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Campus Anápolis de Ciências Exatas e Tecnológicas - Henrique Santillo
Programa de Pós-Graduação *Stricto Sensu* em Recursos Naturais do Cerrado

VITOR SANTOS DUARTE

**CHALCONAS E BENZIMIDAZÓIS:
DESENVOLVIMENTO DE ADITIVOS EM MISTURAS DE
BIOCOMBUSTÍVEIS**

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2023

VITOR SANTOS DUARTE

**CHALCONAS E BENZIMIDAZÓIS:
DESENVOLVIMENTO DE ADITIVOS EM MISTURAS DE
BIOCOMBUSTÍVEIS**

Tese apresentada ao Programa de Pós-Graduação *Stricto Sensu* em Recursos Naturais do Cerrado, da Universidade Estadual de Goiás, para a obtenção do título de Doutor em Recursos Naturais do Cerrado.
Orientador: Prof. Dr. Hamilton Barbosa Napolitano.

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Dados do autor (a)

Nome Completo: Vitor Santos Duarte
E-mail: vitorvsd132@gmail.com

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Aos 30 dias do mês de Março do ano de 2023, às 09h00min, reuniu-se no auditório do bloco IV do Câmpus Central da UEG, a banca Examinadora composta pelos: Dr. Hamilton Barbosa Napolitano (Universidade Estadual de Goiás), Dr. Leonardo Luiz Borges (Universidade Estadual de Goiás), Dr. Everton Tizo Pedroso (Universidade Estadual de Goiás), Dr. Eduardo Coelho da Mata Faria (Centro de Pesquisas e Eficiência Energética – CPEE/CAOA), Dra. Vânia Mori (Instituto Nacional de Tecnologia) para sob a presidência do primeiro, procederem à **defesa de doutorado** intitulada: *Chalconas e Benzimidazóis: Desenvolvimento de aditivos em misturas de biocombustíveis*, de Vitor Santos Duarte, discente do PPG Recursos Naturais do Cerrado, nível doutorado. Foi realizada a avaliação oral no sistema de apresentação e defesa de tese de autoria do(a) discente. Terminada a avaliação oral, a Banca Examinadora reuniu-se emitindo os seguintes pareceres mediante as justificativas e sugestões abaixo:

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RESUMO

A escassez de recursos naturais e os desafios das mudanças climáticas são problemas relacionados à crise que permeia o sistema econômico mundial. Líderes de todo o mundo discutem soluções para esses problemas ambientais, tais como a redução das emissões de poluentes convencionais e de gases de efeito estufa (GEE), bem como alternativas para a crise energética, considerada uma emergência mundial. O sistema econômico mundial é essencialmente dependente de recursos naturais, sendo que mais de 80% da energia utilizada provém de combustíveis fósseis (petróleo, carvão e gás natural). A iminente escassez desses recursos é uma preocupação cada vez mais presente, devido ao desenvolvimento humano e ao crescimento populacional, além da crescente poluição gerada pela combustão de combustíveis fósseis. Nesse contexto, o sinergismo de combustíveis fósseis com combustíveis renováveis representa uma opção sustentável que pode reduzir a emissão de poluentes criando uma matriz energética alternativa. Os biocombustíveis, por exemplo, representam uma alternativa viável para a redução de poluentes e, ao mesmo tempo, uma opção energética sustentável. O biodiesel é um exemplo de biocombustível renovável e promissor, que pode ser obtido a partir de biomassa renovável. Ele é biodegradável e pode ser utilizado em motores de ciclo diesel sem grandes adaptações. Além disso, apresenta menores índices de emissão de poluentes e toxicidade quando comparado aos combustíveis fósseis. Contudo, a menor disponibilidade energética e a baixa estabilidade oxidativa deste combustível geram uma série de problemas que dificultam sua utilização. Devido a isso, tecnologias são estudadas todos os dias para mitigação desses problemas. Um bom exemplo são os aditivos, que são substâncias que retardam a oxidação e degradação precoce do combustível. Os aditivos podem ser desenvolvidos a partir de moléculas orgânicas que possuam propriedades desejadas como antioxidantes ou antimicrobianas. Nesse intuito, essa tese apresenta um estudo dos aspectos estruturais de moléculas orgânicas da classe das chalconas e dos benzimidazóis. Estudos teóricos também foram realizados para compreender propriedades físico-químicas dessas moléculas, aliado a simulações e métodos de *machine learning* que contribuirão para o entendimento de aspectos ligados a atividade antioxidante. Direcionados do ponto de vista estrutural e teórico, testes experimentais determinaram as moléculas dessa tese como agentes antioxidantes, atuando como um aditivo para misturas diesel-biodiesel. Ressaltamos ainda que essas moléculas agindo como um aditivo poderão contribuir para utilização de biocombustíveis, corroborando assim, para manutenção dos recursos naturais e do meio ambiente.

Palavras-Chave: *biocombustíveis, meio ambiente, aditivos, chalconas, benzimidazóis.*

ABSTRACT

The scarcity of natural resources and the challenges posed by climate change are problems that are related to the crisis permeating the global economic system. Leaders from all around the world are discussing solutions to these environmental problems, such as reducing emissions of conventional pollutants and greenhouse gases (GHG), as well as exploring alternatives to the energy crisis, which is considered a global emergency. The global economic system is highly dependent on natural resources, particularly fossil fuels such as oil, coal, and natural gas. In fact, more than 80% of the energy consumed worldwide comes from these non-renewable sources. The imminent scarcity of these resources is worrying, due to human development and population growth, in addition to the increasing pollution generated by the combustion of fossil fuels. In this context, the synergism of fossil fuels with renewable fuels represents a sustainable option that can reduce pollutant emissions by creating an alternative energy matrix. Biofuels, for example, represent a viable alternative for reducing pollutants and a sustainable energy option. Biodiesel is an example of a renewable and promising biofuel that can be obtained from renewable biomass. It is biodegradable and can be used in diesel engines without major adaptations, in addition to presenting lower levels of pollutant emissions and toxicity compared to fossil fuels. However, the lower energy availability and low oxidative stability of this fuel generate a series of problems that hinder its use. Due to this, technologies are studied every day to mitigate these problems. A good example is additives, which are substances that delay the oxidation and early degradation of the fuel. Additives can be developed from organic molecules that have desired properties such as antioxidants or antimicrobials. In this sense, this thesis presents a study of the structural aspects of organic molecules from the class of chalcones and benzimidazoles. Theoretical studies were also carried out to understand the physicochemical properties of these molecules, combined with simulations and machine learning methods that contributed to the understanding of aspects related to antioxidant activity. From a structural and theoretical perspective, experimental tests have determined that the molecules studied in this thesis act as antioxidant agents, making them suitable additives for diesel-biodiesel blends. We also emphasize that these molecules acting as an additive can contribute to the use of biofuels, thereby supporting the maintenance of natural resources and the environment.

Keywords: *biofuels, environment, additives, chalcones, benzimidazoles.*

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1. INTRODUÇÃO

A escassez dos recursos naturais é um problema atual, frequentemente associado à crise que afeta o sistema econômico mundial, sendo palco para previsões de um futuro incerto devido ao esgotamento de muitos recursos essenciais para manutenção da vida (HANCOCK, 2011, RATTNER, 1977, ZHANG, SIAL, *et al.*, 2021, Tan, Su *et al.* 2023). Os recursos naturais podem ser classificados em dois tipos: renováveis e não renováveis, sendo a diferenciação entre eles determinada pela possibilidade ou limitação de uso ao longo do tempo. Os recursos renováveis seriam em tese infinitos, não acabariam ou conseguiriam se recompor dentro de uma escala de tempo humana, enquanto os recursos não renováveis teriam uma reserva finita em nosso planeta ou ainda podendo levar milhares de anos para renovação, como os combustíveis fósseis (GÜNEY, 2019, PAO, FU, 2013). Neste contexto de escassez de recursos naturais para a matriz energética, deparamo-nos com uma quantidade finita de combustíveis fósseis, juntamente com o desafio da poluição gerada pela sua combustão.

A poluição causada pela queima dos combustíveis fósseis representa um dos maiores fatores da poluição atmosférica (BLACKSMITH INSTITUTE, SWITZERLAND, 2012). A queima destes combustíveis causa a emissão de diversos gases tóxicos, como o dióxido de carbono (CO_2) que é um dos principais responsáveis pela intensificação do efeito estufa e do aquecimento global. Nessa lista ainda temos o dióxido de nitrogênio (NO_2) e o monóxido de carbono (CO) que são extremamente tóxicos, temos ainda o dióxido de enxofre (SO_2) que é responsável pelas chuvas ácidas, dentre outros (BLACKSMITH INSTITUTE, SWITZERLAND, 2012). De acordo com um modelo global 3D de química atmosférica, a queima de combustíveis fósseis resultou em mais de 8 milhões de mortes em 2018, correspondendo a 1 em cada 5 mortes no mundo. A poluição do ar gerada por esse processo foi apontada como a principal causa dessas mortes (VOHRA, VODONOS, *et al.*, 2021). De acordo com dados do *Our World in Data*¹, houve um aumento drástico no número absoluto de mortes atribuídas à poluição do ar ambiente (ao ar livre) por material particulado de 1990 a 2015, sendo a China responsável pelos maiores índices com 945 300 mortes em 1990, que aumentaram para 1,11 milhões em 2015. Em seguida, a Índia apresentou números alarmantes, com 795 200 mortes em 2005, subindo para 1,09 milhões em 2015. O Brasil também registrou um aumento de 24% no número de mortes, passando de 42 200 em 2005 para 52 300 em 2015.

Os combustíveis fósseis mais comuns no mundo são o petróleo, o carvão mineral e o

¹ **Our world in data** é uma publicação digital especializada em expor pesquisas empíricas e dados analíticos sobre mudanças nas condições de qualidade de vida ao redor do mundo, e pode ser acessado pelo link: <https://ourworldindata.org/>.

gás natural, que juntos correspondem a mais de 80% da matriz energética global utilizada pela humanidade (ARMAROLI, BALZANI, 2011, “International Energy Agency, Key world energy statistics”, 2010). O petróleo além de estar ligado com a produção de combustíveis poluentes para atmosfera, também é considerado um dos maiores poluentes dos mares, estima-se que anualmente sejam derramados milhões de toneladas de petróleo nos oceanos (BLUMER, SANDERS, *et al.*, 1971, SOLBERG, 2012). Portanto investir em combustíveis derivados de fontes renováveis, substituindo combustíveis fósseis, é uma alternativa de sustentabilidade.

No contexto da nova Política Nacional de Biocombustíveis (RenovaBio) e seguindo a recomendação do Conselho Nacional de Política Energética (CNPE), o Brasil estabeleceu metas de redução das emissões de gás carbônico da matriz de combustíveis em 10,1% até o final de 2028, o que impulsiona uma nova projeção na produção de biocombustíveis no país (LINDNER, MONTEIRO, *et al.*, 2018). Os biocombustíveis são obtidos a partir de biomassa renovável e podem ser utilizados como substitutos dos combustíveis fósseis derivados de petróleo e gás natural em motores de combustão (MINISTÉRIO DE MINAS E ENERGIA, 2018). No Brasil, os dois principais biocombustíveis utilizados são o etanol, produzido a partir da cana-de-açúcar, e o biodiesel, derivado de fontes renováveis como óleos e gorduras. O biodiesel é um combustível interessante, podendo ser utilizado em motores de ciclo diesel sem a necessidade de grandes adaptações e apresenta baixos teores de poluentes e menor toxicidade do que outros combustíveis fósseis (MEDEIROS, CORDEIRO, *et al.*, 2014).

Temos a concepção de um futuro promissor com a utilização do biodiesel, com chances de reduzir problemas causados pela poluição. Muitos países adotam a adição de biodiesel no diesel (as chamadas misturas²), atualmente o Brasil mantém em 10% esse percentual de biodiesel a ser acrescido no diesel vendido. Contudo, alguns problemas relacionados a estabilidade do biodiesel podem afetar a qualidade do produto. A estabilidade do biodiesel é um fator crítico na sua produção, armazenamento, transporte e comercialização (KUMAR, Sanjeev, YADAV, *et al.*, 2018, PULLEN, SAEED, 2012a, SALUJA, KUMAR, *et al.*, 2016). A estrutura molecular do biodiesel é mais suscetível à degradação oxidativa, térmica ou microbiológica quando comparado a outros combustíveis fósseis (KNOTHE, 2007a, YAAKOB, NARAYANAN, *et al.*, 2014a). O biodiesel é composto por uma mistura de ésteres metílicos ou etílicos, sendo rico em insaturações com grupos oxigenados polares, além do seu

² Misturas diesel-biodiesel dizem respeito a porcentagem de biodiesel adicionado ao diesel. O termo BX: onde X refere-se a porcentagem por volume do biodiesel, sendo 10% a 20% as misturas mais comuns (B10 – B20). Essas quantidades variam segundo a legislação de cada país. (AMERICAN SOCIETY FOR TESTING AND MATERIALS, 2020, DE OLIVEIRA, COELHO, 2017, EUROPEAN COMMITTEE FOR STANDARDIZATION, 2019a, b, TRANSPORT & ENVIRONMENT, 2021)

acentuado caráter higroscópio que retém mais água no combustível, contribuindo para a proliferação de microrganismos (JAKERIA, FAZAL, *et al.*, 2014, KUMAR, Niraj, 2017a, SUNDUS, FAZAL, *et al.*, 2017). As condições climáticas locais e a matéria-prima³ utilizada para a produção do biodiesel também afetam a qualidade do produto. Essa baixa estabilidade oxidativa do biodiesel o torna mais propenso à degradação, e o armazenamento desse combustível por longos períodos pode torná-lo impróprio para uso, podendo gerar resíduos no combustível que podem ocasionar na danificação dos motores, (PULLEN, SAEED, 2012b, TRINDADE, 2018) acarretando manutenções em períodos menores, gerando maiores custos e prejuízos para indústria automobilística (BARTHOLOMEU, PÉRA, *et al.*, 2016). Todos esses fatores dificultam a consolidação deste combustível na matriz energética. Tecnologias são desenvolvidas todos os dias para reduzir esses problemas relacionados a estabilidade do biodiesel, como o uso de aditivos que retardam a oxidação do biodiesel e preservam suas propriedades evitando uma maior degradação. Estudos com moléculas orgânicas têm sido realizados para o uso como agentes antioxidantes e podem ser aplicadas em estudos como potenciais aditivos (KARAVALLAKIS, STOURNAS, 2010, KIVEVELE, MBARAWA, *et al.*, 2011, VARATHARAJAN, PUSHPARANI, 2018a).

Neste contexto, essa tese propõe uma abordagem com estudo estrutural e teórico de moléculas orgânicas buscando fatores e aspectos estruturais que estejam ligados com as atividades necessárias em um aditivo. A partir desse direcionamento estrutural e teórico, ensaios experimentais com essas moléculas foram realizados em misturas de biocombustíveis. Apresentamos o estudo de moléculas orgânicas da classe das chalconas e dos benzimidazóis que foram avaliados como possíveis agentes antioxidantes, realizando o papel de um aditivo para misturas diesel-biodiesel. As moléculas avaliadas podem se tornar futuros produtos que favoreçam o uso de biocombustíveis, proporcionando assim uma redução da poluição atmosférica, e contribuindo diretamente para manutenção dos recursos naturais e do meio ambiente. Os resultados obtidos foram publicados em forma de artigos científicos que são apresentados na seção 4 – Resultados. Após atingir o nível 4 (TRL4) de prontidão tecnológica, (*Technology Readiness Level – TRL*)⁴ a propriedade intelectual das moléculas avaliadas no combustível foi requerida em forma de registro de pedido de patente no Instituto Nacional da

³ O biodiesel pode ser produzido a partir de várias matérias primas como: soja, palma, milho, gordura animal, resíduos, etc (PULLEN, SAEED, 2014, WANG, Wenchao, LI, *et al.*, 2020, YANG, HOLLEBONE, *et al.*, 2013).

⁴ Os Níveis de Prontidão Tecnológica foram criados pela NASA (National Aeronautics and Space Administration) como um método para avaliar a maturidade técnica de uma determinada tecnologia, variando de TRL1 a TRL9. O TRL4 corresponde à validação dos componentes da tecnologia em laboratório (MANKINS, 1995).

Propriedade Industrial (INPI)⁵ - (BR 10 2022 006539 0 – Anexo 01) e (BR 10 2023 006206 7 – Anexo 02).

⁵ O processo de pedido dessas patentes pode ser acompanhado pelo número de Registro: [BR 10 2022 006539 0] e [BR 10 2023 006206 7] através do site do INPI, na seção “patentes”. - <https://www.gov.br/inpi/pt-br>.

2. OBJETIVOS

(i) Determinar a estrutura química de moléculas orgânicas das classes: chalcona e benzimidazol.

(ii) A partir da estrutura química buscar uma relação entre estrutura-atividade, determinando algumas propriedades físico-químicas através de cálculos teóricos.

(iii) A partir do conhecimento estrutural e teórico, realizar as análises experimentais destas moléculas aditivadas em biocombustíveis para avaliar o seu desempenho como aditivos, expandindo o conhecimento entre estrutura-atividade para um aditivo.

(iv) Propor novas moléculas como novos aditivos.

3. REFERENCIAL TEÓRICO E TÓPICOS METODOLÓGICOS

O uso de moléculas orgânicas seja de fontes sintéticas ou de origem natural é amplo em vários setores, como na indústria farmacêutica, engenharia, indústria alimentícia e indústria energética. Na indústria farmacêutica temos diversos estudos envolvendo novas moléculas ou aprimoramento de moléculas já existentes para fins biológicos, (ALTOMONTE, ZANDA, 2012, KLOPMAN, 1984, LESLIE, HERGENROTHER, 2008, MANN, 1987, MOHSIN, AHMAD, 2018, WANG, Bin-Gui, GLOER, *et al.*, 2013, WANG, Lirong, MA, *et al.*, 2013, YU, LI, *et al.*, 2010) Na engenharia, são realizados estudos das propriedades físico-químicas de novos compostos com o intuito de desenvolver novos materiais (ADITYA PRASAD, MUTHU, *et al.*, 2015, CHEMLA, ZYSS, 2012, CUSTODIO, D'OLIVEIRA, *et al.*, 2019, KOWALSKI, SU, *et al.*, 2016, LEDOUX, ZYSS, 1994, MORLEY, 1988, RIBEIRO, Gabriela C, ALMEIDA, *et al.*, 2016, VALVERDE, VAZ, *et al.*, 2017). Na indústria alimentícia, o uso de moléculas orgânicas como conservantes ou pesticidas (ALLA, YOUNIS, 1995, BRUL, 1999, DELVES-BROUGHTON, 1990, DENG, HE, *et al.*, 2010, DÍAZ-TIELAS, GRAÑA, *et al.*, 2016, GOMES, CHRISTINA, *et al.*, 2018, KEYMANESH, SOLTANI, *et al.*, 2009, NGUYEN, ERLINKAMP, *et al.*, 2016) e na indústria energética, temos novas fontes de energia mais limpas como os biocombustíveis que necessitam de aditivos, que podem ser desenvolvidos a partir de moléculas orgânicas (FARIA, E. C. M., DUARTE, *et al.*, 2021a, GARCÍA, BOTELLA, *et al.*, 2017, KARAVALLAKIS, STOURNAS, 2010, MOREIRA, FARIA, *et al.*, 2022a, VARATHARAJAN, PUSHPARANI, 2018a).

Um biocombustível é um tipo de combustível de origem biológica não fóssil, produzido a partir de processos que envolvem a biomassa e que tem o potencial de substituir completamente os combustíveis fósseis, normalmente derivados do petróleo e gás natural (DEMIRBAS, Ayhan, 2009, NAIK, GOUD, *et al.*, 2010). O biodiesel é exemplo de biocombustível que pode ser obtido tanto de fontes animais quanto vegetais (NAIK, GOUD, *et al.*, 2010, NAQVI, YAN, 2015) que são renováveis e pode ser produzido com alguns resíduos, como óleos utilizados em fritura ou sebo animal,⁶ cujo descartes representam problemas ambientais (NAIK, GOUD, *et al.*, 2010). A Tabela 01 mostra alguns tipos de biodiesel produzidos. Além ser um combustível renovável e uma fonte de energia alternativa, o biodiesel apresenta baixo índice de emissão de poluentes, reduz em 78% as emissões líquidas de CO comparado a outros combustíveis fósseis (BIODIESELBR, 2011). Contudo; a utilização do biodiesel está atrelada ao uso de aditivos, estes aditivos podem ter sua origem em moléculas

⁶Sebo de origem animal utilizado na produção do biodiesel inclui o sebo bovino, suíno e de aves.

orgânicas e são fundamentais para conservar as propriedades físico-químicas do combustível (VARATHARAJAN, PUSHPARANI, 2018a).

