

DUARTE, L. F. B.; NASCIMENTO, N. M.; PERIN, G.; LUQUE, R.; ALVES, D.; SCHUMACHER, R. F. Et_2NH-Mediated 1,3-Dipolar Cycloaddition: Synthesis of 1-(2-(Organylselanyl) pyridin-3-yl)-1H-1,2,3-triazole-4-carboxylate Derivatives. *Chemistry Select* 2 **(2017)** 6645 – 6649.

ECKER, A.; SILVA, R.S. DA; SANTOS, M.M. DOS; ARDISSON-ARAUJO, D.; RODRIGUES, O.E.D; ROCHA, J.B.T. DA; BARBOSA, N.V. Safety profile of AZT derivatives: Organoselenium moieties confer different cytotoxic responses in fresh human erythrocytes during in vitro exposures. *Journal of Trace Elements in Medicine and Biology* 50 **(2018)** 240–248.

EICHER, T; HAUPTMANN, S. **The chemistry of heterocycles structure, reaction, synthesis and application**. 2 ed. Wiley, NY, 2003.

FONSECA, S. F.; LIMA, D. B.; ALVES, D.; JACOB, R. G.; PERIN, G.; LENARDÃO, E. J.; SAVEGNAGO L. Synthesis, characterization and antioxidant activity of organoselenium and organotellurium compounds derivatives of chrysin. *New Journal of Chemistry* **(2015)** doi 10.1039/C4NJ02329C.

GAETKE, L. M.; CHOW, C. K. Copper toxicity, oxidative stress, and antioxidant nutrients. *Toxicology* 189 **(2003)** 147-163.

GHIANO, D. G.; IGLESIA, A. DE LA; LIU, N.; TONGE, P. J.; MORBIDONI, H. R.; LABADIE, G. R. Antitubercular activity of 1,2,3-triazolyl fatty acid derivatives. *Eur J Med Chem.* 125 **(2017)** 842–852.

GIERLICH, J.; BURLEY, G. A.; GRAMLICH, P. M. E.; HAMMOND, D. M.; CARELL, T. Click Chemistry as a Reliable Method for the High-Density Postsynthetic Functionalization of Alkyne-Modified DNA. *Org. Lett.* 8 **(2006)** 3639-3642.

GONTIJO, V. S.; OLIVEIRA, M. E.; RESENDE, R. J.; FONSECA, A. L.; NUNES, R. R.; JUNIOR, M. C.; TARANTO, A. G.; TORRES, N. M. P. O.; VIANA, G. H. R.; SILVA, L. M.; ALVES, R. B.; VAROTTI, F. P.; FREITAS, R. P. Long-chain alkyltriazoles as antitumor agents: synthesis, physicochemical properties, and biological and computational evaluation. *Med Chem Res* 24 **(2015)** 430–441.

HACK, C. R. L.; PORCIUNCULA, L.; WEBER, A. C. H.; D'OCA, C. R. M.; RUSSOWSKY, D.; MOURA, J. M.; PINTO, L. A. A.; D'OCA, M. G. M. N-Alkylated Sulfamic Acid Derivatives as Organocatalyst in Multicomponent Synthesis of Fatty Dihydropyrimidinones. *J. Braz. Chem. Soc.* 29 **(2018)** 2342-2349.

HIMO, F.; LOVELL, T.; HILGRAF, R.; ROSTOVTSEV, V. V.; NOODLEMAN, L.; SHARPLESS, K. B., FOKIN, V. V. *J.* Copper(I)-Catalyzed Synthesis of Azoles. DFT Study Predicts Unprecedented Reactivity and Intermediates. *Am. Chem. Soc* 127 (**2005)** 210-216.

HUISGEN, R. 1,3-Dipolar Cycloadditions. *Angew. Chem.Int.* 2 **(1963)** 565-598.

ISRAR, M.; YE, C.; MUHAMMAD, M. T.; LI, Y.; BAO, H. Copper(I)-catalyzed tandem reaction: synthesis of 1,4-disubstituted 1,2,3-triazoles from alkyl diacyl peroxides, azidotrimethylsilane, and alkynes. *Beilstein J. Org. Chem.* 14 **(2018)** 2916–2922.