Tabela 01. Alguns tipos de biocombustíveis produzidos. BD: Biodiesel. BD BX, onde X refere-se a porcentagem por volume do biodiesel.

Combustível
BD-B100 (<i>Opuntia cochenillifera</i> - metílica)(CAVALCANTE, CONCEIÇÃO, <i>et al.</i> , 2012)
BD-B100 (<i>Opuntia cochenillifera</i> - etílica)(CAVALCANTE, CONCEIÇÃO, <i>et al.</i> , 2012)
BD-B100 (<i>Opuntia cochenillifera</i> - propílica)(CAVALCANTE, CONCEIÇÃO, <i>et al.</i> , 2012)
BD-B100 (<i>Opuntia cochenillifera</i> - butílica)(CAVALCANTE, CONCEIÇÃO, <i>et al.</i> , 2012)
BD-B100 (<i>Opuntia cochenillifera</i> - pentílica)(CAVALCANTE, CONCEIÇÃO, <i>et al.</i> , 2012)
BD-B100 (<i>Maclura pomifera</i>)(SALOUA, SABER, <i>et al.</i> , 2010)
BD-B100 (<i>Terminalia bellirica</i>)(CHAKRABORTY, BARUAH, <i>et al.</i> , 2009)
BD-B100 (<i>Milletia pinnata</i>)(SURESHKUMAR, VELRAJ, <i>et al.</i> , 2008)
BD-B100 (<i>Brassica napus</i>)(ABUHABAYA, FIELDHOUSE, <i>et al.</i> , 2010a)
BD-B100 (resíduos de óleo vegetal)(ABUHABAYA, FIELDHOUSE, <i>et al.</i> , 2010b)
BD-B100 (<i>Chondrichthyes</i>)(MARTINS, SECCO, <i>et al.</i> , 2015)
BD-B100 (<i>Ricinus communis</i>)(NASCIMENTO, LORA, <i>et al.</i> , 2006)
BD-B100 (<i>Argemone mexicana</i>)(SINGH, Dipti, SINGH, 2010)
BD-B100 (<i>Cynara cardunculus</i>)(LAPUERTA, ARMAS, <i>et al.</i> , 2005)
BD-B100 (<i>Pongamia pinnata</i>)(BANAPURMATH, TEWARI, <i>et al.</i> , 2008)
BD-B100 (<i>Madhuca longifolia</i>)(PUHAN, VEDARAMAN, <i>et al.</i> , 2005)
BD-B100 (<i>Arachis hypogaea</i>)(KAYA, HAMAMCI, <i>et al.</i> , 2009)
BD-B100 (<i>Calophyllum inophyllum</i>)(SAHOO, DAS, <i>et al.</i> , 2007)
BD-B100 (<i>Hevea brasiliensis</i>)(RAMADHAS, JAYARAJ, <i>et al.</i> , 2005)
BD-B100 (<i>Sesamum indicum</i>)(SAYDUT, DUZ, <i>et al.</i> , 2008)
BD-B10 (<i>Glycine max</i>)(RIGOTTE, 2014a)
BD-B100 (<i>Glycine max</i>) (RIGOTTE, 2014b)
BD-B100 (<i>Gallus gallus domesticus</i> - gordura)(SILVA, M. J., SOUZA, <i>et al.</i> , 2012)
BD-B100 (<i>Olea europaea</i> L.)(KALLIGEROS, ZANNIKOS, <i>et al.</i> , 2003)
BD-B100 (<i>Cucurbita</i>)(SCHINAS, KARAVALLAKIS, <i>et al.</i> , 2009)
BD-B100 (<i>Oryza sativa</i> - farelo)(SINHA, AGARWAL, <i>et al.</i> , 2008)
BD-B100 (<i>Helianthus annuus</i>)(ABUHABAYA, FIELDHOUSE, <i>et al.</i> , 2010b)
BD-B100 (<i>Jatropha curcas</i> L.)(KAISAN, ABUBAKAR, <i>et al.</i> , 2021a)
BD-B100 (<i>Azadirachta indica</i>)(KAISAN, ABUBAKAR, <i>et al.</i> , 2021b)
BD-B100 (<i>Gossypium hirsutum</i> L.)(KAISAN, ABUBAKAR, <i>et al.</i> , 2021b)
BD-B30 (<i>Citrullus lanatus</i>)(XAVIER, 2020)
BD-B25 (<i>Olea europaea</i> L. - Bagaço) (ÇAYNAK, GÜRÜ, <i>et al.</i> , 2009)
BD-B10 (<i>Crambe</i>)(RIGOTTE, 2014b)
BD-B100 (<i>Crambe</i>)(RIGOTTE, 2014b)
BD-B100 (<i>Hibiscus sabdariffa</i>) (NAKPONG, WOOTHKANOKKHAN, 2010)
BD-B100 (óleo de fritura)(RIGOTTE, 2014b)

3.1 Biocombustíveis e os recursos naturais

O mundo depende de energia, e mais de 80% da energia utilizada pela humanidade é proveniente de combustíveis fósseis (ARMAROLI, BALZANI, 2011, “International Energy Agency, Key world energy statistics”, 2010). A combustão destes combustíveis é a principal fonte de poluição atual, sendo direta ou indiretamente responsáveis pelas mudanças climáticas, desencadeando catástrofes naturais, perda de recursos naturais essenciais a vida, extinção de

espécies da fauna e da flora, e a destruição de biomas.

De acordo com um monitoramento divulgado em 2018 pelo IBGE⁷, a poluição tem causado perdas significativas de recursos naturais no Brasil. Entre 2000 e 2016, o país perdeu cerca de 7,5% de sua cobertura vegetal, com uma área de vegetação que diminuiu de 4.017.505 km² para 3.719.801 km² (AGÊNCIA BRASIL, 2020). Sabemos que essa perda de cobertura vegetal não é exclusivamente causada pela poluição dos combustíveis fósseis, mas incluem o desmatamento, queimadas, expansão das fronteiras agrícolas etc. Segundo dados divulgados pelo INPE⁸ em 2018, o Cerrado Brasileiro perdeu cerca de 6.657 km², índice que aumentou em 2020 para 7.340 km² de área suprimida, atualmente a perda da vegetação do Cerrado é estimada em torno de 51%, além da poluição que tem impactos negativos na fauna e flora do Cerrado, o avanço do agronegócio é um dos principais fatores responsáveis pela supressão de sua vegetação (VEGETAÇÃO NATIVA, 2020, TERRABRASILIS, 2020, WORLD WIDE FUND FOR NATURE (WWF), 2020).

Sugerir soluções radicais, como conter a atividade agrícola e interromper completamente o uso de combustíveis fósseis, é uma tarefa complexa devido a uma estrutura de cadeia bem estabelecida, questões políticas profundamente enraizadas e leis ineficazes para lidar com a poluição. No entanto, devido à futura escassez dos combustíveis fósseis e à necessidade iminente de reduzir as emissões de gases do efeito estufa, há uma crescente demanda por combustíveis mais limpos e renováveis. Os biocombustíveis apresentam muitas vantagens em relação aos combustíveis fósseis, que serão detalhadas nas próximas seções. A substituição dos combustíveis fósseis pelos biocombustíveis poderia preservar e salvar os recursos naturais e biomas, não só do Brasil, mas de todo mundo, através da redução dos índices de gases poluentes lançados na atmosfera.

3.2 Biocombustíveis e o Cerrado

O Cerrado é uma savana brasileira com uma extensão de aproximadamente 2 milhões de km², abrangendo 11 estados do país, é conhecida por sua rica biodiversidade e alta taxa de endemismo. Apesar de ser considerado um dos ecossistemas mais ricos do mundo, o Cerrado é um *hotspot* da biodiversidade altamente ameaçado pela ação humana e tem sofrido com a poluição do ar, resultante da emissão de gases poluentes pela queima de combustíveis fósseis (SAWYER, MESQUITA, *et al.*, 2018). A combustão desses combustíveis libera uma série de

⁷IBGE: Instituto Brasileiro de Geografia e Estatística. (<https://www.ibge.gov.br/>)

⁸INPE: Instituto Nacional de Pesquisas Espaciais. (<https://www.gov.br/inpe/pt-br>)

poluentes no ar que podem se espalhar por grandes distâncias e afetar a qualidade do ar no Cerrado, o que pode ter efeitos graves na saúde das pessoas e dos animais que vivem na região (VALENZUELA, RAMALHO, *et al.*, 2017). Além disso, a poluição do ar pode ter efeitos diretos na vegetação do Cerrado, como redução da taxa fotossintética e alterações na estrutura das folhas, afetando assim a produção de alimentos e fibras vegetais. Outra consequência preocupante da queima de combustíveis fósseis é o aumento das temperaturas globais e o consequente agravamento do aquecimento global (DRUMM, GERHARDT, *et al.*, 2014). Esse fenômeno pode afetar ainda mais a biodiversidade do Cerrado, que já é altamente vulnerável às mudanças climáticas. As mudanças na temperatura e no regime de chuvas afetam a disponibilidade de água, e a umidade da região, o que pode levar a mudanças significativas na vegetação e na fauna que habitam o Cerrado (MOLION, C. B., 2008). Além disso, a mudança climática pode aumentar a frequência e a intensidade de eventos extremos, como secas e incêndios, que já são comuns no Cerrado. O Cerrado é uma das regiões mais afetadas pelos incêndios florestais no país. De acordo com o Instituto Nacional de Pesquisas Espaciais (INPE), em 2022 foram registrados cerca de 56 mil focos de incêndio no Cerrado. Esses incêndios são intensificados pela combinação de altas temperaturas e baixa umidade, condições cada vez mais frequentes na região devido às mudanças climáticas (INPE, 2022).

Ao longo das últimas décadas, as temperaturas médias na região do Cerrado têm apresentado um aumento significativo. Durante a estação seca, em particular, a temperatura subiu entre 2,2 °C e 4 °C, enquanto a umidade relativa do ar caiu cerca de 15%, esse aumento na temperatura afeta diretamente a vegetação, a fauna e os recursos hídricos do bioma (HOFMANN, CARDOSO, *et al.*, 2021). A poluição presente na região pode ter efeitos negativos na saúde tanto das pessoas quanto dos animais que ali habitam. Além disso, a presença de poluentes pode reduzir significativamente a capacidade das plantas de realizar a fotossíntese de forma adequada (LOCOSSELLI, CAMARGO, *et al.*, 2019, TJOELKER, VOLIN, *et al.*, 1995).

Os desafios enfrentados pelo Cerrado, como as mudanças climáticas, os incêndios florestais e a poluição do ar, exigem soluções urgentes e eficazes. Dentre as alternativas, para mitigar esses problemas, podemos citar a utilização de biocombustíveis, que podem ser produzidos partindo de matérias-primas renováveis, como a soja, milho e cana-de-açúcar. A adoção de biocombustíveis pode contribuir de forma significativa para a redução das emissões de gases de efeito estufa no Cerrado e em todo o país. O etanol produzido da cana-de-açúcar emite menos gases de efeito estufa em comparação com a gasolina e o diesel, além disso, o biodiesel, pode reduzir em cerca de 70% as emissões líquidas de CO comparado a outros

combustíveis fósseis (BIODIESELBR, 2011, SOARES, ALVES, *et al.*, 2009).

A produção de biocombustíveis pode impulsionar a economia local e gerar empregos em várias etapas da cadeia produtiva, seja no Cerrado ou em outras regiões do país. Além do que, a utilização de biocombustíveis pode reduzir a dependência do Brasil em relação aos combustíveis fósseis importados, melhorando a segurança energética do país. Em resumo, os biocombustíveis podem ser uma solução promissora para os desafios enfrentados pelo Cerrado, contribuindo para redução das emissões de gases de efeito estufa, a promoção da economia local e a melhoria da segurança energética do país (DEMIRBAS, A., 2009).

3.3 Estabilidade do biodiesel

O biodiesel é um combustível altamente promissor, apresentando diversas vantagens em relação a outros tipos de combustíveis. Ele pode ser usado em motores de ciclo diesel com algumas adaptações, é biodegradável, tem baixos níveis de poluentes e é menos tóxico do que os combustíveis fósseis convencionais (MEDEIROS, CORDEIRO, *et al.*, 2014). Em veículos de combustão interna, produz redução de emissões de CO₂ e poluentes atmosféricos, além de favorecer a lubrificação do sistema de injeção de combustível aumentando a durabilidade das peças (VARATHARAJAN, PUSHPARANI, 2018a).

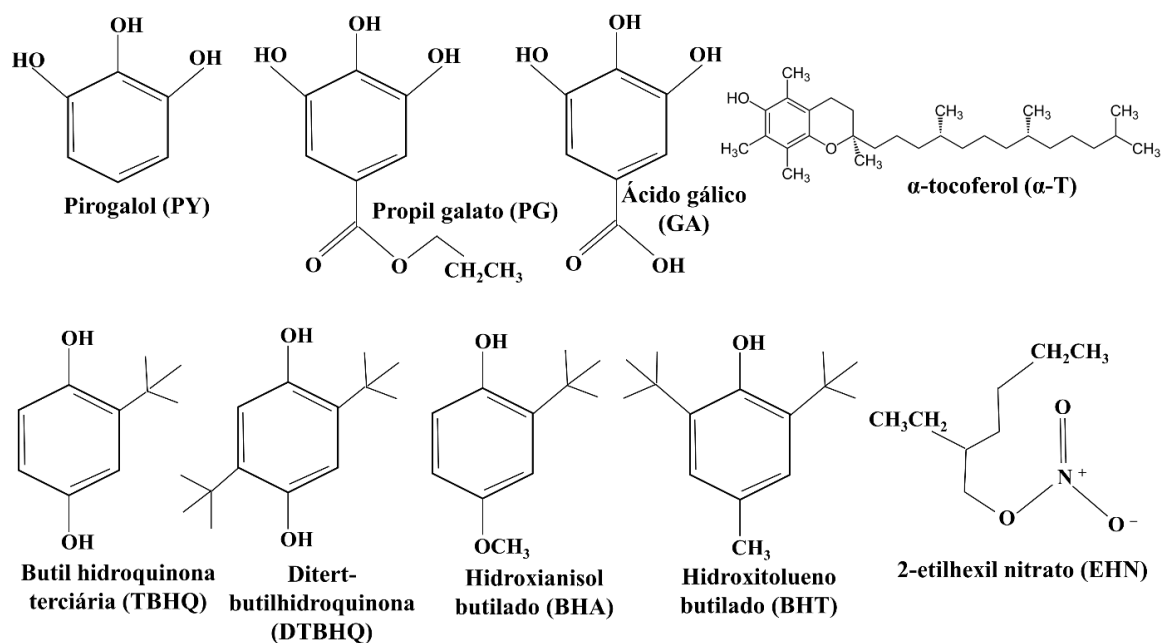
Contudo, a baixa estabilidade oxidativa do biodiesel é atualmente um ponto crítico sendo uma barreira na sua consolidação na matriz energética mundial (ALIZADEH, LUND, *et al.*, 2020, KNOTHE, RAZON, 2016). A oxidação do biodiesel se caracteriza por uma reação de transferência de elétrons ou hidrogênio de um composto para um agente oxidante e afeta o combustível em estágios iniciais de uso, durante o transporte e o armazenamento, quando entra em contato com ar, e quando expostos a altas temperaturas (KNOTHE, 2007b). A oxidação do biodiesel influencia significativamente na sua qualidade, com o aumento da oxidação, o biodiesel se torna mais denso devido a hidrogenação das ligações insaturadas, tornando-o impróprio ao uso. A degradação do biodiesel está ligada a variações de outras propriedades físico-químicas, como variação iodométrica, índice de peróxidos, nível de acidez e viscosidade cinemática. Nesse cenário, a oxidação do biodiesel pode contribuir com vários problemas no sistema mecânico de um veículo, causando corrosão do motor e tubulações, além da obstrução e formação de depósitos no interior do motor (KNOTHE, RAZON, 2016, KUMAR, NIRAJ, 2017b). Para evitar a oxidação do biodiesel, existem alguns métodos, tais como a utilização de compostos com ação antioxidante e conservantes como é o caso dos aditivos (KARVALAKIS, STOURNAS, 2010).

3.4 Aditivos para (Bio)combustíveis

Como vimos, o biodiesel possui um problema relacionado diretamente à sua estabilidade oxidativa, portanto o uso de compostos que retardem a oxidação e mitiguem esses problemas, se faz necessário. Os aditivos são compostos que retardam processos de degradação do combustível, melhoram seu desempenho e contribuem para longevidade do motor e peças do veículo (ALAGU, NAGAPPAN, *et al.*, 2018). A Figura 01 mostra a estrutura química de alguns dos aditivos comerciais mais utilizados atualmente.

O desenvolvimento de um aditivo é um processo complexo que consiste em uma série de testes visando avaliar o desempenho do composto, que vão desde a elucidação molecular até a aplicação em misturas com combustíveis, estabelecendo a relação entre estrutura molecular e propriedades (VARATHARAJAN, PUSHPARANI, 2018b). Como a oxidação do biodiesel é associada com a proliferação de microrganismos (fungos e bactérias) que causariam sua oxidação, (JOSE, ANAND, 2016, KUMAR, NIRAJ, 2017b, MITTELBACH, SCHOBER, 2003, PULLEN, SAEED, 2012c, STAMPS, BOJANOWSKI, *et al.*, 2020, YAAKOB, NARAYANAN, *et al.*, 2014b) compostos ou moléculas com propriedades antimicrobianas ou antioxidantes são desejáveis como aditivos (MEDEIROS, CORDEIRO, *et al.*, 2014, SINGH, D, SHARMA, *et al.*, 2020). Logo, a busca por moléculas orgânicas com tais propriedades é um caminho promissor nesse contexto de biocombustíveis e aditivos. Pontuemos que não é qualquer molécula orgânica que irá apresentar propriedades para alguma aplicação, existem classes de moléculas e grupos funcionais que ao longo do tempo têm se mostrado mais interessantes de uma perspectiva para aplicação, a conformação estrutural também é levada em consideração, devido a relação entre estrutura e atividade molecular (DUDEK, ARODZ, *et al.*, 2006). Portanto, neste trabalho são analisadas moléculas orgânicas de classes descritas na literatura por apresentarem atividades antioxidantes e antimicrobianas, que são propriedades interessantes e desejáveis em um aditivo.

Figura 01. Estrutura química de alguns dos aditivos comerciais mais utilizados atualmente.



Fonte: Elaborada pelo autor.

3.5 Moléculas orgânicas com potencial para aditivos de biocombustíveis

Na literatura encontramos algumas moléculas com atividades biológicas interessantes, vamos destacar aqui 3 classes, as Chalconas, as Quinolinonas e os Benzimidazóis. As Chalconas (1,3-diaril-2-propan-1-ona) são compostos orgânicos pertencentes a família dos flavonóides, obtidas em vários tipos de plantas ou por meio de síntese, (DA SILVA, CARAPINA, PACHECO, *et al.*, 2018, PATIL, MAHAJAN, *et al.*, 2009, ZHUANG, ZHANG, *et al.*, 2017) suas estruturas são formadas por dois anéis aromáticos ligados por uma cadeia aberta formada por uma porção olefina e um sistema carbonila α,β -insaturado, com diferentes substituintes nos anéis aromáticos (PATIL, MAHAJAN, *et al.*, 2009, ZHUANG, ZHANG, *et al.*, 2017) (Figura 02(a)). Diversos trabalhos envolvendo chalconas e seus análogos mostram a sua ação antioxidante (BANDGAR, GAWANDE, *et al.*, 2010, FRANCESCHELLI, PESCE, *et al.*, 2011, MATHEW, ADENIYI, *et al.*, 2017, OHKATSU, SATOH, 2008, SULPIZIO, ROLLER, *et al.*, 2016) e antimicrobiana (antibactérias e antifungos) (AJANI, OBAFEMI, *et al.*, 2010, DENG, HE, *et al.*, 2010, ELSOHLY, JOSHI, *et al.*, 2001, ÖZDEMİR, GÜVENÇ, *et al.*, 2009, RAJAT GHOSH, 2014, SILVA, WENDER A., ANDRADE, *et al.*, 2013, SIVAKUMAR, PRABHAWATHI, *et al.*, 2010). Xue *et al.* (2012) (XUE, ZHENG, *et al.*, 2012) realizou um estudo teórico da estrutura-atividade de chalconas-hidroxiladas com atividade

antioxidante, enquanto Mittelbach *et al.* (2003)(MITTELBAACH, SCHOBER, 2003) mostrou a influência de antioxidantes na estabilidade de oxidação do biodiesel.