JANA, S; THOMAS, J.; DEHAEN, W. A One-Pot Procedure for the Synthesis of "Click-Ready" Triazoles from Ketones. *J. Org. Chem.* 81 **(2016)** 12426−12432.

JOMOVA, K.; VALKO, M. Advances in metal-induced oxidative stress and human disease. *Toxicology* 283 **(2011)** 65–87.

KANTARIA, T.; KANTARIA, T.; TITVINIDZE, G.; OTINASHVILI, G.; KUPATADZE, N.; ZAVRADASHVILI, N.; TUGUSHI, D.; KATSARAVA, R. New 1,2,3-Triazole Containing Polyesters via Click Step-Growth Polymerization and Nanoparticles Made of Them. *International Journal of Polymer Science* **(2018)** doi.org/10.1155/2018/6798258.

KENNEDY, D. C.; MCKAY, C. S.; LEGAULT, M. C. B.; DANIELSON, D. C.; BLAKE, J. A.; PEGORARO, A. F.; STOLOW, A.; MESTER, Z.; PEZACKI, J. P. Cellular consequences of copper complexes used to catalyze bioorthogonal click reactions. *J. Am. Chem. Soc.* 133 **(2011)** 17993–18001.

KIM, H.; LEE, S.; CHOI, Y.; KIM, B. HBV polymerase-derived peptide exerts an anti-HIV-1 effect by inhibiting the acetylation of viral integrase. *Biochemical and Biophysical Research Communications* 501 **(2018)** 541 - 546.

KLIMESOVA V.; ZAHAJSKA L.; WAISSER K.; KAUSTOVA, J.; MÖLLMANN U. Synthesis and antimycobacterial activity of 1,2,4-triazole 3-benzylsulfanyl derivatives. *IL Farmaco* 59 **(2004)** 279–288.

KOLB, H. C.; SHARPLESS, K. B. The growing impact of click chemistry on drug discovery. *Drug. Disc. Today* 8 **(2003)** 1128-1137.

KOSIOVA, I.; KOVACKOVA S.; KOIS P. Synthesis of coumarin–nucleoside conjugates via Huisgen 1,3-dipolar cycloaddition. Tetrahedron 63 **(2007)** 312–320.

KRIM, J.; TAOURIRTE, M.; GRÜNEWALD, C.; KRSTIC, I.; ENGELS, J. W. Microwave-Assisted Click Chemistry for Nucleoside Functionalization: Useful Derivatives for Analytical and Biological Applications. *Synthesis* 45 **(2013)** 396–405.

KUMAR, J. M.; IDRIS, M. M.; SRINIVAS, G.; KUMAR, P. V.; MEGHAH, V.; KAVITHA, M.; REDDY, C. R.; MAINKAR, P. S.; PAL, B.; CHANDRASEKAR, S.; NAGESH, N. Phenyl 1,2,3-Triazole-Thymidine Ligands Stabilize GQuadruplex DNA; Inhibit DNA Synthesis and Potentially Reduce Tumor Cell Proliferation over 3'-Azido Deoxythymidine. *Plos One* 8 **(2013)**.

LALLANA, E.; FERNANDEZ-MEGIA, E.; RIGUERA, R. Surpassing the Use of Copper in the Click Functionalization of Polymeric Nanostructures: A Strain-Promoted Approach. *J. Am. Chem. Soc.* 131 **(2009)** 5748–5750.

LEWANDOWSKA, M.; RUSZKOWSKI, P.; BARANIAK, D; CZARNECKA, A.; KLECZEWSKA, N.; CELEWICZ, L. Synthesis of 3'-azido-2',3'-dideoxy-5-fluorouridine phosphoramidates and evaluation of their anticancer activity. *European Journal of Medicinal Chemistry* 67 **(2013)** 188-195.

LI, Z.; QIAO, R.; YANG, Z.; ZHANG, L.; ZHANG, L. One-step synthesis of novel tricyclic isomeric azidonucleosides. *Tetrahedron: Asymmetry* 17 **(2006)** 1056–1061.

LIN, J.; ROY, V.; WANGA, L.; YOU, L.; AGROFOGLIO, L.; DEVILLE-BONNE, D.; MCBRAYER, T.; COATS, S.; SCHINAZI, R.; ERIKSSON, S. 3'-(1,2,3-Triazol-1-yl)-3'-deoxythymidine analogs as substrates for human and Ureaplasma

parvum thymidine kinase for structure–activity investigations. *Bioorganic & Medicinal Chemistry* 18 **(2010)** 3261–3269.

MACAN, A. M.; HAREJ, A.; CAZIN, I.; KLOBUCAR, M.; STEPANIC, V.; PAVELIC, K.; PAVELIC, S. K.; SCHOLS, D.; SNOECK, R.; ANDREI, G.; RAIC-MALIC, S. Antitumor and antiviral activities of 4-substituted 1,2,3-triazolyl-2,3-dibenzyl-L-ascorbic acid derivatives. *European Journal of Medicinal Chemistry* 184 **(2019)** 111739.

MALANI, A. H.; MAKWANA, A. H.; MAKWANA, H. A brief review article: Various synthesis and therapeutic importance of 1, 2, 4-triazole and its derivatives. *Mor. J. Chem.* 5 **(2017)** 41-58.

MANNEGANTI, V.; BETHALA, L. A. P. D.; RACHAPUDI, B. N. P.; SINGH, A.; UMMANNI R. Design, synthesis and anticancer activities of novel unsaturated fatty acid-based β-hydroxy 1,2,3-triazoles. *International Journal of Pharmaceutical Sciences and Research* 6 **(2015)** 1635-1649.

MAO, L.; XU, G.; SUN, B; JIANG, Y.; DONGA, W; ZHANG, S; SHENA, J.; HEC, X. Design, synthesis and antibacterial evaluation of novel 1,2,3-triazole derivatives incorporating 3′-deoxythymidine. *Journal of Chemical Research* 41 **(**2017**)** 645–649.

MENENDEZ, J.; GARCIA B.; HIDALGO Y. New Method for the Selection of Multicopy Transformants of Pichia pastoris, Using 3-Amino-1,2,4 Triazol. *Biotechniques* 29 **(2000)**1094-1099.

MIECZKOWSKI, A.; WINSKA, P.; KACZMAREK, M.; MROCZKOWSKA, M.; GARBICZ, D.; PILŻYS, T.; MARCINKOWSKI, M.; PIWOWARSKI, J.; GRZESIUK E. 2′-Deoxy-2′-azidonucleoside analogs: synthesis and evaluation of antitumor and antimicrobial activity. *Chem. Pap.* 72 **(2018)** 981–990.

MINISTÉRIO DA SAÚDE. **Disponível em:** <http://indicadoresclinicos.aids.gov.br/ > **Acesso em:** jan de 2020.

MUNCHEN, T. S.; SONEGO, M. S.; SOUZA D. DE; DORNELLES, L.; SEIXAS, F. K.; COLLARES, T.; PICCOLI,B. C.; SILVA, F.; ROCHA, J. B. DA; QUOOS, N.; RODRIGUES, O E. D. New 3'-Triazolyl-5'-aryl-chalcogenothymidine: Synthesis and Anti-oxidant and Antiproliferative Bladder Carcinoma (5637) Activity. *ChemistrySelect* 3 **(2018)** 3479 – 3486.

NAIDU, B.N.; WALKER, M.A.; SORENSON, M.E.; UEDA, Y.; MATISKELLA, J.D.; CONNOLLY, T.P.; DICKER, I.B.; LIN, Z.; BOLLINI, S.; TERRY, B.J.; HIGLEY, H.; ZHENG, M.; PARKER, D.D.; WU, D.; ADAMS, S.; KRYSTAL, M.R.; MEANWELL, N.A. The discovery and preclinical evaluation of BMS-707035, a potent HIV-1 integrase strand transfer inhibitor. *Bioorganic & Medicinal Chemistry Letters* **(2018)**.

NAINAR, S.; BEASLEY, S.; FAZIO, M.; KUBOTA, M.; DAI, N.; CORRÞA, I. JR.; SPITALE, R. C. Metabolic Incorporation of Azide Functionality into Cellular RNA. *ChemBioChem* 17 **(2016)** 2149 – 2152.