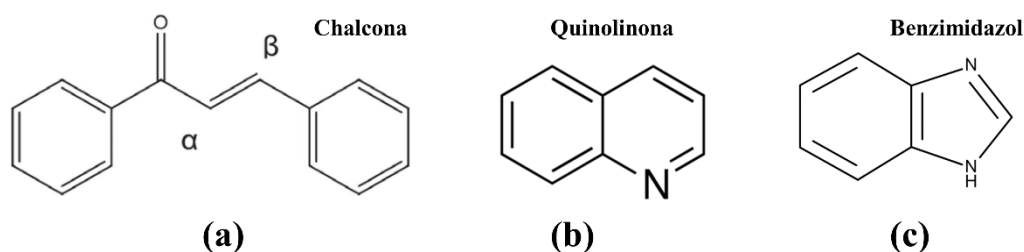
Encontramos alguns trabalhos que mostram diretamente chalconas com propriedades para preservar a estabilidade oxidativa de uma mistura diesel-biodiesel (DA SILVA, C, PACHECO, *et al.*, 2018, MOREIRA, FARIA, *et al.*, 2022a, PIVA, DE OLIVEIRA, *et al.*, 2013). Da Silva *et al.* (2018)(DA SILVA, CARAPINA, PACHECO, *et al.*, 2018) avaliou hidroxi-chalconas como alternativas sintéticas para melhorar a estabilidade oxidativa do biodiesel, Lenardão *et al.* (2017)(LENARDÃO *et al.*, 2017) cita o glicerol como principal coproduto na produção do biodiesel e mostra a utilização de chalconas no processo do glicerol como solvente na síntese orgânica e Piva *et al.* (2013)(PIVA, DE OLIVEIRA, *et al.*, 2013) solicitou uma patente no INPI sobre um grupo de chalconas com aplicação como reagente antioxidante em biodiesel.

As Quinolinonas (1-aza-naftaleno ou benzo[b]piridina) são compostos orgânicos de origem natural ou sintética(CHEN, FANG, *et al.*, 2001, KOUZNETSOV, MELÉNDEZ GÓMEZ, *et al.*, 2019, OLIVA, MEEPAGALA, *et al.*, 2003), sendo uma base terciária fraca com caráter aromático heterocíclico, sua estrutura possui dois anéis, em que um carbono é substituído pelo heteroátomo nitrogênio (Figura 02(b)) (MARELLA, TANWAR, *et al.*, 2013, NAINWAL, TASNEEM, *et al.*, 2019). Muitos trabalhos mostram atividades biológicas dessa classe de compostos, o núcleo quinolinona é comum em diversos fármacos comerciais (nedocromil, ciprofloxacino, norfloxacin, elvitegravir e ivacaftor)(RAGA, ESCOLANO, *et al.*, 2019, SHI, WANG, *et al.*, 2017) e encontramos diversos estudos relatando suas atividades antioxidante (ORHAN PUSKULLU, TEKINER, *et al.*, 2013, PRAVEEN, DHEENKUMAR, *et al.*, 2010, SANKARAN, KUMARASAMY, *et al.*, 2010, SAVEGNAGO, VIEIRA, *et al.*, 2013, YOON, JEONG, *et al.*, 2006), antibacteriana (CHU, FERNANDES, 1991, FUHR, ANDERS, *et al.*, 1992, KAMINSKY, MELTZER, 1968, WENTLAND, CORNETT, 1985) e antifúngica (MOUSSAOUI, BYADI, *et al.*, 2021, MUSIOL, SERDA, *et al.*, 2010, OLIVA, MEEPAGALA, *et al.*, 2003, POLAK, 1990, ZHANG, 2019). O núcleo quinolinona pode ser hibridizado com outras moléculas (com chalconas, por exemplo), a fim de potencializar alguma atividade desejada, podemos encontrar em diversos trabalhos que citam quinolinonas-chalconas (moléculas chalconas que contém o núcleo quinolinona em sua estrutura química) com diversas atividades biológicas, como antioxidante (FERREIRA, CARDOSO, *et al.*, 2020, HAMLAOUI, BENCHERAJET, *et al.*, 2018, KOSTOPOULOU, DIASSAKOU, *et al.*, 2021), antimicrobiana (ABDULLAH, MAHMOOD, *et al.*, 2014, PRAVEEN KUMAR, KATAGI, *et al.*, 2022, RAO, SHAIK, *et al.*, 2017, SARVESWARI, VIJAYAKUMAR, *et al.*, 2015, ZHENG, JIANG, *et al.*,

2011), dentre outras (ATUKURI, S, *et al.*, 2020, COA, GARCÍA, *et al.*, 2017, GUAN, LIU, *et al.*, 2021, MIRZAEI, HADIZADEH, *et al.*, 2020, MOHAMED, ABUO-RAHMA, 2020, ROUSSAKI, HALL, *et al.*, 2013, SASHIDHARA, AVULA, *et al.*, 2015).

Os benzimidazóis também são uma classe de moléculas orgânicas (naturais ou sintéticas) aromáticas heterocíclicas formadas a partir do anel benzeno e imidazol (BENINCORI, SANNICOLÒ, 1988, GRIMMETT, 2005) (Figura 02(c)). Benzimidazóis são amplamente utilizados como fármacos (ROSENBLUM, MERIWETHER, 1970) devido suas propriedades antimicrobianas (FEI, ZHOU, 2013, SINGH, Namrata, PANDURANGAN, *et al.*, 2012) e antioxidantes (KOSOLAPOV, SPASOV, *et al.*, 2019, MAVROVA, YANCHEVA, *et al.*, 2015, RAJASEKARAN, GOPALKRISHNA, *et al.*, 2012). Além disso, vários fungicidas comerciais são feitos à base de benzimidazóis, como o carboxin, (BITTENCOURT, MENTEN, *et al.*, 2007) Benomyl, (HAUPTMANN, WIDHOLM, *et al.*, 1985) carbendazim (“Carbendazim”, 2019) e thiophanate-methyl (APVMA., 2010, NAUHA, SAXELL, *et al.*, 2009, USEPA. UNITED STATES ENVIRONMENTAL PROTECTION AGENCY., 2014).

Figura 02. Estruturas químicas das Chalconas (a) Quinolinonas (b) e Benzimidazóis (c).



Fonte: Elaborada pelo autor.

3.6 Conhecimento estrutural a partir da metodologia cristalográfica

O estudo de um composto para alguma aplicação específica é um trabalho interdisciplinar que envolve várias etapas. Os estudos dessa tese propõem um estudo de moléculas orgânicas com características antioxidantes e antimicrobianas que possam ser utilizadas como um aditivo para biocombustíveis.

Para realizarmos a descrição e estudo estrutural precisamos cristalizar os compostos que foram sintetizados, uma vez que eles não estejam na forma cristalina. No estudo estrutural, descrevemos a estrutura química, o arranjo supramolecular, as interações e as conformações moleculares do composto. A partir do conhecimento estrutural realizamos o estudo e previsões

teóricas, para níveis energéticos, reatividade da molécula, polaridade, estabilidade cinética e as simulações das possíveis atividades biológicas desejáveis. Se a molécula apresentar uma boa predição teórica podemos realizar o pedido da patente para assegurar a propriedade intelectual da molécula em estudo. A partir da síntese dos compostos orgânicos, realizamos a execução dos experimentos de cristalização. Esses experimentos envolvem uma análise quantitativa e qualitativa dos reagentes a serem utilizados em cada processo de solubilização química, para cada um dos compostos propostos, reagentes específicos devem ser empregados, junto ao cálculo da quantidade das substâncias envolvidas na reação química. Tudo isso baseado nas leis reacionais, e auxiliadas com equações químicas correspondentes. Realçamos que para aplicação dos compostos como possíveis aditivos não é necessário o estado cristalino, contudo para os nossos estudos de análise estrutural, a obtenção do cristal é fundamental para tomarmos posse da metodologia cristalográfica de raios X de monocristal, que é a melhor metodologia para caracterizar estruturalmente um composto, pois está fundamentada na densidade eletrônica (CULLITY, STOCK, 2001).

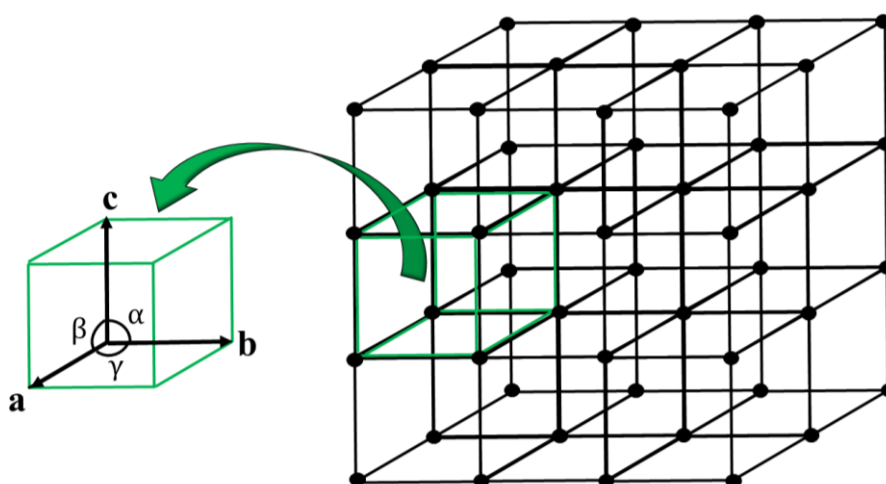
A amostra cristalina do composto é obtida por meio da técnica de cristalização a partir da formação gradual de uma solução saturada do sólido. As etapas de supersaturação, nucleação e crescimento cristalino são acompanhadas para avaliar possíveis erros na formação do cristal, uma vez detectados, tais erros são corrigidos com intuito de maximizar a qualidade da amostra (MÜLLER, 2004). A supersaturação é uma etapa crítica no processo de formação de cristais, pois é responsável por impulsionar as próximas etapas de nucleação e crescimento. É a força motriz para a nucleação, que é o surgimento de novos núcleos de cristal, e para o crescimento, que é a fase de aumento no tamanho dos cristais à medida que o soluto é depositado na solução (MÜLLER, 2004). Existem muitas variáveis que podem influenciar no processo de cristalização, como: composição da amostra, solvente utilizado, temperatura, pressão, volume, tempo, possíveis impurezas, luminosidade, método de cristalização utilizado, controle da difusão, convecção, dentre outros (MÜLLER, 2004). Existem diversos métodos para a cristalização de compostos em solução, incluindo: evaporação lenta (direta ou indireta), difusão de solvente, convecção, adição de aditivos, resfriamento lento difusão a vapor. Adicionalmente, também existem métodos de cristalização por crescimento de cristais sem solvente, como: derretimento e sublimação, ou ainda cristalização em gel ou modificação química (CUNHA, 2008).

Para cada rendimento cristalino ou composto cristalizado são analisadas algumas propriedades físicas do cristal. São avaliadas propriedades como faces planas e definidas, hábito cristalino e polarização da luz, tais propriedades podem ser analisadas com auxílio de

microscópio eletrônico. Para os compostos que não atenderem essas características ou não forem adequados para coleta de dados, é realizado a repetição dos experimentos avaliando melhores condições de formação cristalina. Os cristais podem ser definidos como sólidos com ordem de repetibilidade de longo alcance em termos de simetria atômica. No cristal existe periodicidade atômica, ou seja, o arranjo dos átomos é recíproco em qualquer ponto equivalente do cristal (GLUSKER, TRUEBLOOD, 2010). Essa periodicidade ou repetitividade atômica permite estudos que possibilitam determinar a estrutura molecular, interações moleculares e o empacotamento cristalino para um sólido (GIACOVAZZO, 2011).

A cela unitária é a menor unidade de volume que contém todas as informações necessárias para descrever a estrutura de um cristal. Essa cela é definida por seis parâmetros: os vetores unitários não coplanares **a**, **b** e **c**, e os ângulos entre esses vetores⁹: α , β e γ (Figura 03) (GLUSKER, J, TRUEBLOOD, 2010, STOUT, G, JENSEN, 1989, WOOLFSON, 1997). A comutação destes parâmetros, por simetria, gera sete métricas, ou sete celas unitárias distintas (os chamados sistemas cristalinos¹⁰ (Figura 04)) (CULLITY, STOCK, 2001). Os sete sistemas cristalinos combinados com as centragens de rede levam a 14 redes de Bravais que combinadas com os elementos de simetria geram os 230 grupos espaciais para o estado cristalino (CULLITY, STOCK, 2001, GIACOVAZZO, 2011).

Figura 03. Representação de cela unitária e rede.



Fonte: Elaborada pelo autor.

A cela unitária é a menor parte da estrutura cristalina que se repete periodicamente para formar o cristal. A *unidade assimétrica* é a porção estrutural única dentro da cela unitária. A unidade assimétrica pode consistir em uma fração de uma molécula, uma molécula inteira ou

⁹ O ângulo α (entre o vetor **b** e **c**), β (entre **a** e **c**) e γ (entre **a** e **b**).

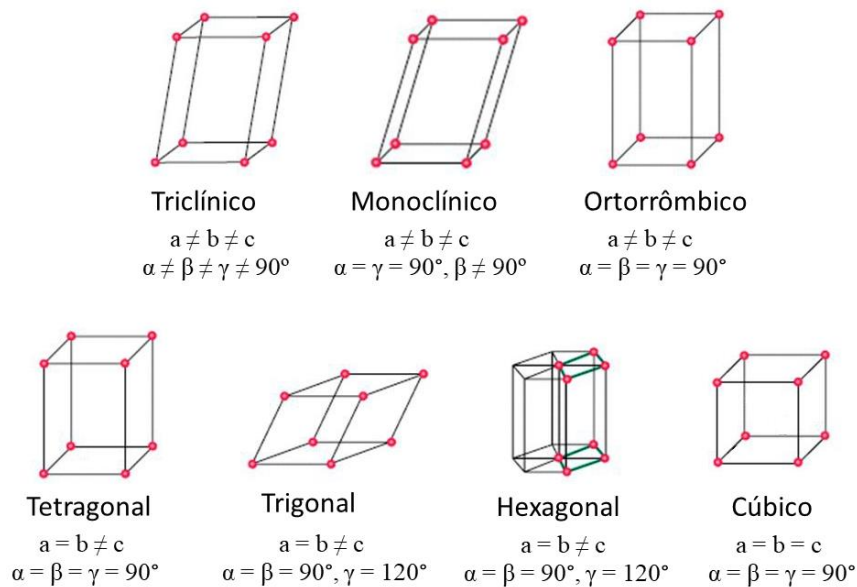
¹⁰ Sete sistemas cristalinos: triclinico, monoclinico, ortorrômbico, tetragonal, trigonal, hexagonal e cúbico.

grupos de moléculas. A repetição tridimensional e periódica da cela unitária resulta na rede cristalina, também conhecida como retículo cristalino. Essa rede pode ser descrita por meio das magnitudes u , v , e w que representam as distâncias nas direções dos vetores $\mathbf{a}$, $\mathbf{b}$ e $\mathbf{c}$ (Equação 01). δ é a função delta de Dirac e $L(\mathbf{r})$ é a rede de difração (CLEGG, BLAKE, *et al.*, 2009, GIACOVAZZO, 2011).

$$L(\mathbf{r}) = \sum \delta[\mathbf{r} - (u\mathbf{a} + v\mathbf{b} + w\mathbf{c})] \quad (01)$$

Em termos de cristalinidade de um sólido, podemos conceber sobre a simetria, que é um padrão de repetição atômico dentro do cristal, a simetria é uma das propriedades essenciais do estado cristalino, permitindo a rede de difração dos raios X (CLEGG, BLAKE, *et al.*, 2009). A simetria pode ser classificada em pontual ou translacional. A simetria pontual descreve a repetição periódica de uma unidade assimétrica em torno de um ponto na cela unitária enquanto a simetria translacional descreve a repetição tridimensional e periódica da cela unitária por meio de eixos de translação (GIACOVAZZO, 2011).

Figura 04. Representação dos sete sistemas cristalográficos.



Fonte: Elaborada pelo autor.

3.7 Obtenção dos dados através da difração de raios X

Os cristais que atendem características como polarização da luz, dimensões adequadas e hábito cristalino são selecionados para a coleta de dados. Nesta etapa, o cristal é colocado a um capilar de vidro ou semelhante, e alocado em um difratômetro de raios X, onde recebe

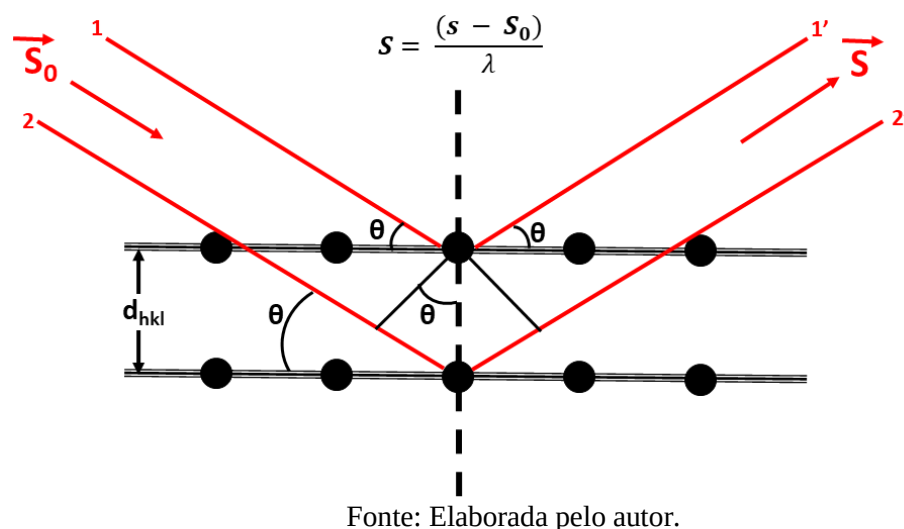
radiação monocromática¹¹ gerada geralmente por molibdênio ou cobre. Os raios X são radiações eletromagnéticas altamente energéticas com poder de penetração. O comprimento de onda dos raios X é da ordem das distâncias interatômicas ($\lambda = 0,1$ a $100 \text{ \AA}$), valor que está dentro do necessário para a metodologia cristalográfica ($0,6$ a $3,0 \text{ \AA}$) (GLUSKER, Jenny Pickworth., TRUEBLOOD, 2010). O fenômeno da difração ocorre devido ao contato entre a radiação incidente e o campo elétrico dos elétrons contidos no cristal, em que ocorre um desvio da onda (radiação incidente) quando encontra os elétrons, que atuam como espalhadores pontuais (NAPOLITANO, CAMARGO, *et al.*, 2007, STOUT, GEORGE, JENSEN, 1989).

A difração ocorre em cristais devido à sua simetria interna, na qual a distribuição angular da radiação espalhada pode ser entendida por meio da Lei de Bragg (Equação 02). Essa lei indica as condições necessárias para que ocorra difração em um cristal (BRAGG, BRAGG, 1913b, NAPOLITANO, CAMARGO, *et al.*, 2007, STOUT, GEORGE, JENSEN, 1989).

$$2d_{hkl}\sin\theta = n\lambda \quad (02)$$

Nesta equação, d_{hkl} é a distância entre dois planos de reflexão, θ é o ângulo de incidência da radiação, enquanto λ é o comprimento de onda do feixe incidido (BRAGG, BRAGG, 1913a, b). Podemos representar a Lei de Bragg através de um esquema que mostra que a diferença de caminho entre duas ondas incidentes, necessita ser um múltiplo inteiro do comprimento de onda para que haja a interferência construtiva (Figura 05).

Figura 05. Representação esquemática da Lei de Bragg.



¹¹ O feixe de raios X é colimado para incidir na amostra cristalina.