NOBRE, P. C.; VARGAS, H. A.; JACOBY, C. G.; SCHNEIDER, P. H.; CASARIL, A. M.; SAVEGNAGO L.; SCHUMACHER R. F.; LENARDÃO E. J.; AVILA D. S.; RODRIGUES JUNIOR, L. B.L.; PERIN G. Synthesis of enantiomerically pure

glycerol derivatives containing an organochalcogen unit: In vitro and in vivo antioxidant activity. Arabian Journal of Chemistry 13 **(2020)** 883–899.

PATHAK, T. Azidonucleosides: Synthesis, Reactions, and Biological Properties. *Chem. Rev.* 102 **(2002)** 1623-1667.

POECKE, S.; NEGRI A.; GAGO, F.; DAELE I.; SOLAROLI, N.; KARLSSON, A.; BALZARINI, J.; CALENBERGH, S. 3'-[4-Aryl-(1,2,3-triazol-1-yl)]-3'-deoxythymidine Analogues as Potent and Selective Inhibitors of Human Mitochondrial Thymidine Kinase. *J. Med. Chem.* 53 **(2010)** 2902–2912.

RAHMAN, V.P. M.; MUKHTAR, S.; ANSARI, W. H.; LEMIERE, G. Synthesis, stereochemistry and biological activity of some novel long alkyl chain substituted thiazolidin-4-ones and thiazan-4-one from 10-undecenoic acid hydrazide. *European Journal of Medicinal Chemistry* 40 **(2005)** 173–184.

RAJASEKAR, S.; ANBARASAN, P. A General Proline Catalyzed Synthesis of 4,5-Disubstituted NSulfonyl-1,2,3-Triazoles from 1,3-Dicarbonyl Compounds and Sulfonyl Azide. *Chem. Asian J.* **(2019)** doi 10.1002/asia.201901015.

RAMACHARY, D. B.; CHOWDARI, N. S.; BARBAS, C. F. Amine-catalyzed direct self Diels–Alder reactions of α,β-unsaturated ketones in water: synthesis of pro-chiral cyclohexanones. *Tetrahedron Letters* 43 **(2002)** 6743–6746.

RAMACHARY, D. B.; GUJRAL, J.; PERAKA, S.; REDDY, G. S. Triazabicyclodecene as an Organocatalyst for the Regiospecific Synthesis of 1,4,5-Trisubstituted N-Vinyl-1,2,3-triazoles. Eur. J. Org. Chem. **(2017d)** 459–464.

RAMACHARY, D. B.; RAMAKUMAR, K.; V. NARAYANA V. Organocatalytic Cascade Reactions Based on Push-Pull Dienamine Platform: Synthesis of Highly Substituted Anilines. *J. Org. Chem.* 72 **(2007)** 1458-1463.

RAMACHARY, D. B.; REDDY, G. S.; PERAKA, S.; GUJRAL, J. An Organocatalytic Vinyl Azide-Carbonyl [3 + 2]-Cycloaddition: High-yielding Synthesis of Fully Decorated N-Vinyl-1,2,3-Triazoles. *ChemCatChem* **(2016)**.

RAMACHARY, D. B.; SHASHANK, A. B.; KARTHIK S. An Organocatalytic Azide–Aldehyde [3+2] Cycloaddition: High- Yielding Regioselective Synthesis of 1,4-Disubstituted 1,2,3-Triazoles. *Angew. Chem. Int. Ed.* 53 **(2014)** 10420 –10424.

RAMACHARY, D. B; SHASHANK, A. B. Organocatalytic Triazole Formation, Followed by Oxidative Aromatization: Regioselective Metal-Free Synthesis of Benzotriazoles. *Chem. Eur. J.* 19 **(2013)** 13175 – 13181.

RAUF, A.; PARVEEN, H. Preparation, characterization and antimicrobial activity of fatty alkenoates. Indian Journal of Chemistry 44B (2005) 1273-1276.

RAVANELLO, B. B. **Síntese e avaliação como fotossensibilizadores de novos triazoil-fulerenos funcionalizados com AZT e calcogeno derivados de azt**. Dissertação (Mestrado), Universidade Federal de Santa Maria- UFSM. Santa Maria: 2014.

RICHARD, D.; KEFI, K.; BARBE, U.; BAUSERO, P.; VISIOLI, F. Polyunsaturated fatty acids as antioxidants. *Pharmacological Research* 57 **(2008)** 451–455.

SALMAN, S. M. Triazoles with long chain alkyl groups as a potential biological compounds. *Int. J. Res. Pharm. Sci.* 10 **(2019)** 2334-2341.

SANTOS, C.; MORAIS, J.; GOUVEIA, L.; CLERCQ, E.; PANNECOUQUE, C.; NIELSEN, C.; STEFFANSEN, B.; MOREIRA, R; GOMES, P. Dipeptide Derivatives of AZT: Synthesis, Chemical Stability, Activation in Human Plasma, hPEPT1 Affinity, and Antiviral Activity. *ChemMedChem* 3 **(2008)** 970 – 978.

SAVEGNAGO, L.; SACRAMENTO, M.; BROD, L.; FRONZA, M. G.; SEUS, N.; LENARDAO, E. J.; PAIXAO M. W.; ALVES D. Phenylselanyl-1*H*-1,2,3-triazole-4-carbonitriles: Synthesis, Antioxidant Properties and Use as a Precursor to Highly Functionalized Tetrazoles. *RSC Adv.* **(2015)** doi 10.1039/C5RA22445D.

SEUS, N. **Organocatálise na síntese de arilselanil-1,2,3-triazóis: Reações entre arilselanil fenilazidas com β-cetoésteres ou β-cetoamidas.** Tese (Doutorado), Universidade Federal de Pelotas- UFPEL. Pelotas: 2014.

SHASHANK, A. B.; KARTHIK,S.; MADHAVACHARY, R.; RAMACHARY, D. B. An Enolate-Mediated Organocatalytic Azide–Ketone [3+2]-Cycloaddition Reaction: Regioselective High-Yielding Synthesis of Fully Decorated 1,2,3-Triazoles. *Chem. Eur. J.* 20 **(2014)** 1 – 6.

SHIE, J.; LIU, Y.; LEE, Y.; LIM, C.; FANG, J.; WONG, C. An Azido-BODIPY Probe for Glycosylation: Initiation of Strong Fluorescence upon Triazole Formation. *J. Am. Chem. Soc.* 136 **(2014)** 9953−9961.

SOLYEV, P. N.; NOVIKOV, R. A.; KUKHANOVAA, M. K.; JASKOA, M. V. 1,3-Dipolar cycloaddition of alkenes to 3'-azido-3'-deoxythymidine as a route to 3'-deoxythymidin-3'-yl derivatives. *Mendeleev Commun*. 24 **(2014)** 206–208.

SONEGO, M. S.; SEGATTO, N. V.; DAMÉ L.; FRONZA, M.; GOMES, C. B.; OLIVEIRA, T. L.; SEIXAS, F. K.; SAVEGNAGO, L.; SCHACHTSCHNEIDER, K. M.; ALVES, D.; COLLARES, T. 7-Chloroquinoline-1,2,3-triazoyl carboxamides induce cell cycle arrest and apoptosis in human bladder carcinoma cells. *Investigational New Drugs* **(2019)** doi.org/10.1007/s10637-019-00861-w.

SOUZA, D. de; MARIANO, D. O. C.; NEDEL, F.; SCHULTZE, E.; CAMPOS, V. F.; SEIXAS, F.; SILVA, R. S. da; MUNCHEN, T. S.; ILHA, V.; DORNELLES, L.; BRAGA, A. L.; ROCHA, J. B. T.; COLLARES, T.; RODRIGUES, O. E. D. New Organochalcogen Multitarget Drug: Synthesis and Antioxidant and Antitumoral Activities of Chalcogenozidovudine Derivatives. *J. Med. Chem.* **(2014)**.

SRIVASTAVA, S.; MAIKHURI, V. K.; KUMARA, R.; BOHRA, K.; SINGLA, H.; JYOTIRMOY MAITY; ASHOK K. PRASAD. Synthesis and Photophysical Studies on N1-(2′-O,4′-C-Methyleneribofuranonucleoside-3′-yl)-C4-(coumarin-7-oxymethyl)-1,2,3-triazoles. *Carbohydrate Research* 470 **(2018)** 19–25.