Como mencionamos, a difração é um fenômeno que ocorre quando a radiação incidente interage com o campo elétrico dos elétrons do cristal. Quando a onda encontra os elétrons, eles atuam como espalhadores pontuais e causam um desvio na trajetória da onda. Esse desvio ocorre devido à interferência construtiva e destrutiva da onda incidente com as ondas dispersas pelos elétrons. Como resultado, a onda incidente é difratada em várias direções. O fenômeno de difração é amplamente utilizado em diversas áreas da ciência e da tecnologia, como na análise de estruturas cristalinas, na produção de padrões de difração para diagnóstico de doenças, na detecção de partículas subatômicas e na síntese de materiais. Em resumo, o fenômeno de difração é uma consequência da interação entre a radiação eletromagnética e a estrutura dos materiais (NAPOLITANO, CAMARGO, *et al.*, 2007, STOUT, GEORGE, JENSEN, 1989).

Como um cristal é composto por átomos arranjados de maneira ordenada e periódica, os átomos atuam como espalhadores pontuais, podemos definir espalhamento atômico pela Equação 03:

$$f_j = f_j \cdot e^{2\pi i \mathbf{r}_j \cdot \mathbf{s}} \quad (03)$$

cada átomo é um espalhador pontual e a contribuição somática desses centros espalhadores é definida como fator de estrutura $F(\mathbf{h})$ (Equação 04) (MASSA, 2004, WOOLFSON, 1997).

$$F(\mathbf{h}) = \sum_{j=1}^N f_j e^{2\pi i \mathbf{h} \cdot \mathbf{r}_j} \quad (04)$$

No experimento de difração de raios X (coleta de dados) obtemos as intensidades que correspondem ao fator de estrutura, então assumimos por hipótese que a operação matemática da transformada de Fourier (inversa) do fator de estrutura representa a densidade eletrônica $\rho(\mathbf{r})$ da estrutura (Equação 05) (CULLITY, STOCK, 2001, GIACOVAZZO, 2011, WOOLFSON, 1997).

$$\rho(\mathbf{r}) = \frac{1}{V} \sum_{\mathbf{h}} |F(\mathbf{h})| e^{-2\pi i \mathbf{h} \cdot \mathbf{r} + i\phi(\mathbf{h})} = \frac{1}{V} \sum_{\mathbf{hkl}} |F(\mathbf{hkl})| e^{-2\pi i [\mathbf{h}\mathbf{x} + \mathbf{k}\mathbf{y} + \mathbf{l}\mathbf{z} + \phi(\mathbf{hkl})]} \quad (05)$$

O tempo de exposição à radiação para cada tipo de amostra varia de acordo com a complexidade da estrutura. Durante essa exposição, um número de reflexões é coletado, permitindo o cálculo dos parâmetros da melhor cela unitária e da matriz de orientação com base

nas reflexões centradas e indexadas. As informações gerais da coleta são registradas em arquivos de texto no formato ASCII¹² que contêm dados cruciais para a análise posterior da estrutura cristalina (GIACOVAZZO, 2011, GLUSKER, TRUEBLOOD, 2010, STOUT, GEORGE, JENSEN, 1989).

Na coleta são obtidos os módulos dos fatores de estrutura $|F(\mathbf{h})|$, a partir das intensidades coletadas através das reflexões. Nesse processo, temos a correção de eventuais erros e a redução das intensidades totais para as intensidades mais significativas que representem adequadamente o conteúdo da amostra, esse processamento de dados utiliza softwares que aplicam várias correções como: absorção, Lorentz, polarização, extinção primária e secundária para determinar os valores de “incerteza padrão” (σ) para cada reflexão (GIACOVAZZO, 2011).

Na resolução dos dados serão realizados procedimentos baseados na construção dos mapas de densidade eletrônica $\rho(\mathbf{r})$, a partir do melhor conjunto de fases, o qual será indicado pelas figuras de mérito. Os mapas são resultado da síntese de Fourier utilizando como coeficientes de série os fatores de estrutura normalizados. Para a resolução dos dados, serão utilizados procedimentos baseados na construção dos mapas de densidade eletrônica $\rho(\mathbf{r})$. Esses mapas serão gerados a partir do melhor conjunto de fases, que será selecionado com base nas figuras de mérito. Os mapas de densidade eletrônica são gerados através da síntese de Fourier, que a partir dos fatores de estrutura normalizados utiliza coeficientes de série (GIACOVAZZO, 2011, GLUSKER, TRUEBLOOD, 2010, STOUT, GEORGE, JENSEN, 1989). Dentre os softwares utilizados na resolução dos dados, destacamos o SHELXS (SHELDRICK, George M, 2008, SHELDRICK, G. M., 1990) presente na plataforma WinGX (FARRUGIA, 1999, 2012) e Olex2 (DOLOMANOV, BOURHIS, *et al.*, 2009).

O refinamento é a etapa em que o modelo cristalográfico é construído, utilizando um processo de minimização da discordância entre os módulos dos fatores de estrutura observados e calculados. Esse processo é baseado no princípio dos mínimos quadrados, através da função M: (MULLER, HERBST-IRMER, *et al.*, 2006, SHELDRICK, G, 2008, SHELDRICK, GEORGE, 2015a, b).

$$M = \sum_h W_h [|F(h)_{obs}| - |F(h)_{cal}|]^2. \quad \text{Eq. (01)}$$

O refinamento é um processo iterativo orientado por indicadores que buscam a

¹² ASCII: *American Standard Code for Information Interchange*. Em português: “Código Padrão Americano para o Intercâmbio de Informação”. É um código binário (cadeias de bits: 0s e 1s), usada para representar textos em computadores.

convergência e coerência química. Nesta etapa é que elucidamos a estrutura química do composto, e conseguimos definir os parâmetros geométricos e a conformação molecular. Utilizamos o software SHELXL (SHELDRICK, GEORGE, 2014) que opera inicialmente dois arquivos de entrada, o input das reflexões hkl e um arquivo de instrução (.ins). O input contém as intensidades e desvios (incertezas) das reflexões coletadas no experimento, enquanto o arquivo de instrução possui informações de operacionalização, bem como, os parâmetros da cela unitária, que são os comprimentos dos eixos **a**, **b**, **c** e os ângulos entre eles α , β e λ (MULLER, HERBST-IRMER, *et al.*, 2006).

3.8 Análise estrutural dos aditivos de biocombustíveis

A determinação da estrutura cristalográfica permite não apenas a identificação das espécies atômicas presentes, mas também a caracterização da conformação molecular e das interações responsáveis pelo empacotamento cristalino e arranjo supramolecular. Por meio da análise da estrutura cristalográfica, é possível estudar as distâncias e ângulos entre os átomos, a geometria das ligações químicas e a orientação dos grupos funcionais na molécula. Essas informações são cruciais para compreender as propriedades químicas e físicas dos materiais, bem como para otimizar processos de síntese e desenvolver novos materiais com propriedades desejáveis. Além disso, a análise da estrutura cristalográfica permite identificar as interações intermoleculares presentes na estrutura, como interações eletrostáticas, ligações de hidrogênio e forças de van der Waals. Essas interações são responsáveis pelo empacotamento dos cristais e pelo arranjo supramolecular, que influenciam diretamente as propriedades macroscópicas do material (GIACOVAZZO, 2011, WOOLFSON, 1997).

Utilizamos alguns softwares que ajudam a identificar e quantificar as interações e o arranjo supramolecular, como o software Mercury (MACRAE, BRUNO, *et al.*, 2008) que realiza análises através de parâmetros geométricos que foram obtidos experimentalmente na difração de raios X, bem como o software CrystalExplorer (WOLFF, GRIMWOOD, *et al.*, 2012) que nos permite uma análise das interações através da densidade eletrônica.

Os Cálculos de propriedades eletrônicas¹³ são realizados através da análise teórica do modelo estrutural permitindo determinar algumas propriedades físico-químicas. Os cálculos de propriedades eletrônicas são realizados com base na otimização teórica dos dados experimentais. O cálculo dessas propriedades permite-nos avaliar alguns parâmetros como

¹³ Os cálculos teóricos foram realizados no Centro de Computação de Alta Performance da Universidade Estadual de Goiás (UEG). Cluster - 72 núcleos físicos e 400GB memória.

estabilidade cinética e química, reatividade molecular, regiões e grupos moleculares mais suscetíveis a interações, reações eletrofílicas/nucleofílicas, energias de excitação e ativação, comportamento molecular em diferentes tipos de meios (solventes) entre outros. Esses cálculos teóricos estão fundamentados em princípios da mecânica quântica através da resolução da função de onda, onde previsões probabilísticas são computadas para a molécula em estudo. O tempo computacional necessário para conseguir a otimização energética adequada deve ser avaliado com base na estrutura química e nas propriedades a serem calculadas (KRISHNAN, BINKLEY, *et al.*, 1980, MCLEAN, CHANDLER, 1980). Em geral, esses cálculos são realizados usando a teoria do funcional de densidade (density functional theory - DFT) implementado no pacote do Gaussian09 (FRISCH, TRUCKS, *et al.*, 2009), utilizando de funcionais e conjuntos de base específicos para cada molécula.

Após as análises estruturais e teóricas, validamos possíveis erros na solução estrutural e avaliamos a precisão dos resultados, garantindo a confiabilidade das estruturas. Utilizamos softwares como o Platon (SPEK, 2003) e Mogul (COTTRELL, OLSSON, *et al.*, 2012) para tais análises e validação.¹⁴ Esses softwares avaliam o modelo obtido, a coerência química, e utilizam de parâmetros moleculares definidos para determinar a veracidade do modelo encontrado experimentalmente, além de realizar uma comparação dos parâmetros geométricos encontrados com outras estruturas depositadas nos bancos de dados (SPEK, 2003).

3.9 Análise experimental das atividades antioxidantes e energéticas

A partir de um direcionamento estrutural e teórico das moléculas, é possível projetar aditivos para biocombustíveis com atividades biológicas específicas. Para avaliar a eficácia desses aditivos, são realizados testes experimentais mais assertivos, que buscam contemplar e confirmar as atividades biológicas previstas. Avaliamos a estabilidade e a eficiência energética dessas moléculas como um processo de um aditivo que busque a otimização de características de um combustível veicular. Neste contexto, o combustível é armazenado em tanques, simulando condições de armazenamento normalmente aplicadas no mercado. Sob frequências pré-estabelecidas, alíquotas de combustível são retiradas dos tanques para avaliação das principais propriedades físico-químicas. Alternativamente os ensaios físico-químicos podem ser conciliados com avaliação da eficiência energética. Essas análises podem ser executadas

¹⁴ Depois de todas essas etapas descritas, se uma propriedade interessante for prevista ou confirmada, uma solicitação de patente pode ser realizada sobre a estrutura da molécula. A solicitação da patente envolve pedido junto ao INPI, e a patente sobre as estruturas elucidadas detém os direitos sobre sua propriedade intelectual e aplicações. (MINISTERIO DA ECONOMIA, 2023).

através dos ensaios de emissão e consumo aplicando o aditivo em veículos a serem avaliados em dinamômetro. Algumas das análises realizadas para avaliar a estabilidade e qualidade de combustíveis são apresentadas na Tabela 02.

Tabela 02. Análises para avaliar a estabilidade e qualidade de combustíveis.

Propriedade/ característica	Metodologia	Propriedade/ característica	Metodologia
Massa específica	ASTM D4052	Poder calorífico	ASTM D4809
Condutividade elétrica	ASTM D4308	Estabilidade oxidativa	EN 15751
Cor e aspecto	Visual	Teor e água	ASTM D6304
Destilação	ASTM D86	Lubricidade	ASTM D6079
Teor de cinzas	ASTM D482	Emissões de poluentes	ABNT NBR 6601
Viscosidade cinemática	ASTM D445	Consumo de combustível	ABNT NBR 7024

O poder calorífico de um combustível indica a energia liberada pela combustão por unidade de massa. O teste de determinação do poder calorífico é realizado em bomba calorimétrica com combustor rodeado de água. Esta análise segue a metodologia ASTM D4809 standard (ASTM, 2018) usando um equipamento IKA C200. O combustor é pressurizado (30 bar) e a amostra é aquecida por uma corrente elétrica que promove a queima. A queima libera energia para o meio e troca calor com água, gerando uma mudança em sua temperatura. A variação da temperatura em função do tempo é medida por um sensor resistivo de alta precisão e, após correlação com a massa da amostra obtida antes da queima, é relatado o resultado do valor calorífico da amostra (FARIA, E, DUARTE, *et al.*, 2020, SELVAGANAPATHY, MUTHUVELAYUDHAM, *et al.*, 2020).

O teste de estabilidade à oxidação pelo método de oxidação acelerada, também conhecido como teste Rancimat¹⁵, é realizado de acordo com os requisitos descritos na norma EN 15751 (STANDARDIZATION, 2014a). Esta metodologia se aplica a ésteres metílicos de ácidos graxos (em inglês: Fatty Acid Methyl Ester – FAME) usados como biocombustíveis em sua forma pura ou como aditivos para diesel mineral em concentrações de FAME de pelo menos 2% (v/v). No teste de Rancimat (acelerado)¹⁶, a amostra de combustível é aquecida a uma temperatura de 110 – 130°C e submetida a um fluxo de ar purificado que fornece oxigênio ao meio, promovendo uma lenta reação de oxidação, formando peróxidos. Devido à alta

¹⁵ Rancimat é uma marca comercial registrada pela empresa suíça Metrohm AG para um equipamento de laboratório utilizado para medir a estabilidade oxidativa de óleos e gorduras, o termo Rancimat é frequentemente usado como sinônimo desse tipo de instrumento ou análise.

¹⁶ No Rancimat acelerado, a amostra é submetida a um maior fluxo de ar e uma temperatura mais alta do que a usada no método convencional ou modificado, podendo chegar a 150°C.

temperatura, os peróxidos são dissociados formando aldeídos, cetonas e ácidos carboxílicos, ambos voláteis. O ar e os compostos formados são direcionados para um recipiente hermético cheio de água desionizada (desmineralizada)¹⁷ e equipado com um eletrodo de condutividade. O eletrodo é conectado a um dispositivo de medição e registro que detecta o final do período de indução, aumentando rapidamente a condutividade da água que é diretamente proporcional à concentração de compostos dissociados presentes no meio (LI, LI, *et al.*, 2019, ZHOU, XIONG, *et al.*, 2017). O resultado da oxidação de estabilidade pelo método Rancimat é dado pelo período desde o início do teste até o instante em que o rápido aumento da condutividade é detectado. Geralmente é relatado como o período de indução (PI) ou o índice de estabilidade de oxidação (IEO), normalmente sendo dado em horas. Para nossos estudos foi utilizado o equipamento modelo Metrohm 873, seguindo os requisitos da norma EN 15751: 2014 standard (STANDARDIZATION, 2014b).

Os compostos estudados e apresentados nessa tese (chalconas e benzimidazóis) passaram pela análise estrutural e teórica brevemente descrita nos parágrafos anteriores, bem como pelos testes experimentais envolvendo análise da disponibilidade energética e estabilidade oxidativa. Os resultados são apresentados no próximo tópico na forma de artigos científicos publicados, a metodologia para cada estudo é detalhada em seu respectivo artigo, assim como os resultados e conclusões.

¹⁷ Deionização é um processo utilizado para produzir solventes puros, isentos de íons, com grande destaque para a água.

4. RESULTADOS

Essa tese tem a composição de cinco artigos¹⁸, resultantes dos objetivos dispostos no tópico 2 (pág. 10).¹⁹ Os frutos dessa tese foram obtidos mediante a colaboração entre a Universidade Estadual de Goiás (UEG) com o Centro de Pesquisas e Eficiência Energética (CPEE) da CAO A montadora de veículos LTDA – (Acordo de cooperação nº 001/2021/2021 – UEG (Anexo 02)) através do estágio por mim realizado com o projeto “Chalconas e seus análogos como potenciais antioxidantes para biocombustíveis”. Deste modo, vivenciei os benefícios e os efeitos da sinergia de uma colaboração entre Universidade e Indústria, onde dialoguei com os conhecimentos acadêmicos e científicos para resoluções de problemas socioeconômicos e ambientais.

O primeiro artigo que compõe essa tese, intitulado: *Benzodioxol Group Driving Supramolecular Arrangement of Two Tri-Methoxy Chalcones onto B-Secretase 1 Enzyme Active Site* - [DOI: 10.21577/0103-5053.20190101], foi publicado no periódico *Journal of the Brazilian Chemical Society*. O artigo apresenta um estudo sobre a influência de um grupo substituinte (benzodioxol) nas conformações moleculares de duas moléculas da classe chalcona. Os resultados mostraram que ambos os compostos são estabilizados apenas por interações intermoleculares fracas, a presença de um grupo substituinte em uma das moléculas corrobora para uma menor planaridade na estrutura, e os orbitais moleculares de fronteira indicaram menor estabilidade cinética. Os resultados de modelagem através de docagem molecular propõem as chalconas analisadas como potenciais candidatas aos inibidores da beta-secretase humana 1 (BACE-1).²⁰ Esse primeiro trabalho, mesmo sendo direcionado para inibição de uma enzima, mostra o aprendizado e amplia o entendimento sobre os efeitos dos substituintes nas conformações moleculares de moléculas orgânicas, além de sedimentar a compreensão de algumas propriedades físico-químicas e o potencial de aplicação das chalconas, esse estudo subsidia outras aplicações das chalconas, guiados a luz do entendimento estrutural e pela modificação de grupos substituintes numa perspectiva da relação estrutura-atividade.

¹⁸ Os materiais suplementares para os artigos não foram incorporados à tese, no intuito de expor um texto mais enxuto. Todavia, todos os materiais suplementares podem ser encontrados na web page dos respectivos artigos.

¹⁹ Todos os artigos apresentados nessa tese possuem permissão de reuso para dissertação/tese segundo as normas de direitos autorais de cada revista (Anexo 03).

²⁰ BACE-1 é uma protease (enzimas que catalisam a hidrólise). Essa enzima representa uma chave proteína-alvo no desenvolvimento de novos medicamentos potenciais para o tratamento assintomático da doença de Alzheimer. Estudos mostram que os níveis dessa enzima se mostram elevados no Alzheimer esporádico de início tardio.(JONSSON, ATWAL, *et al.*, 2012, KIM, CAREY, *et al.*, 2007)

Minha contribuição neste artigo foi a proposta e a estruturação, juntamente com o estudo estrutural.

O segundo artigo, intitulado: *A new quinolinone-chalcone hybrid with potential antibacterial and herbicidal properties using in silico approaches* – [DOI: 10.1007/s00894-022-05140-9], foi publicado no periódico *Journal of Molecular Modeling*. O artigo descreve parâmetros estruturais e teóricos relacionados às propriedades físico-químicas e à atividade biológica de uma nova quinolinona-chalcona. As interações fracas C–H $\cdots$ O, C–H $\cdots$ π e C–H $\cdots$ Br foram responsáveis pelo crescimento do cristal e estabilizaram o arranjo supramolecular. Os cálculos teóricos através da análise DFT mostraram que a região do grupo sulfonamida é mais suscetível a interações, enquanto os orbitais moleculares de fronteira indicam alta estabilidade cinética. A análise de farmacóforos²¹ revelou potencial antibacteriano e atividade herbicida. A molécula mostrou encaixe dentro do sítio ativo de TtgR, a análise ainda revelou que a ativação de TtgR depende da ligação de compostos aromáticos, que desempenha um papel crucial na evasão bacteriana.²²

Este segundo trabalho amplia mais um pouco sobre o entendimento estrutural de chalconas e seus substituintes, além de inclinar algumas interessantes propriedades das chalconas, como o potencial antibacteriano que é substancial, para aplicação em um aditivo de biocombustíveis. O entendimento dos aspectos estruturais das chalconas ligados à atividade antibacteriana é imperativo para os ensaios futuros que confirmem sua efetividade como aditivos para biocombustíveis. Nesse artigo podemos notar o amadurecimento científico alinhado com a proposta dessa tese. Iniciando-se com a compreensão estrutural das chalconas, e neste trabalho seu potencial biológico sendo testado através da análise de farmacóforos. Neste artigo ainda podemos ver a importância da cooperação e o crescimento proporcionado pelas parcerias acadêmicas, uma vez que esse artigo concebe uma colaboração interna no Programa de Pós-Graduação em Recursos Naturais do Cerrado com o professor Leonardo L. Borges, além da colaboração do professor Pal Perjesi da Universidade Unievangélica e do professor Allen G.

²¹ Farmacóforo pode ser compreendido na química farmacêutica como a região da molécula de um ligante que está intimamente ligada ao seu receptor. O conhecimento dessa região possibilita o planejamento de drogas sintéticas.

²² TtgR é um regulador de transcrição para a bomba de efluxo TtgABC do altamente resistente *Pseudomonas putida* (P. putida) cepa DOT-TIE. Podemos ainda dizer que TtgR é um tipo de proteína reguladora presente em algumas bactérias, sendo responsável por controlar a expressão de genes relacionados à resistência a compostos tóxicos, como certos antibióticos. Estudos recentes têm explorado o potencial de inibir a função de TtgR como uma estratégia para aumentar a sensibilidade de bactérias patogênicas aos antibióticos e reduzir a sua capacidade de se adaptar a ambientes hostis. Portanto, o estudo da proteína TtgR é relevante o desenvolvimento de novos compostos contra bactérias.

Oliver da Universidade de Notre Dame e o doutorando Jean M. F. Custodio. Neste artigo fui responsável pela proposta e estruturação, juntamente com o estudo estrutural e a análise teórica por DFT.

O terceiro artigo, intitulado: “*A New Synthetic Route and Comprehensive Topological Study of a Benzimidazole Derivative* – [DOI: 10.21577/0103-5053.20210149], foi publicado no periódico *Journal of the Brazilian Chemical Society*. O artigo apresenta uma nova rota sintética e estudo dos aspectos estruturais que podem ser vinculados com relações de estrutura-propriedade de uma molécula da classe benzimidazol. A síntese do benzimidazol na presença de óxido de grafite é simples e ambientalmente viável ocorrendo na ausência de solventes. O arranjo supramolecular é suportado por interações $C-H\cdots N$ e $C-H\cdots \pi$ que foram confirmadas pela densidade eletrônica e análise topológica QTAIM²³.

Este terceiro trabalho expande o aprendizado sobre moléculas da classe benzimidazol juntamente com as conformações moleculares e suas propriedades físico-químicas. Assim como o entendimento estrutural das chalconas que possuíam indícios de aplicações como aditivos para biocombustíveis, o estudo de moléculas da classe benzimidazol também apresenta um potencial sistema fúngico descrito na literatura e comercializado como fármacos, tal propriedade também é desejada no desenvolvimento de um aditivo. Esse trabalho representa uma colaboração com o professor Guilherme R. Oliveira e a doutoranda Raquel F. Naves da Universidade Federal de Goiás (UFG) que foram responsáveis pela síntese do composto. Destacamos ainda que esse é um dos trabalhos publicados em parceria com o CPEE da CAO A montadora de veículos LTDA. Minha contribuição para este trabalho foi a proposta, estudo estrutural e a análise topológica.

O quarto artigo, intitulado: *Insights on sustainable fuels: a new benzimidazole derivative with potential as a diesel-biodiesel blend additive* – [DOI: 10.1080/17597269.2022.2132726], foi publicado no periódico *Biofuels*.²⁴ O artigo apresenta uma avaliação estrutural, teórica e experimental de um novo benzimidazol como potencial aditivo para misturas diesel-biodiesel. A análise estrutural mostrou que o arranjo supramolecular possui apenas interações $C-H\cdots O$ e $C-H\cdots \pi$ que estão relacionadas à atividade antibacteriana e antioxidante. Os grupos alcóxi na

²³ QTAIM – *Quantum Theory of Atoms in Molecules*, que em português significa “Teoria Quântica dos Átomos em Moléculas”; é uma análise topológica da densidade eletrônica em moléculas. Essa teoria permite uma descrição mais detalhada e fundamental da estrutura molecular e propriedades químicas, permitindo uma caracterização precisa das ligações químicas e interações.

²⁴ This is an Accepted Manuscript of an article published by Taylor & Francis in *Journal of Biofuels* on 19 Oct 2022, available online: <http://www.tandfonline.com/DOI>.

posição *para* do anel aromático atuam como substituintes doadores de elétrons – tais conformações desejáveis para a atividade antioxidante. Para compostos da classe benzimidazol, uma revisão na literatura mostrou que vários trabalhos atuais indicam a atividade antioxidante e antimicrobiana com valores de energia dos orbitais moleculares inferiores aos encontrados para o benzimidazol estudado, indicando assim boa estabilidade cinética para o nosso composto. A análise experimental do potencial oxidativo foi realizado em parceria com a empresa CAO A montadora de veículos e com auxílio do Instituto Nacional de Tecnologia (INT). O combustível aditivado com o benzimidazol foi estocado por um período de 140 dias em condições semelhantes ao tanque de combustível de veículos. Os resultados mostraram que na mistura diesel-biodiesel (B20) o período de indução (estabilidade oxidativa) foi em torno de 26 horas, resultado que está acima dos valores mínimos exigidos pela Resolução brasileira ANP 798/2019 que é de 12 horas após 60 dias. Conforme a revisão da literatura realizada, o resultado encontrado para a estabilidade oxidativa do benzimidazol no combustível se mostra melhor do que muitos aditivos comerciais. Os resultados obtidos e apresentados no artigo indicam ótimo potencial do benzimidazol como um aditivo para misturas diesel-biodiesel.

Nesse artigo observa-se o amadurecimento científico dos objetivos e propostas dessa tese. O caminho foi sendo sedimentado e construído com os trabalhos anteriores, iniciando-se com a investigação e entendimento estrutural dos benzimidazóis e as previsões teóricas, e neste trabalho o potencial antioxidante como um aditivo foi testado experimentalmente em misturas diesel-biodiesel. Neste trabalho temos a colaboração da síntese com a Universidade Federal de Goiás (UFG), enquanto a estruturação e os testes experimentais sendo realizados em parceria com a CAO A e o Instituto Nacional de Tecnologia (INT). Minha contribuição neste artigo foi a proposta, estruturação, estudo estrutural e teórico, além da preparação e planejamento dos experimentos e discussão dos resultados.

O quinto artigo, intitulado: *Arylsulfonamide chalcones as alternatives for fuel additives: antioxidant activity and machine learning protocol studies* – [DOI: 10.1039/D3NJ00255A], foi publicado no periódico *New Journal of Chemistry*. O trabalho apresenta um estudo estrutural com algumas chalconas através de análise experimental e teórica com aprendizado de máquina para atividade antioxidante que é desejada em um aditivo. O arranjo supramolecular e a topologia dessas moléculas mostram o arranjo estabilizado apenas por interações fracas, que estão relacionadas à ação antioxidante e antibacteriana, com os grupos substituintes podendo atuar como doadores de elétrons. A análise de DFT na faixa de energia de 593,1 a 570,2 kJ/mol nos orbitais moleculares de fronteira indicou alta estabilidade estrutural, e os grupos sulfonamida corroborando para ataques eletrofílicos. Os índices teóricos de Fukui alinhados

com parâmetros cinéticos obtidos por protocolos de aprendizado de máquina propiciaram informações sobre os aspectos antioxidantes das chalconas, mediados pela captura de radicais livres. A análise experimental do poder calorífico mostrou boa disponibilidade energética (6.530,5 a 7.306,5 kcal/kg), que é próximo aos combustíveis convencionais. Enquanto, a estabilidade oxidativa na mistura diesel-biodiesel (B20) manteve-se em torno de 27 horas, após 140 dias de armazenamento, resultado que é superior a alguns aditivos comerciais.

Este trabalho demonstra o amadurecimento científico e a consolidação da tese, uma vez que o conhecimento prévio da estrutura das chalconas, obtido em trabalhos anteriores, foi fundamental para orientar a seleção das moléculas testadas neste estudo. Neste trabalho destacamos ainda a parceria dos ensaios experimentais realizados no CPEE – CAO A e INT, além do aprendizado de máquina em colaboração com o professor Valter H. Carvalho-Silva do Programa de Pós-Graduação em Ciências Moleculares. Minha contribuição neste trabalho foi a proposta, estruturação, estudo estrutural e teórico, além da preparação e planejamento dos experimentos e discussão dos resultados. Algumas moléculas das publicações descritas acima, resultaram em patentes que estão solicitadas no INPI, a fim de proteger e assegurar as propriedades de aplicações destes compostos.

Benzodioxol Group Driving Supramolecular Arrangement of Two Tri-Methoxy Chalcones onto Beta-Secretase 1 Enzyme Active Site

Vitor S. Duarte,^a Jean M. F. Custodio,^b Murilo M. dos Anjos,^b Nádia M. Borges,^a
Guilherme R. Oliveira^b and Hamilton B. Napolitano ^{*,a}

^aCampus de Ciências Exatas e Tecnológicas, Universidade Estadual de Goiás,
75132-903 Anápolis-GO, Brazil

^bInstituto de Química, Universidade Federal de Goiás, 74001-970 Goiânia-GO, Brazil

Chalcones are compounds with wide interesting biological activities including Alzheimer's disease. A comparative study was performed between the chalcones (*E*)-1-(2-aminophenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one and 1-(6-amino-1,3-benzodioxol-5-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one regarding the influence of benzodioxol group on their molecular conformations. The first chalcone was neutralized with dilute hydrochloric acid, while solid of the second was filtered and recrystallized from ethanol, both on centrosymmetric space group P2₁/c. Their molecular packing were evaluated by Hirshfeld surfaces, and both frontier molecular orbitals and molecular electrostatic potential (MEP) map were carried out by density functional theory (DFT) calculations. The compounds are stabilized by C–H···O and C–H··· π interactions, as observed on MEP map, while the HOMO-LUMO gap indicated the conformational stability. The pharmacophore mapping approach was carried out for the identification of potential target candidates and then, further molecular docking analysis targeting the beta-secretase 1 (BACE-1) protein as a tactic to develop potential AD inhibitors, was performed. The AutoDock Vina score in redocking result for 2OHQ is –7.4 and –7.6 kcal mol^{–1}. Additionally, the docking results for compounds inside the active site of the 2OHQ structure showed that both compounds bound to the BACE-1 active site with AutoDock Vina score of –6.0 kcal mol^{–1}.

Keywords: tri-methoxy chalcones, Hirshfeld surfaces, molecular docking, DFT

Introduction

Chalcones are chemical compounds often obtained in various types of plants or synthetic sources,^{1–3} usually derived from the condensation of aromatic aldehyde with acetophenones in the presence of catalyst, being the principal precursors for the biosynthesis of flavonoids and isoflavonoids.^{1,2,4} Basically, their structures are formed by two aromatic rings bounded by an open chain formed by an olefin portion and an α,β -unsaturated carbonyl system.^{4,5} This compound class has attracted interest due to broad biological activities, such as anti-inflammatory, anti-fungal, anti-cancer, antibacterial, antiprotozoal, anti-consulant, anti-oxidant, anti-malarial, cytotoxic, insecticidal and treatment of Alzheimer's disease.^{6–12}

Since many biological activities are attributed to chalcones, the understanding on how substituents affect their

conformation and supramolecular arrangement is important because such activities are related to the molecular structure. For instance, some articles^{13–15} show that the structure-activity relationship (SAR) for different substituents can affect the biological activity. In this sense, chalcones containing the benzodioxol group were evaluated against bacteria and fungi,⁹ Cruzain from *Trypanosoma cruzi*, antihyperglycemic¹⁶ and larvicidal activity.¹⁷ Furthermore, several enzymatic studies have demonstrated inhibitory activity of chalcone derivatives against monoamine oxidase-B^{16,17} and beta-secretase 1 (BACE-1).¹⁸ In this context, molecular docking studies can be used on investigations of a molecular target. Inverse virtual screening (IVS) is a technique to find the molecular targets,¹⁹ it is applied to several compounds and plays an important role in identifying potential bioactive substances. Additionally, IVS is useful to evaluate molecular targets in the context of drug discovery, e.g., of study on antitumor targets,²⁰ besides a comprehensive investigation about chemical universe with the proteome.²¹

*e-mail: hbnapolitano@gmail.com

In this article, we report a comparative analysis between chalcones ((*E*)-1-(2-aminophenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one), $C_{18}H_{19}NO_4$, (**I**) and (1-(6-amino-1,3-benzodioxol-5-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one), $C_{19}H_{19}NO_6$, (**II**).²² The supramolecular arrangements of compounds **I** and **II** were analyzed and characterized from Hirshfeld surfaces (HS), and theoretical calculations were performed to explain the chemical stability. Also, the potential target candidates through pharmacophore mapping for both chalcones were predicted and the beta-secretase 1 structure was used for docking studies.

Experimental

Synthesis and crystallization

Compound **I** was synthesized based on the procedure described by Bandgar *et al.*²³ In a balloon it was added 10 mL of ethanol and catalytic amount of NaOH (67 mg). The system was stirred until the solution became homogeneous. Next, it was added *o*-aminoacetophenone (1 mmol, 0.135 mg) and 3,4,5-trimethoxybenzaldehyde (1 mmol, 0.196 mg) (Figure 1). The reaction was stirred at room temperature for 20 h, followed by thin layer chromatography. The solution was neutralized with dilute hydrochloric acid, occurring at precipitation of a solid. The solid of **II** was filtered and recrystallized from ethanol.

Single crystal X-ray analysis

The crystal of compound **I** was measured on a Bruker D8 VENTURE system at room temperature and a CuK_{α} microfocus sealed tube ($\lambda = 1.54178 \text{ \AA}$). The structure was solved and refined using the Bruker SHELXTL software package,²⁴ using the space group $P2_1/c$. The final anisotropic full-matrix least-squares refinement on F^2 with 218 variables converged at $R1 = 0.0473$, for the observed data and $wR2 = 0.1453\%$ for all data and the goodness-of-fit 1.060. The crystallographic information files of compound **I** were deposited in the Cambridge Crystallographic Data Centre (CCDC)²⁵ under the code 1866290 (Supplementary Information section). The data of compound **II** were obtained from CCDC with code 180169 (Supplementary

Information section).²² The crystallographic information of compounds **I** and **II** are shown in Table 1 for comparison.

Table 1. Crystallographic data and structure refinement for compounds **I** and **II**

Parameter	$C_{18}H_{19}NO_4$ (I)	$C_{19}H_{19}NO_6$ (II)
Formula weight / (g mol ⁻¹)	313.35	357.35
Temperature / K	293(2)	150 (1)
Wavelength / $\text{\AA}$	1.54178	0.71073
Crystal size / mm	$0.07 \times 0.14 \times 0.26$	$0.4 \times 0.1 \times 0.1$
Crystal habit	yellow block	orange block
Crystal system	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/c$
a / $\text{\AA}$	12.7264(3)	23.5477 (4)
b / $\text{\AA}$	8.6478(2)	4.9605 (1)
c / $\text{\AA}$	15.2955(4)	14.2556 (8)
α, γ / degree	90	90
β / degree	103.8320 (10)	100.702 (1)
Volume / $\text{\AA}^3$	1634.54(7)	1636.21 (10)
Z	4	4
Density (calculated) / (mg m ⁻³)	1.273	1.451
Absorption coefficient / mm ⁻¹	0.739	0.109
$F(000)$	664	752
Refinement method	full-matrix least-squares on F^2	full-matrix least-squares on F^2
Goodness-of-fit (S)	1.060	1.030
Final R indices ($I > 2\sigma(I)$)	0.0473	0.044

a - c and α - γ : unit cell parameters; Z : formula unit *per* unit cell; $F(000)$: structure factor in the zeroth-order case; F^2 : squared structure factor.

Hirshfeld surface analysis

The Hirshfeld surface (HS) is a graphical tool based on the electronic density of molecules related to their chemical environment, providing both interpretation and quantification of the intermolecular interactions that occur in a molecule.²⁶ These surfaces can be understood as a space of partition in the crystal with regions where there is distribution of electrons of a sum of spherical atoms.²⁷ Hirshfeld *et al.*²⁸ defined a weight function for each atom in a molecule as:²⁹

$$w(r) = \sum_{a \in \text{molecule}} \rho_a(r) / \sum_{a \in \text{crystal}} \rho_a(r) = \rho_{\text{molecule}}(r) / \rho_{\text{crystal}}(r) \quad (1)$$

where $w(r)$ is a continuous function with $0 < w(r) < 1$, the term $\rho_a(r)$ [$\rho_{\text{molecule}}(r)$] is a sum over the atoms in the molecule of interest and $\rho_a(r)$ [$\rho_{\text{crystal}}(r)$] is an analogous sum

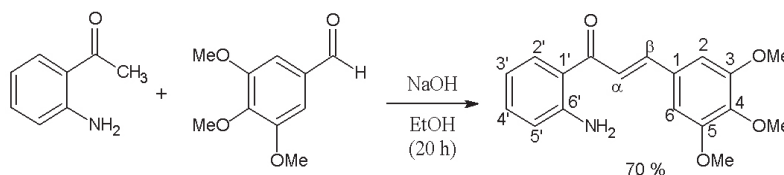


Figure 1. Synthesis scheme for compound **I**.

over the crystal.²⁶ In the Hirshfeld surface (HS), d_e is the distance from the surface to the nearest nucleus in another molecule and the d_i is the distance from the surface to the nearest atom in the molecule itself. The combination d_e with d_i , gives rise to the normalized surface d_{norm} , in which any close intermolecular contact will be characterized by two identical red regions.^{27,30}

$$d_{\text{norm}} = \frac{d_i - r_i^{\text{vdW}}}{r_i^{\text{vdW}}} + \frac{d_e - r_e^{\text{vdW}}}{r_e^{\text{vdW}}} \quad (2)$$

where r^{vdW} is the van der Waals (vdW) radius of atom internal or external to the surface.³⁰ A final analysis of the intermolecular contacts can be conducted by two-dimensional mapping which summarizes quantitatively the nature and type of intermolecular interaction and presents it in a graphical format, namely fingerprints.³¹

Theoretical analysis

Theoretical calculations were performed for both chalcones from the crystallographic data. Both geometries were optimized only for the hydrogen atoms (opt = readfreeze and atoms = H noatoms = C, O, N), using the density functional theory (DFT) accomplished in the Gaussian09 package.³² We used M062X³³ as functional and 6-311pG(d,p)^{34,35} as basis set. This functional is recommended for noncovalent interaction such as C–H···O and C–H··· π .³⁶ The wavefunction generated using M062X / 6-311pG(d,p) was used for frontier molecular orbitals and molecular electrostatic potential map (MEP). The frontier molecular orbitals (highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO)) is often associated with the electron donating ability of a molecule.³⁷ The energy of these orbitals can be calculated and are associated with the chemical stability index and the difference between them (gap) is related to the chemical reactivity, being described as to the minimum energy needed to excite an electron in the molecule.³⁸ The MEP presents the charge distribution of molecules three-dimensionally, and can determine regions of higher and lower electron densities of the molecule, contributing to interpret electrophilic and nucleophilic processes.^{39,40} For the two compounds shown, this mapping contributes to the comparison of the reactive sites in the presence of the benzodioxol group.

Molecular docking

In order to identify potential target candidates for the given chalcones, the pharmacophore mapping approaches

were carried out. Binding properties for compounds **I** and **II** on potential target were estimated by PharmMapper Server.⁴¹ Just human protein target set was used for pharmacophore mapping, whatever remains of parameters was set to default. All the predicted target candidates were ranked by normalized fit score. Between the different targets predicted we had explored the molecule for its inhibitor activity against human beta-secretase 1 (BACE-1). BACE-1 represents a key target protein in the development of new potential drugs for the non-symptomatic treatment of Alzheimer's disease. Since BACE-1 was identified, a scope of work has been done in the drug discovery of new BACE-1 inhibitors.⁴² Molecular docking includes the expectation of the complex among protein and ligand into the protein active site, and empowers the most positive conformation to be resolved. Molecular docking was carried out to evaluate the binding affinity of the compounds with the BACE-1 active site. The protein X-ray crystal structure was downloaded from the Protein Data Bank (PDB).⁴³

The active site of protein was predicted using CASTp.⁴⁴ The best binding pocket was selected for further analysis. The 3D structures of BACE-1 and ligand were prepared as input for docking experiments using Dock Prep tool of Chimera software.⁴⁵ During the protein preparation, all missing hydrogen atoms were added, all water molecules and ligand deleted, and the energy minimized. Protein and ligand were dealt with the general AMBER force field 12SB.⁴⁶ All other settings were kept as default setting. The molecular docking calculations were performed on AutoDock Vina software.⁴⁷ First, the active site of the enzyme was defined within two different grid size $12.45 \times 12.69 \times 13.70$ Å and $20 \times 20 \times 20$ Å centred at the geometric point (70.32, 47.34, 5.34 Å) on co-crystallized ligand. For each docking calculation nine docking runs were carried out with an exhaustiveness option of eight, and the poses with the highest absolute values of affinity were saved with maximum energy difference of 3 kcal mol⁻¹.