TAKAHASHI, H.; KOSAKA, M.; WATANABE, Y.; NAKADE, K.; FUKUYAMA, Y. Synthesis and neuroprotective activity of bergenin derivatives with antioxidant activity. Bioorg. Med. Chem. 11 (2003) 1781-1788.

THATIPAMULA, R. K.; NARSIMHA, S.; BATTULA, K.; CHARY, V. R.; MAMIDALA E.; REDDY, N. V. Synthesis, anticancer and antibacterial evaluation of novel (isopropylidene) uridine-[1,2,3]triazole hybrids. *Journal of Saudi Chemical Society* **(2015)**.

THI, T.; NHAT, T.; HANH, T.; QUANG, T.; THE C.; THI, T.; NGUYEN, H; NGUYEN, T; THI, P.; NGUYEN, T. Synthesis and cytotoxic evaluation of novel

indenoisoquinoline substituted triazole hybrids. *Bioorganic & Medicinal Chemistry Letters* 26 **(2016)** 3652–3657.

TIAN, L.; GONG, L.; ZHANG, X. Copper-Catalyzed Enantioselective Synthesis of b-Amino Alcohols Featuring Tetrasubstituted Tertiary Carbons. *Adv. Synth. Catal.* 360 **(2018)** 2055 – 2059.

TORNØE, C. W.; CHRISTENSEN, C.; MELDAL, M. Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides. *J. Org. Chem*. 67 (**2002)** 3057-3064.

UNAIDS. **Disponível em:** <http://unaids.org.br/estatisticas/> **Acesso em:** ago de 2018.

VASILYEVA, S. V.; LEVINA, A. S.; LI-ZHULANOV, N. S.; SHATSKAYA, N. V.; BAIBORODIN, S. I.; REPKOVA, M. N.; ZARYTOVA, V. S.; MAZURKOVA, N. A.; SILNIKOV, V. N. SiO_2 nanoparticles as platform for delivery of 3'-triazole analogues of AZT-triphosphate into cells. *Bioorganic & Medicinal Chemistry* 23 **(2015)** 2168–2175.

VENEPALLY, V; JALA, R. C. R. An insight into the biological activities of heterocyclic-fatty acid hybrid molecules. *European Journal of Medicinal Chemistry* 141 **(2017)** 113-137.

VENEPALLY, V; JALA, R. C. R. An insight into the biological activities of heterocyclic-fatty acid hybrid molecules. *European Journal of Medicinal Chemistry* 141 **(2017)** 113-137.

VERNEKAR, S. K.; QIU,L.; ZHANG, J.; LI, J. K. H.; GERAGHTY, R. J.; WANG, Z. 5'-Silylated 3'-1,2,3-triazolyl thymidine analogues as inhibitors of West Nile virus and Dengue virus. *J. Med. Chem.* **(2015)**.

WANG X. L.; WAN K.; ZHOU C.H. Synthesis of novel sulfanilamide derived 1,2,3-triazoles and their evaluation for antibacterial and antifungal activities. *Eur J Med Chem* 45 **(2010)** 4631–4639.

WANG, Q.; HU, W.; WANG, S.; PAN, Z.; TAOB, L.; GUO, X.; QIAN, K.;CHEN, C.; LEE, K.; CHANG, J. Synthesis of new 2'-deoxy-2'-fluoro-4'-azido nucleoside analogues as potent anti-HIV agents. *European Journal of Medicinal Chemistry* 46 **(2011)** 4178-4183.

WANG, Q.; LI, Y.; SONG, C.; QIAN, K.; CHEN, C.; LEE, K.; CHANG, J. Synthesis and anti-HIV activity of 2'-deoxy-2'-fluoro-4'-C-ethynyl nucleoside analogs. *Bioorganic & Medicinal Chemistry Letters* 20 **(2010)** 4053–4056.

VIEIRA, B. M.; THUROW, S.; COSTA, M. DA; CASARIL, A. M.; DOMINGUES, M.; SCHUMACHER, R. F.; PERIN, G.; ALVES, D.; SAVEGNAGO, L.; LENARDÃO E. J. Ultrasound-Assisted Synthesis and Antioxidant Activity of 3-Selanyl-1H-indole and 3-Selanylimidazo[1,2-a]pyridine Derivatives. *Asian J. Org. Chem.* 6 **(2017)** 1635 – 1646.