Results and Discussion

Solid state characterization

The molecular structure of compound **I** was crystallized under monoclinic $P2_1/c$ space group with unit cell parameters $a = 12.7264$ (3) Å, $b = 8.6478$ (2) Å, $c = 15.2955$ (4) Å and $\beta = 103.8320$ (10)°. Compound **II** was crystallized under $P2_1/c$ monoclinic space group with cell parameters, $a = 23.5477$ (4) Å, $b = 4.9605$ (1) Å, $c = 14.2556$ (8) Å and $\beta = 100.702$ (1)°. ORTEP representation of compounds **I** and **II** are presented in Figure 2.

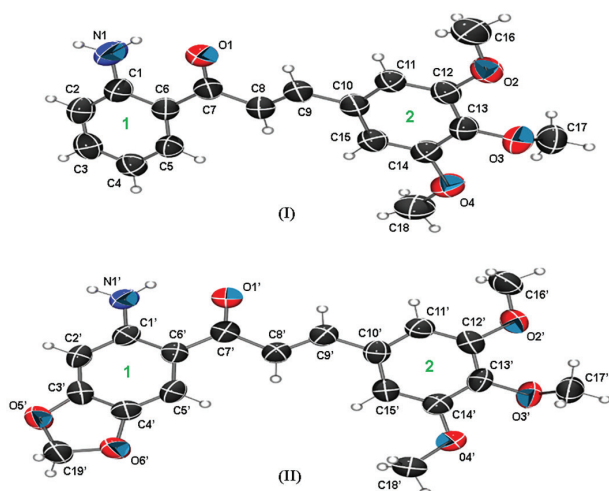


Figure 2. ORTEP representation at 50% of probability for compounds **I** and **II**. Hydrogen atoms are shown as spheres of arbitrary radii.

Both compounds **I** and **II** have a trimethoxy group at one of the extremities, attached to C12, C13 and C14 atoms from ring 2 in compound **I** and C12', C13' and C14' from ring 2 in compound **II**. On the other hand, they differ in the aromatic ring 1, since compound **I** has an amino group attached to the aromatic ring, while compound **II** has a benzodioxol group attached to the aromatic ring, according to ORTEP representations in Figure 2. Besides that, although methoxy groups have similar angles (C13–O3–C17 = 113.74° for **I** and C13'–O3'–C17' = 114.08° for **II**), they are oriented in opposite directions (Figure 3).

The observed planarity in **I** and **II** is confirmed from dihedral angles ω_1 , ω_2 , ω_3 , ω_4 , ω_5 , ω_6 , ω_7 and ω_8 (Table 2). Structural differences between **I** and **II** are evidenced from dihedral angles ω_2 and ω_6 (–4.77°; 1.03°), ω_3 and ω_7 (7.71°; 9.40°), ω_4 and ω_8 (9.05°; 12.18°).

The Figure 3 shows on overlap, relating the angles formed by planes of aromatic ring of **I** and the benzodioxol

Table 2. Dihedral angles for **I** and **II**

Atoms	Dihedral angles / degree	
C8–C9–C10–C15	5.65	ω_1
C9–C8–C7–O1	–4.77	ω_2
C1–C6–C7–O1	7.71	ω_3
C5–C6–C7–C8	9.05	ω_4
C8'–C9'–C10'–C15'	4.35	ω_5
C9'–C8'–C7'–O1'	1.03	ω_6
C1'–C6'–C7'–O1'	9.40	ω_7
C5'–C6'–C7'–C8'	12.18	ω_8

ring of **II** ($\delta_1 = 12.47$ and $\delta_2 = 18.58^\circ$ respectively). The difference between planes angles (δ_1 and δ_2) is 6.11° , showing that the presence of the benzodioxol group increases the distance from the plane when compared to the aromatic ring of **I**.

The crystal packing of **I** is stabilized by C–H...O, N–H... π and C–H... π interactions (Figure 4a), while **II** by C–H...O, N–H...O and C–H... π interactions (Figure 4b). Both structures have an intramolecular interaction involving amine and carbonyl groups. The interactions C3–H3...O1 and C5–H5...O2 form chains running along [001] and [010], respectively. In contrast, interactions C11'–H11'...O6' and C9'–H9'...O6' (bifurcate) contribute to the periodicity along [001], while interactions C19'–H19A'...Cg1', C18'–H18A'...Cg2' and C16'–H16A'...Cg2' are observed along [010]. Compound **II** form a dimer stabilized by interaction N1'–H1B'...O5' which contributes for the crystalline packing, occurring due to the presence of the benzodioxol group. For both **I** and **II**, intramolecular interactions N1–H1A...O1 and N1'–H1A'...O1' collaborate for the structure's planarity, but with benzodioxol group it is observed a smaller planarity, increasing the δ value from 12.47 (**I**) to 18.58° (**II**). This planarity deviation is result of

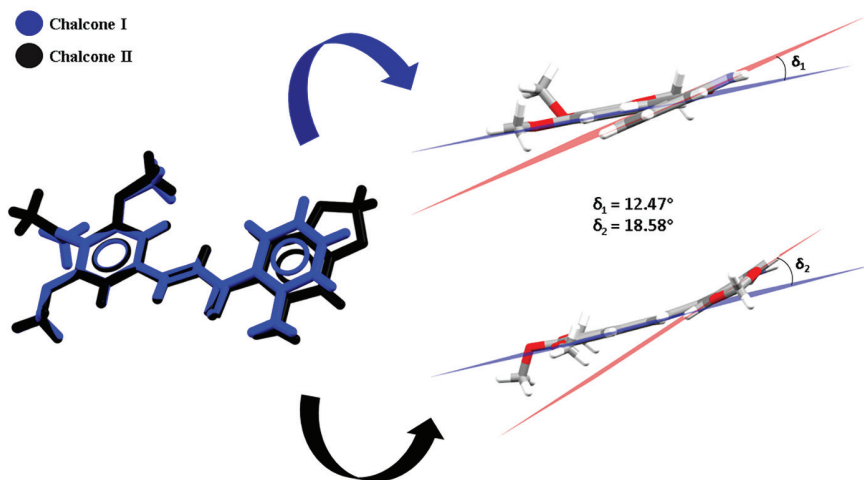


Figure 3. Overlapping for compounds **I** and **II**.

the benzodioxol group electronegativity, which causes more intermolecular interactions. The total information about the interactions of **I** and **II** are shown in Table 3.

HS was used to improve the intermolecular interactions description.²⁷ Figure 5 shows the Hirshfeld surface d_{norm} for both analyzed compounds. This surface normalizes d_e and d_i as a function of the van der Waals radius, indicating on its surface both donor and acceptor regions of intermolecular contacts. In this sense, molecular interactions are recognized from a color-based scale, where red indicates strong contacts. In Figures 5a and 5b, are indicated the intermolecular interactions of **I**, while 5c indicates

interactions of **II**. For **I**, the regions (1r), (3r) and (5r) indicate acceptor regions of interactions N1–H1B...Cg1, C5–H5...O2 and C3–H3...O1, while (4d), (2d) and (6d) represent their donor regions. For **II**, (2r'), (4r') and (6r') indicate acceptor regions of interactions N1'–H1B'...O5', C1'–H11'...O6' and C9'–H9'...O6', while (1d'), (3d') and (5d') describe their donor regions, respectively. For **I**, the more intense color of (1r) and (4d) indicates that the interaction N1–H1B...Cg1 plays an important role on its crystals packing, while the crystal packing **II** is stabilized mainly by the interaction C1'–H11'...O6', as seen in (4r') and (6d') contacts.

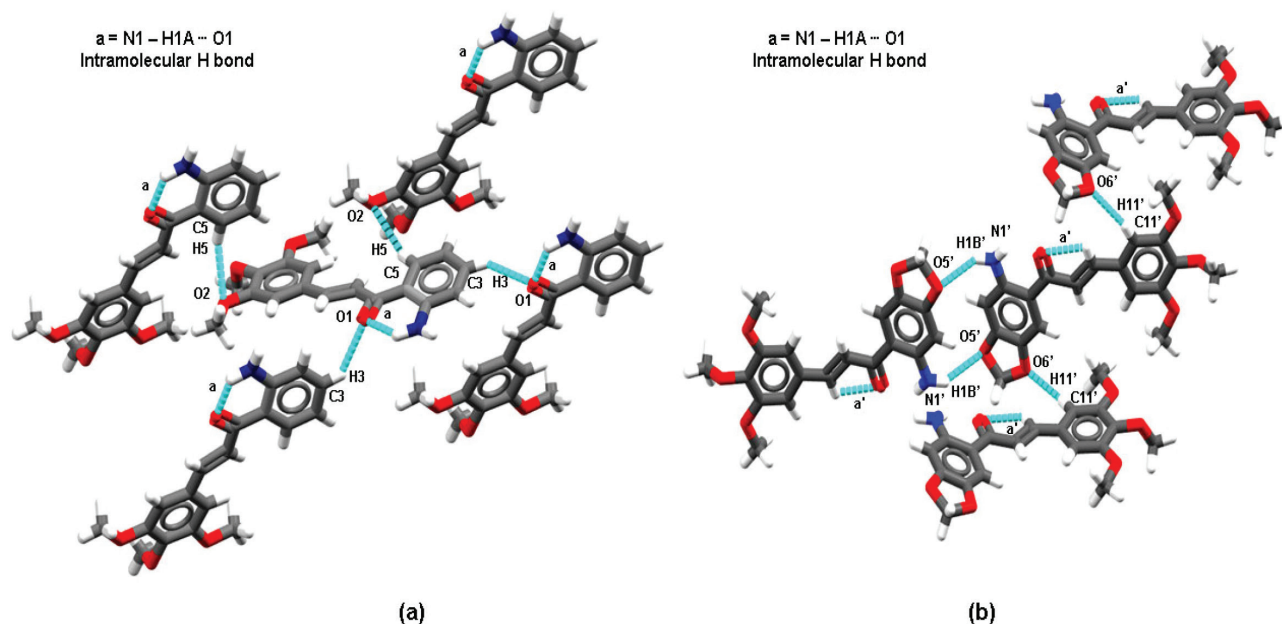


Figure 4. Representation of interactions for compounds **I** and **II**.

Table 3. Total interactions for compounds **I** and **II**

Compound	D–H...A	d(D–H) / Å	d(H...A) / Å	d(D...A) / Å	d(D–H...A) / degree
I	C3–H3...O1 ^a	0.930	2.619	3.344	135.25
	C5–H5...O2 ^b	0.930	2.690	3.539	153.20
	C9–H9...Cg1 ^c	0.930	2.879	3.647	140.82
	N1–H1B...Cg1 ^d	0.866	3.197	4.005	156.22
	C4–H4...Cg2 ^b	0.930	3.496	3.954	113.09
	N1–H1A...O1 (intra)	1.017	1.844	2.621	130.40
II	C19'–H19A'...Cg1 ^e	0.990	2.923	3.564	123.30
	C11'–H11'...O6' ^b	0.951	2.510	3.398	155.43
	C9'–H9'...O6' ^b	0.950	2.694	3.546	149.53
	C18'–H18A'...Cg2 ^e	0.981	2.814	3.675	146.93
	C16'–H16A'...Cg2 ^e	0.980	2.754	3.626	148.60
	N1'–H1B'...O5' ^f	0.880	2.645	3.357	138.69
	N1'–H1A'...O1' (intra)	0.880	2.007	2.651	129.09

^ax, 3/2 – y, 1/2 + z; ^bx, 1/2 – y, 1/2 + z; ^cx, 3/2 – y, –1/2 + z; ^d–x, 1/2 + y, 3/2 – z; ^ex, –1 + y, z; ^f–x, 1 – y, –z.

In addition, the shape index assists in the interpretation of interactions occurring between delocalized π systems ($\pi\pi$, $C-H\cdots\pi$ or $N-H\cdots\pi$ interactions). Figure 6 shows that both **I** and **II** are stabilized by $C-H\cdots\pi$ interactions, represented by a concave red region over the aromatic ring (Figure 6b for **I** and Figure 6d for **II**). Figures 6a and 6b show that **I** is stabilized by $N1-H1B\cdots Cg1$ (i), $C9-H9\cdots Cg1$ (ii) and $C4-H4\cdots Cg2$ (iii) interactions. Figures 6c and 6d show that **II** is stabilized by three $C-H\cdots\pi$ interactions, $C19'-H19B'\cdots Cg1'$ (i'), $C18'-H18C'\cdots Cg2'$ (ii') and $C16'-H16C'\cdots Cg2'$ (iii'). Note that for **I**, a $N-H\cdots\pi$ interaction is present involving the ring 1 (Cg1), while for **II**, a $C-H\cdots\pi$ interaction occurs in the ring 1 (Cg1'), due to the presence of the benzodioxol group.

A plot of the d_e vs. d_i distribution, called the fingerprint, was constructed and represents the percentage of all interactions present in the molecules (Figure 7). Both **I** and **II** are organic molecules, so the hydrogen interactions represented by $H\cdots H$ in Figure 7, represent almost 50% of the total interactions. In addition, $C\cdots H$ contacts corresponds to $C-H\cdots\pi$ or $N-H\cdots\pi$ interactions, while $O\cdots H$ contacts indicate the $C3-H3\cdots O1$ and $C5-H5\cdots O2$ interactions for **I** and $C11'-H11'\cdots O6'$, $C9'-H9'\cdots O6'$ and $N1'-H1B'\cdots O5'$ for **II**.

Theoretical analysis

The MEP map helps to interpret the chemical properties

for a system³⁹ and Figure 8 shows this map for compounds **I** and **II**. The red color regions indicate electrophilic sites, being located over oxygen atoms for both **I** and **II**. On the other hand, blue color sites indicate nucleophile sites and are concentrated in both chalcones over hydrogen atoms and amine groups. Note that in **I** the electrophilic and nucleophile sites, are slightly more pronounced than the corresponding region in **II**, caused by benzodioxol group.

The HOMO and LUMO energies were calculated for both chalcones using M062X/6-311++G (d, p) theory level, and their graphical surfaces are shown in Figure 9. The difference (gap) between HOMO and LUMO energies is an important indicator for molecular chemical reactivity.^{48,49} For **I**, the energies of HOMO, LUMO and gap are -7.022034 eV, -1.365441 eV and 545.778375 kJ mol⁻¹, respectively. The HOMO orbital is spread over nitrobenzene ring, while the LUMO orbital is over carbonyl and olefin portions. For **II** these values are -6.760622 eV, -1.342188 eV, 522.799589 kJ mol⁻¹, respectively. Similar to **I**, the LUMO orbital is spread over ring 1 and HOMO orbital is observed close to open chain. In this sense, the benzodioxol group has not influence on the frontier molecular orbitals location. On the other hand, this group slightly decreases the reactivity of **II** when compared to **I**, as evidenced from gap energies.

Molecular modeling analysis

Compounds **I** and **II** were screened *in silico* with

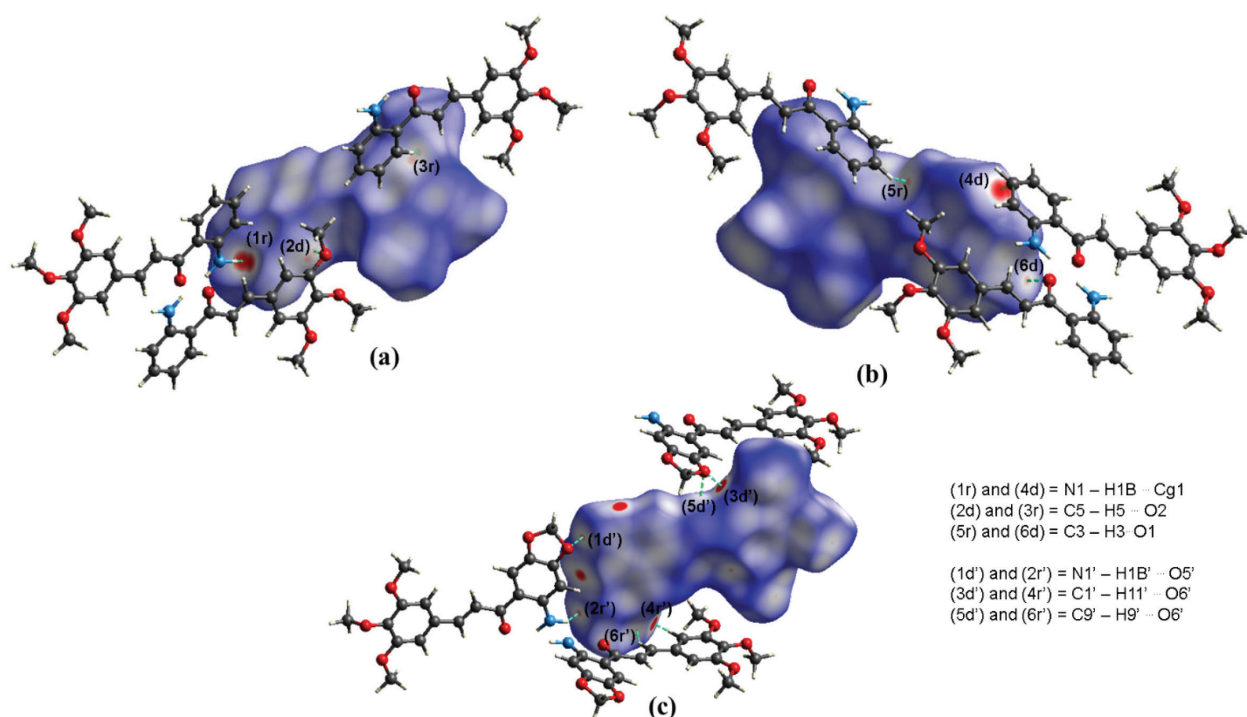


Figure 5. Hirshfeld surface (d_{norm}) evidencing interactions for compound **I**, (a) and (b), and for compound **II**, (c).

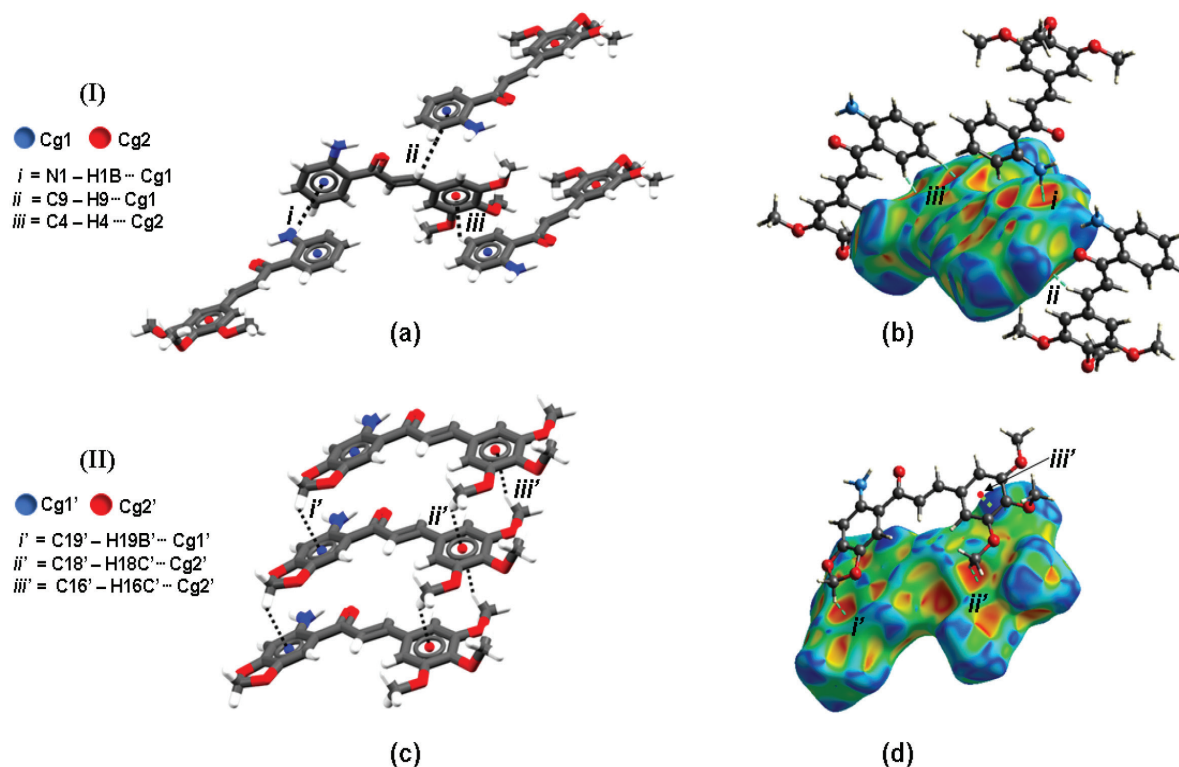


Figure 6. Hirshfeld surface shape index and representation of the interactions C–H... π and N–H... π for compound **I**, (a) and (b). C–H... π interactions for compound **II**, (c) and (d).

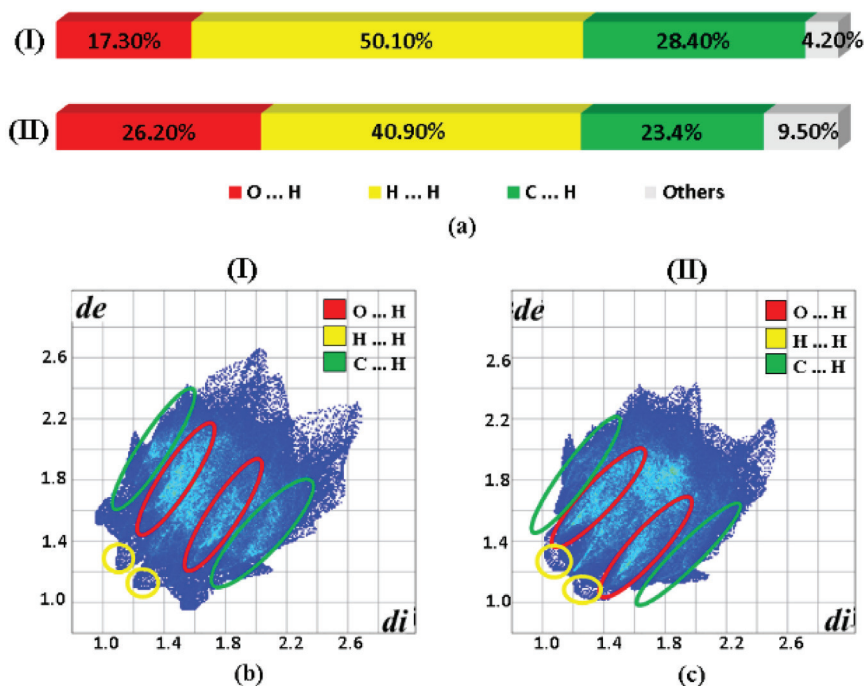


Figure 7. Quantitative analysis of the contacts for compounds **I** and **II** (a), and their fingerprints (b) and (c).

PharmMapper to elucidate their potential protein targets. The PharmMapper server revealed for both compounds **I** and **II** the human protein beta-secretase 1 (PDB code: 2OHQ)⁵⁰ with 3 hydrophobic and 1 hydrogen bond donor

features and the values 0.73 and 0.68 normalized fit score, respectively. Besides that, previous work¹⁸ has shown that chalcone derivatives are very potent inhibitors of protein beta-secretase 1, such as compound **II** ((half maximal

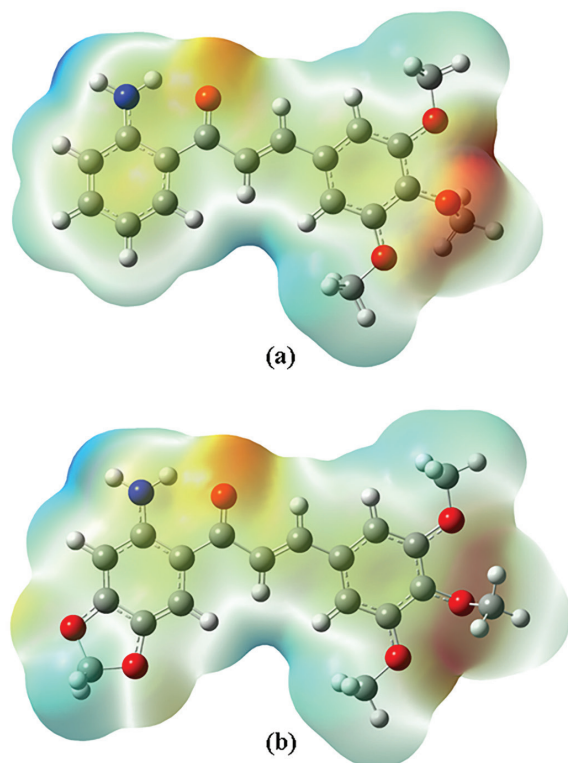


Figure 8. Molecular electrostatic potential (MEP) surface calculated at M062X/6-311þG(d,p) for compounds **I** (a) and **II** (b). The density range for **I** is $-5.367\text{e-}2$ to $5.367\text{e-}2$ hartrees, and for **II** is $-5.902\text{e-}2$ to $5.902\text{e-}2$.

inhibitory concentration (IC_{50}) = $17.7\text{ }\mu\text{M}$) which has maximum common substructure Tanimoto score of 0.75 and 0.66 with the compounds **I** and **II** described in the present work.

Initially, the ligand binding process was validated by redocking of the co-crystallized 6-[2-(3'-methoxybiphenyl-3-yl) ethyl]pyridin-2-amine (7IP) inside of 2OHQ structure to reproduce its binding mode. In this case, root mean square deviation (RMSD) values less than $2\text{ }\text{\AA}$ between the redocking ligand pose and the co-crystallized ligands are satisfactory.^{51,52} The both redocking protocol reproduced the binding mode of the co-crystallized ligand with RMSD values equal to 0.49 and $1.34\text{ }\text{\AA}$ for the two different grid size, respectively. The AutoDock Vina score in redocking result for 2OHQ is -7.4 and $-7.6\text{ kcal mol}^{-1}$, in its turn the experimental affinity of the complex 2OHQ-7IP shows a similar value of $\Delta G_{\text{exp}} = -8.9\text{ kcal mol}^{-1}$ ($\text{IC}_{50}\text{ }25\text{ }\mu\text{mol L}^{-1}$).⁴⁵ These is sufficient to define a docking protocol. Figure 10 shows how this ligand makes good contact with the active site and forms an H-bonding interaction with the catalytic aspartic acid residue Asp32.

The validated protocol was set up and the compounds **I** and **II** were docked inside the BACE-1 active site using the smaller grid size. After docking running the compounds were ranked and the best pose for a given ligand was

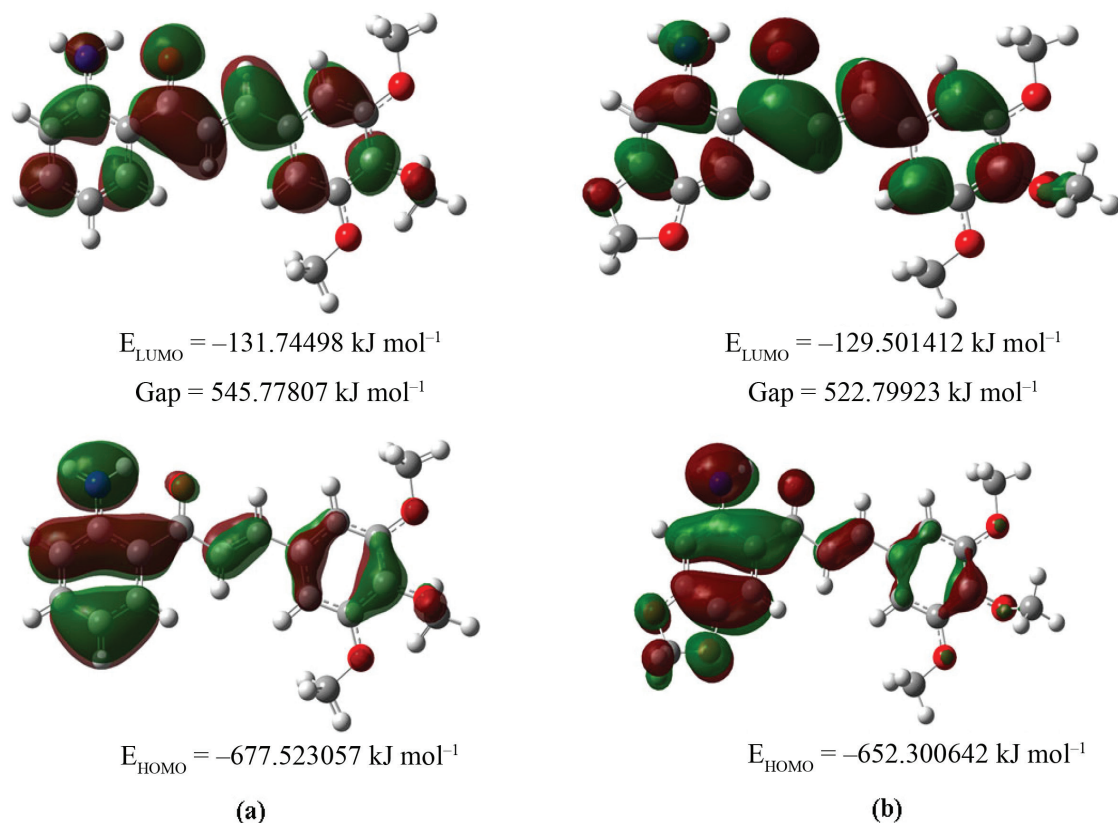


Figure 9. Frontier molecular orbitals of compounds **I** and **II**, with HOMO and LUMO band-gaps distribution.

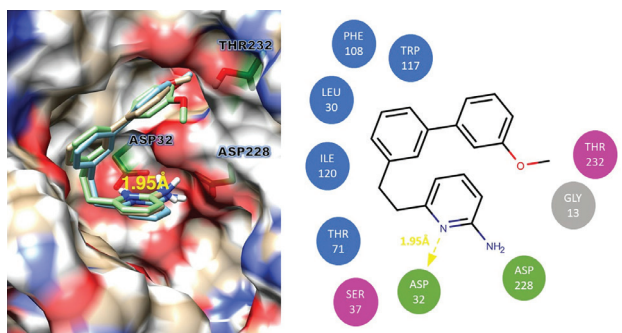
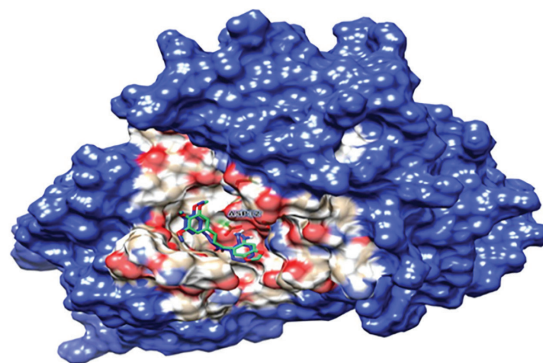


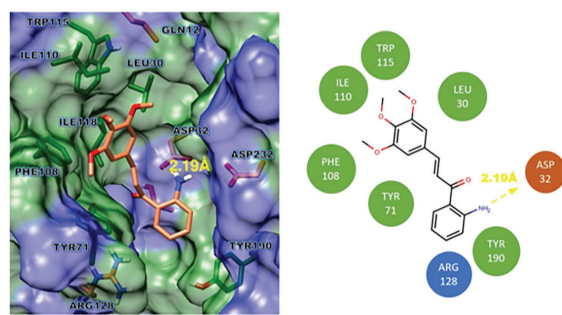
Figure 10. Redocking results of co-crystallized ligand 7IP (0.49 Å - tan) (1.34 Å - green) inside BACE-1 active site (PDB, code 2OHQ). Superposition between co-crystallized in sky blue and the best docking pose predicted in tan and green with the protein surface represented by heteroatom. The residues Asp32, Asp228 and Thr232 are represented in stick. The two-dimensional representation is showed on the right-hand side with the key residues. Yellow dashed lines represent hydrogen bond, blue circles are hydrophobic interactions and purple circles, the polar interactions. Molecular graphic was performed with the UCSF Chimera package.⁴⁵

determined by the AutoDock Vina score.⁴⁷ Figure 11a presents the docking results for **I** and **II** inside the active site of 2OHQ structure. The active site predicted by CASTp is represented by heteroatom surface. It was observed that both compounds bound to the BACE-1 active site with AutoDock Vina score of $-6.0 \text{ kcal mol}^{-1}$.

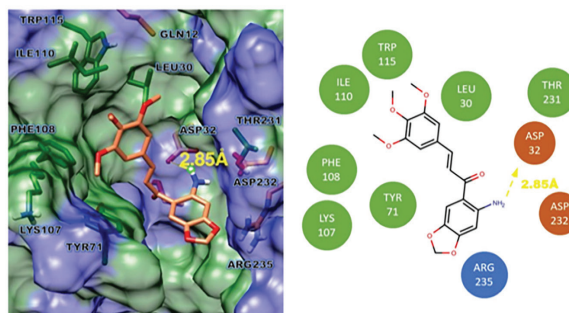
From interactions formed between both compounds and BACE-1, it was verified that some residues in the binding pocket interact with the chalcones derived compounds through hydrogen bonding and hydrophobic interactions as predicted by PharmMapper. From CASTp results, the BACE-1 pocket shows a hydrophobic sub pocket (represented by green residues on Figures 11b and 11c) suggesting that hydrophobic groups should be tolerated in this region. Figures 11b and 11c show how the 3,4,5-trimethoxyphenyl group makes good contact with the hydrophobic sub pocket. In addition, the compounds interact with the flap residue, Tyr71, on hydrophobic sub pocket, the flap conformation is identical to the flap-closed conformation described by Patel *et al.*,⁵³ and Hong and Tang.⁵⁴ The hydrogen bond was observed between the amine group of **I** and **II**, and the catalytic aspartic acid residue (Asp32). BACE-1 is a hydrolytic enzyme, its enzymatic activity is driven by Asp dyad (Asp32 and Asp228) located at active site where the peptides are hydrolysed. The visual inspection helped to identify more “good contacts” between the enzyme and the group benzyl in **I** than the group benzodioxol of **II**. The results analysed by docking studies propose them as potential candidates to BACE-1 inhibitors. Additionally, this binding mode can end up being a decent beginning stage for upgrading further chemical synthesis of chalcones derived compounds to inhibit beta-secretase 1 receptor using trimethoxy chalcones as scaffold.



(a)



(b)



(c)

Figure 11. Docking results for compounds **I** and **II** in the 2OHQ BACE-1 crystallography structure. (a) The active site predicted by CASTp is represented by heteroatom surface, and the blue surface corresponds to the others residues of protein on the left-hand side. (b) and (c) On the middle, the compounds **I** and **II** making hydrogen bond (yellow dashed line) with catalytic aspartic acid residue (brown circle) and interacting with hydrophobic residues (green sticks and blue circles). The two-dimensional representation is appeared on the right-hand side.

Conclusions

The supramolecular arrangement of compound **II** has more interactions than **I** due to the presence of benzodioxole group, which makes **II** less planar than **I**, as observed throughout the angle between planes of aromatic rings. Except for the $\text{N-H}\cdots\pi$ interaction for **I**, the crystalline state of both chalcones is stabilized by $\text{C-H}\cdots\text{O}$ and $\text{C-H}\cdots\pi$ interactions, which were confirmed by the Hirshfeld surfaces. Geometry optimization was carried out using DFT, and MEP maps confirm benzodioxole regions

more susceptible to interactions. The HOMO-LUMO gap for compound **I** is greater than for **II**, indicating high kinetic stability and low chemical reactivity in relation to compound **II**. Molecular docking simulations were used to explore the interactions between BACE-1 and these two chalcones. The binding modes have suggested to be a good starting point for optimizing further chemical synthesis of chalcones derived compounds to inhibit beta-secretase 1 receptor, using tri-methoxy chalcones as scaffold.

Supplementary Information

Crystallographic data (excluding structure factors) for the structures in this work were deposited in the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1866290 and 180169. Copies of the data can be obtained, free of charge, via www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033. E-mail: deposit@ccdc.cam.ac.uk.

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A new quinolinone-chalcone hybrid with potential antibacterial and herbicidal properties using in silico approaches

Vitor S. Duarte^{1,2} · Renata L. G. Paula² · Jean M. F. Custodio³ · Giulio D. C. D'Oliveira⁴ · Leonardo L. Borges^{2,5} · Caridad N. Pérez⁴ · Pal Perjesi^{6,7} · Allen G. Oliver³ · Hamilton B. Napolitano^{2,6} 

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Abstract

Quinolinone-chalcones are hybrid compounds consisting of chalcone and quinolone moieties with biological activity related to their hybrid structure. This work seeks to describe the structural and theoretical parameters related to the physicochemical properties and biological activity of a new quinolinone-chalcone. The synthesis, structural characterization by X-ray diffraction, molecular topology by Hirshfeld surfaces and QTAIM, molecular electronic calculations, and pharmacophore analysis were described. The weak interactions C–H $\cdots$ O, C–H $\cdots$ π , and C–H $\cdots$ Br were responsible for crystal growth and stabilized the crystalline state. The DFT analysis shows that the sulfonamide group region is susceptible to observed interactions, and the frontier molecular orbitals indicate high kinetic stability. Also, pharmacophore analysis revealed potential antibacterial and herbicidal activity; by docking within the active site of TtgR, a transcription regulator for the efflux pump TtgABC from the highly resistant *Pseudomonas putida* (*P. putida*) strain DOT-TIE, we showed that the activation of TtgR relies upon the binding of aromatic-harboring compounds, which plays a crucial role in bacterial evasion. In this context, a new quinolinone-chalcone has a higher binding affinity than tetracycline, which suggests it might be a better effector for TtgR.

Keywords Quinolinone-chalcone · QTAIM analysis · Molecular modeling · Potential herbicide activity

Introduction

The search and development of new chemical compounds with beneficial biological activity are multidisciplinary tasks involving several stages. An interesting starting point is investigating compounds with biological potential that contain two or more active components. Among these are quinolinone-chalcone which possesses both chalcone and quinolone moieties, a structural aspect present in some bio-active compounds [1, 2]. These compounds and derivatives are well known by their activities, as in the pharmaceutical field (anticancer, antibacterial, anti-parasitic, antiparasmodial agents, antimalarial, apoptotic activity, anti-inflammatory, antitubercular) [3–8], in applications as pesticides [9, 10] and cosmetic [11, 12]. Sashidhara et al. [13] identified quinolinone-chalcone hybrids as potential antiulcer agents, finding a very promising compound to be developed. Huang et al. [14] conducted a study with a group of 2-methyl-4-phenylquinoline-chalcone analogs and identified 24 derivatives that exhibited anti-inflammatory, anti-depressant, and analgesic activities. Also, Abonia et al. [15] evaluated quinolinone-2-one-based chalcones finding some of them

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✉ Vitor S. Duarte
vitor.sduarte@seduc.go.gov.br

✉ Hamilton B. Napolitano
hbnapolitano@gmail.com

¹ Research and Energy Efficiency Center, CAO, Vehicle Assembler LTDA, Anápolis, GO, Brazil

² Campus of Exact and Technological Sciences, State University of Goiás, Anápolis, GO, Brazil

³ Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN, USA

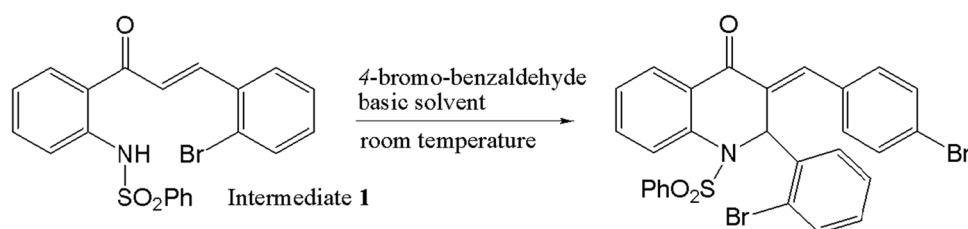
⁴ Institute of Chemistry, Federal University of Goiás, Goiânia, GO, Brazil

⁵ School of Medical and Life Sciences, Pontifical Catholic University of Goiás, Goiânia, GO, Brazil

⁶ Laboratory of New Materials, Evangelical University of Goiás, Anápolis, GO, Brazil

⁷ Institute of Pharmaceutical Chemistry, University of Pécs, Pécs, Hungary

Scheme 1 Conditions for the synthesis of chalcone-quinolinone compounds



with remarkable activity against 50 human tumor cell lines. Roussaki et al. [4] studied a series of novel quinolinone-chalcone hybrids and found good indices for their anti-parasitic activities. The antioxidant and antimicrobial activities [16, 17] can be used in the food industry [18] and the development of biofuel additives [19, 20]. Biodiesels frequently show oxidative stability problems due to the proliferation of microorganisms [21, 22]. All of these studies indicate the quinolinone-chalcones to display promising activity [23].