WIGERINCK, P.; AERSCHOT, A. V.; CLAES, P.; BALZARINI, J.; CLERCQ, E.; HERDEWIJN, P. 3'-(1,2,3-triazol-1-yl)-2',3'-dideoxythyminine and 3'-(1,2,3-triazol-1-yl)-2',3'-dideoxyuridine. *J. Heterocyclic Chem.* 26 **(1989)** 1635.

WILHELM, E. A.; MACHADO, N. C.; PEDROSO, A. B.; GOLDANI, B.S.; SEUS. N.; MOURA, S.; SAVEGNAGO, L.; JACOB, R. G.; ALVES, D. Organocatalytic synthesis and evaluation of 7-chloroquinoline-1,2,3-triazoyl carboxamides as potential antinociceptive, anti-inflammatory andanticonvulsant agent. *RSC Adv*. 4 **(2014)** 41437–41445.

WORRELL, B. T.; MALIK, J. A.; FOKIN, V. V. Direct Evidence of a Dinuclear Copper Intermediate in Cu(I)-Catalyzed Azide-Alkyne Cycloadditions. *Science 340* **(2013)** 457-460.

WU, G.; ZALLOUM, W. A.; MEUSER, M. E.; JING, L.; KANG, D.; CHEN, C.; TIAN, Y; ZHANG, F.; COCKLIN, S.; LEE, K.; LIU, X.; ZHAN, P. Discovery of phenylalanine derivatives as potent HIV-1 capsid inhibitors from click chemistry-based compound library. *European Journal of Medicinal Chemistry* 158 **(2018)** 478-492.

XAVIER, D.M.; GOLDANI, B.S.; SEUS, N.; JACOB, R.G.; BARCELLOS, T.; PAIXÃO, M.W.; LUQUE, R.; ALVES, D. Sonochemistry in organocatalytic enamine-azide [3+2] cycloadditions: A rapid alternative for the synthesis of 1,2,3-triazoyl carboxamides, Ultrasonics Sonochemistry **(2016)** doi: 10.1016/j.ultsonch.2016.05.007.

YAN, S.; LI, Y.; CHEN, X; LIU, D.; CHEN, C.; LI, R. Diterpenes from the stem bark of *Euphorbia neriifolia* and their in vitro anti-HIV activity. Phytochemistry 145 **(2018)** 40-47.

ZHAN, P.; CHEN, X.; LI, X.; LI, D.; TIAN, Y.; CHEN, W.; PANNECOUQUE, C.; CLERCQ, E.; LIU, X. Arylazolylthioacetanilide Part 8: Design, synthesis and biological evaluation of Novel 2-(2-(2,4-Dichlorophenyl)-2H-1,2,4-triazol-3-ylthio)-N-arylacetamides as potent HIV-1 inhibitors. *European Journal of Medicinal Chemistry* 46 **(2011)** 5039-5045.

ZHANG, D.; LIU, H.; WEI, Q.; ZHOU, Q. Structure-activity relationship study of anticancer thymidine-quinoxaline conjugates under the low radiance of long wavelength ultraviolet light for photodynamic therapy. *European Journal of Medicinal Chemistry* 107 **(2016)** 180-191.

ZHANG, D.; ZHANG, Y; LI, J.; ZHAO, T.; GU, Q.; LIN, F. Ultrasonic-assisted synthesis of 1,4-disubstituted 1,2,3-triazoles via various terminal acetylenes and azide and their quorum sensing inhibition. *Ultrasonics Sonochemistry* 36 **(2017)** 343–353.

ZHANG, L.; ZHANG, L.; LUO, T.; ZHOU, J.; SUN, L.; XU, Y. Synthesis and Evaluation of a dipeptide−drug conjugate library as substrates for PEPT1. *ACS Comb. Sci.* 14 **(2012)** 108−114.

ZHOU, X; XU, X; LIU, K; GAO, H; WANG, W.; LI, W. Organocatalytic 1,3-Dipolar Cycloaddition Reaction of β-Keto Amides with Azides – Direct Access to 1,4,5-Trisubstituted 1,2,3- Triazole-4-carboxamides. *Eur. J. Org. Chem.* **(2016)** 1886–1890.