In this sense, understanding how structural aspects affect the physicochemical properties is an essential step toward targeted syntheses and structure–activity relationships description. Several works show that structural features such as planarity [24, 25], electronic delocalization [26, 27], and type of substituent [28, 29] influence particular activities. Along with understanding the chemical structure, we can also highlight pharmacophore modeling, which consists of a structure-based method that can predict the potential biological activity of new molecules, thus guiding future in vitro and in vivo assays [30, 31]. In this work, we present the synthesis, spectroscopy, topological analysis, biological activity prediction, and characterization of a new quinolinone-chalcone (1-benzenesulfonyl-3-(4-bromobenzylidene)-2-(2-bromophenyl)-2,3-dihydro-1H-quinolin-4-one (QC), $C_{28}H_{19}Br_2NO_3S$). Its molecular structure, obtained from single-crystal X-ray diffraction, was experimentally and theoretically analyzed to understand its physicochemical properties. The analysis of intermolecular interactions, packing, and the supramolecular arrangement was carried out from geometric parameters and electron density, using Hirshfeld surface (HS) [32]. The theoretical analysis was performed using the density functional theory (DFT) [33] to describe the topological analysis of interactions and report the differences between the solid state, gas phases, and effects of solvents such as water, ethanol, dichloromethane, and chloroform. Furthermore, to analyze the frontier molecular orbitals [34] and describe electrophilic and nucleophilic processes from the molecular electrostatic potential (MEP) map [35]. Additionally, we performed a pharmacophore analysis that revealed potential antibacterial and herbicidal activity in that QC has a similar pharmacophore site distribution as tetracycline, a widely used commercial antibiotic. We then further investigated QC potential using molecular docking simulations of the protein TtgR, which regulates the production of the efflux pump TtgABC from

the highly resistant *Pseudomonas putida* (*P. putida*) strain DOT-TIE.

Experimental and computational procedures

Synthesis

The synthetic procedure as described by d'Oliveria [36] was used for obtaining the target compound. (*E*)-3-(2-Bromophenyl)-1-(2-(phenylsulfonylamino)phenyl)prop-2-en-1-one (Intermediate 1) was reacted with 4-bromobenzaldehyde to yield the desired quinolinone-chalcone (Scheme 1). Like the previous synthesis of structurally related derivatives, the isolated product proved to be a stereochemically homogeneous solid [36, 37]. Intermediate 1 was synthesized based on the method described by Castro and coauthors [38].

Synthetic procedure Intermediate 1 (1 mmol) and 4-bromobenzaldehyde (2 mmol) were dissolved in 15 mL of basic ethanol (56 mg/1.00 mmol of potassium hydroxide dissolved) and allowed to react (25 °C) for 48 h at room temperature. The resulting precipitate was filtered out and rinsed with 15 mL of ethanol. The precipitate was dissolved in dichloromethane (10 mL), and the solution was extracted with water. The organic phase was allowed to evaporate slowly, yielding the product.

(*E*)-3-(4-bromobenzylidene)-2-(2-bromophenyl)-2,3-dihydro-1-(phenylsulfonyl) quinolin-4(1H)-one (QC). Yellow crystalline solid (339 mg, 55.6%), purity of 98.6%, mp 219–221 °C. 1H NMR ($CDCl_3$) δ 6.74 (*dd*, *J* 1.48 Hz, 7.83 Hz, 1H), δ 6.91 (*s*, 1H), δ 6.98 (*dt*, 1.23 Hz, 7.61 Hz, 1H), δ 7.03–7.06 (*m*, 2H), δ 7.09–7.13 (*m*, 3H), δ 7.22–7.26 (*m*, 2H), δ 7.34 (*ddd*, *J* 3.55 Hz, 5.05 Hz, 7.75 Hz, 1H), δ 7.49–7.53 (*m*, 3H), δ 7.56 (*s*, 1H), δ 7.56–7.59 (*m*, 2H), δ 7.70 (*dd*, *J* 1.23 Hz, 7.98 Hz, 1H), δ 7.86–7.89 (*m*, 1H); ^{13}C NMR ($CDCl_3$) δ 60.86, 124.79, 125.13, 127.22, 127.63, 128.02, 128.10, 128.51, 129.26, 130.23, 130.28, 130.33, 131.40, 131.52, 132.45, 132.55, 133.45, 134.66, 134.75, 136.39, 136.42, 138.99, 139.11, 182.58; IR 1675 (*m*), 1605 (*m*), 1474 (*w*), 1351 (*s*), 1292 (*m*), 1239 (*m*); HRMS calculated for $C_{28}H_{20}Br_2NO_3S$ 607.9531, found 607.9454.

Single-crystal X-ray analysis

The X-ray data were collected using a Bruker APEX-II CCD diffractometer with monochromated MoK α radiation ($\lambda = 0.71073$ Å). The single-crystal was kept at 120 K during data collection. The structure was solved through the Olex2 [39] interface throughout intrinsic phasing (ShelXT) [40] and refined with ShelXL [41] using least-squares minimization. The non-hydrogen atoms were refined with anisotropic atomic displacement parameters, while hydrogen atoms were geometrically positioned and fixed with individual isotropic displacement parameters, according to the model for aromatic groups. Molecular representations, tables, and pictures were generated by Olex2 [39], Mercury [42], and Crystal-Explorer [43] software. Crystallographic data for QC were deposited in the Cambridge Crystallographic Data Centre (CCDC) [44] under the code 1,934,999.

Hirshfeld surface analysis

The HS and the fingerprint plots for QC were realized by CrystalExplorer [43] software. These surfaces are constructed based on the electron density distribution of molecules in their chemical environment and contribute to the analysis of the molecular interactions, defined by a continuous function $w(r)$, shown in Eq. 1 [32]:

$$w(r) = \frac{\sum_{a \in \text{molecule}} \rho_a(r)}{\sum_{a \in \text{crystal}} \rho_a(r)} = \rho_{\text{molecule}}(r) / \rho_{\text{crystal}}(r) \quad (1)$$

The first term of the mathematical operator (numerator) represents the sum of the atoms in the molecule under analysis, while the second term (denominator) is the sum of the entire crystal. The range of $w(r)$ is $0 < w(r) < 1$ [32]. Classical and non-classical hydrogen bonds analyses were studied from the *dnorm* surface, which evaluates the distance from the surface to the nearest nucleus in another molecule (*de*) and the distance from the surface to the nearest atom in the molecule itself (*di*) normalizing them as a function of the van der Waals radius. This surface indicates the regions of possible interactions through red regions [32]. The interactions involving the π -system were recognized by the *shape index* surface as large red regions over aromatic systems and convex blue regions over C-H atoms [32]. *Shape index* is defined by Eq. 2:

$$S = \left(\frac{2}{\pi} \right) \arctan \left[\frac{(K_1 + K_2)}{(K_1 - K_2)} \right] \quad (2)$$

where K_1 and K_2 are eigenvalues of the diagonalization of a Hessian matrix and the formal range of S is $(-1, +1)$.

In addition, fingerprint plots were generated by combination of *de* and *di* to quantify the contribution of each interaction to the stability of the structure [45].

Theoretical analysis

Theoretical calculations were carried out for QC from experimentally determined positions. M06-2X [46] functional with the 6-31 + G(2d,p) basis set were used to optimize the molecule in the gas phase, water, dichloromethane, ethanol, and chloroform using density functional theory (DFT) [33] available in Gaussian09 [47]. The theory level used is recommended for noncovalent interactions [46, 48], presents satisfactory results, has a relatively small computational cost, and considers the electronic correlation [49, 50]. The molecule was optimized within a solvent box for all solvent studies with molecular mechanics methods by the HyperChem software, and the lowest energy conformations were optimized again with the solvent dielectric constants (using DFT through Gaussian09). The geometric parameters for the molecule optimized in the gas phase, water, dichloromethane, ethanol, and chloroform were compared with the experimental values (X-ray). Furthermore, the wave function calculated for QC was used to generate the MEP map and the frontier molecular orbitals.

The MEP map is related to the total electron density. It determines the high and low electronic density regions of the molecule, performed through the potential $V(r)$ created at a point r by the action of the nuclei. The function is expressed in Eq. 3 [35]:

$$V(r) = \sum_a \frac{Z_A}{|r_a - r_A|} - \int \frac{\rho(r)}{r_a - r} dr \quad (3)$$

The first and second terms indicate the electrostatic potential created by the nucleus and the electrostatic potential created by the electrons, respectively [35]. The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) characterize both the bonding and antibonding orbitals, respectively [51]. Their energy is related to the ionization potential and electron affinity, and the difference between them, also called GAP, is an indicator for Kinect stability [51, 52].

The topological interaction analysis was performed by quantum theory of atoms in molecules (QTAIM) [53]. This methodology considers parameters of quantum mechanics and carries out the execution of numerical integrations with the gradient vector $[\nabla \rho(r)]$ as the basic condition for determining molecular topology [54]. The generated wave function was calculated by Gaussian09 and the topological analysis of the interactions by Multiwfn software [55].

Pharmacophore modeling and docking simulation

Using the Binding Database (<https://www.bindingdb.org/bind/index.jsp>), chlorimuron (an N-sulfonylurea-type herbicide) and tetracyclines were identified as analog molecules of QC. The compounds with the lowest IC_{50} values (inhibitory concentration) were selected for further pharmacophore analysis to obtain the models. All structures were generated in mol2 format before pharmacophoric analysis. PharmaGist webserver was used to obtain the models, which detects new pharmacophores using multiple flexible alignments of the set molecules [56]. Each compound fits as a pivot point for the alignment. The input consists of the group of QC with the analogs chlorimuron and tetracyclines, and the output consists of the pharmacophores computed. We used the crystal structure of TtgR, a transcription regulator for the efflux pump TtgABC from the highly resistant *Pseudomonas putida* (*P. putida*) strain DOT-TIE, complexed with tetracycline for further investigation through docking simulations (PDB ID 2UXO). Using the software Autodock Vina [57], we created a box around the TtgR active site (center coordinates: 0.5514, 34.5879, 13.9048; and size 14.4786 Å, 13.0667 Å, 10.8344 Å) and redocked the ligand tetracycline to validate our methodology yielding an RMSD of 1.41 Å. We then docked QC within the same box and calculated the binding energy for both tetracycline and QC. Figures were generated using software PyMol and UCSF Chimera [58].

Results and discussion

The compound QC is a new quinolinone-chalcone, which crystallizes in the centrosymmetric orthorhombic space group *Pbca*, with one independent molecule in the asymmetric unit (Table 1). QC molecule presents a quinolinic core, a sulfonamide group, distributed over its four aromatic rings. Two aromatic rings (2 and 3) have one bromine substituent each, while aromatic ring 4 is attached to the sulfonamide group, and aromatic ring 1 is part of the quinoline core (Fig. 1).

Chalcones usually possess almost planar conformation, and several studies suggest that this feature is associated with antifungal [59], cytotoxic [60], and immunomodulatory effects [61] activities. The title QC compound shows a significant deviation from planarity considering its aromatic rings (1 and 2). The planes formed by aromatic rings 3 and 4 are almost perpendicular (torsional angle of $\delta 1 = 88.70^\circ$), followed by the planes between aromatic rings 2 and 3 (torsional angle ($\delta 4 = 83.14^\circ$)). Note that the chalcone moiety is not planar, and the angle formed by its aromatic rings (1 and 2) is $\delta 6 = 58.21^\circ$. The difference in interplanar angles between the other aromatic rings can be seen in Fig. 2.

Table 1 Crystal data and structure refinement for QC

Parameter	C ₂₈ H ₁₉ Br ₂ NO ₃ S (QC)
Formula weight	609.32 g/mol
Temperature	120.01(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	<i>Pbca</i>
Unit cell dimensions	$a = 10.406(11)$ Å, $\alpha = 90^\circ$ $b = 20.469(2)$ Å, $\beta = 90^\circ$ $c = 22.386(2)$ Å, $\gamma = 90^\circ$
Crystal size	$0.36 \times 0.22 \times 0.158$ mm ³
Volume	4768.3(9) Å ³
Z, Z'	8, 1
Density (calculated)	1.698 g/m ³
Absorption coefficient	3.520 mm ⁻¹
F(000)	2432.0
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit	1.012
Final <i>R</i> indices ($I > 2\sigma(I)$)	$R_1 = 0.0243$; $wR_2 = 0.0530$
<i>R</i> indices (all data)	$R_1 = 0.0353$; $wR_2 = 0.0565$

The supramolecular arrangement of QC is stabilized by C–H...O, C–H... π , and C–H...Br interactions. The C3–H3...O1 and C2–H2...Cg3 interactions form chains contributing to growth and stability along *a*-axis (Fig. 3a), while C1–H1...Br2 and C15–H15...O2 contribute along the *b* axis (Fig. 3b), and C27–H27...O2 and C25–H25...O3 form chains parallel to the *c* (Fig. 3c). These interactions and their geometric parameters are shown in Table 2.

Based on the electron density, the *dnorm* surface contributes to the analysis of the interactions present in QC. Red regions indicate possible interactions (short distances) sites, while blue regions indicate the absence or weak contacts. As shown in Fig. 4, all interactions described so far (except for the C2–H2...Cg3, which was confirmed by shape index) were established with the regions (1d), (3d), (5d), (7d), and (9d) (donor sites) and (2r), (4r), (6r), (8r), and (10r) (acceptor sites). Note that the interaction C25–H25...O3 has the most intense color region ((7d) and (8r)) and shortest distance ($D \cdots A = 3.251$ Å), indicating a strong interaction.

The shape index surface contributes to the analysis of the interactions involving the π -systems, as C–H... π interactions. Figure 5 b and c confirm the C2–H2...Cg3 interaction involving the center of gravity of aromatic ring 3 (Cg3), with the concave red region over it (Fig. 5c) and convex blue regions over the C2–H2 atoms (Fig. 5b).

The fingerprint plot in two dimensions (*de* vs. *di* distribution) represents a mapping of the percentage of each contact present in the molecule (Fig. 6). From this, we deduce the following: from Fig. 6, H...H shows contacts involving hydrogen atoms and represents 35.1% of the contacts of the

Fig. 1 Ortep diagram of QC atomic displacement ellipsoids detected at the 50% probability level. Hydrogen atoms are represented as spheres with arbitrary radii

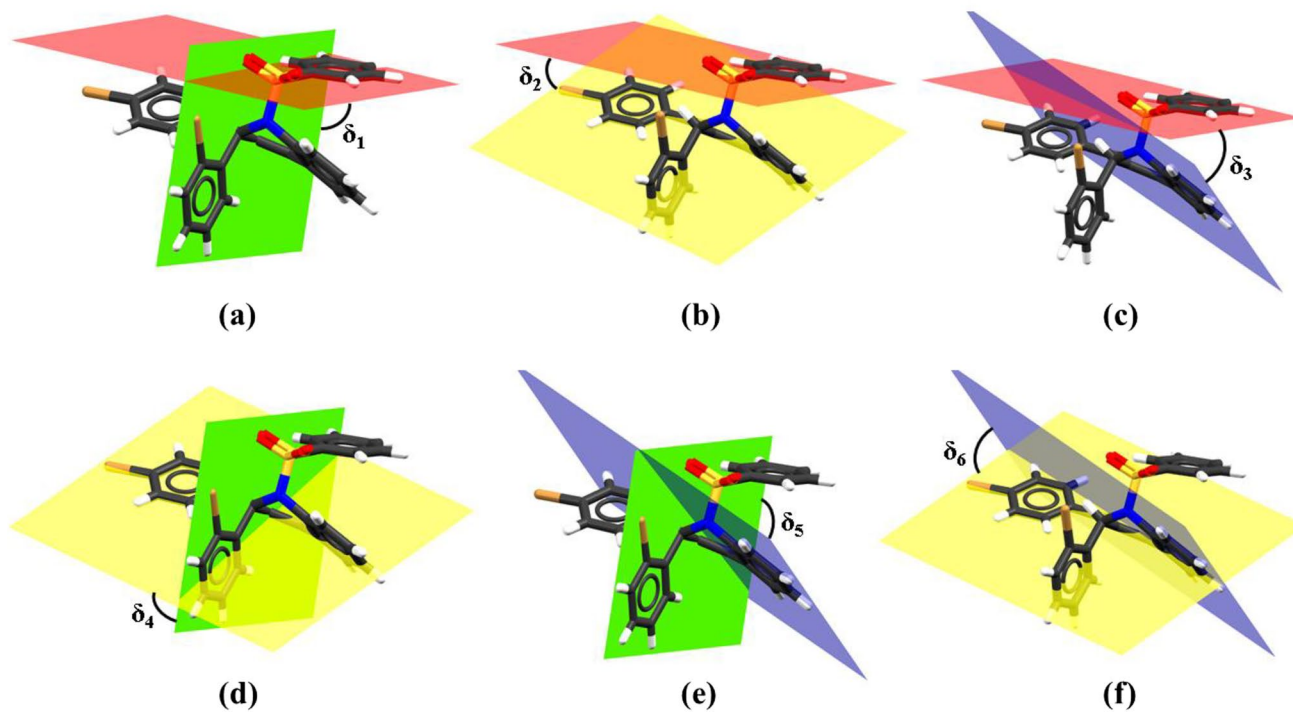
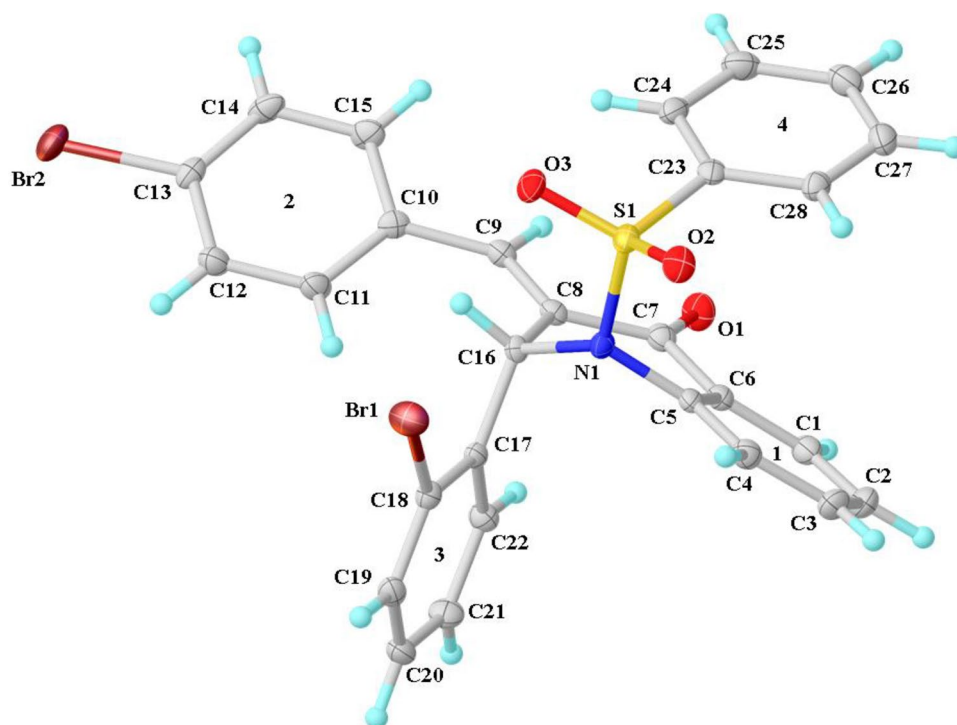


Fig. 2 Angles between the aromatic ring planes of QC. Aromatic ring 1 (blue plane), aromatic ring 2 (yellow plane), aromatic ring 3 (green plane), and aromatic ring 4 (red plane). The indicated angles

in the figure are $\delta_1 = 88.70^\circ$, $\delta_2 = 25.21^\circ$, $\delta_3 = 38.86^\circ$, $\delta_4 = 83.14^\circ$, $\delta_5 = 73.31^\circ$, and $\delta_6 = 58.21^\circ$

Fig. 3 Representations of the main QC interactions. C2–H2...Cg3 and C3–H3...O1 interactions in the a-axis direction (a); C1–H1...Br2 and C15–H15...O2 interactions in the b axis (b); C27–H27...O2 and C25–H25...O3 interactions in the c axis direction (c)

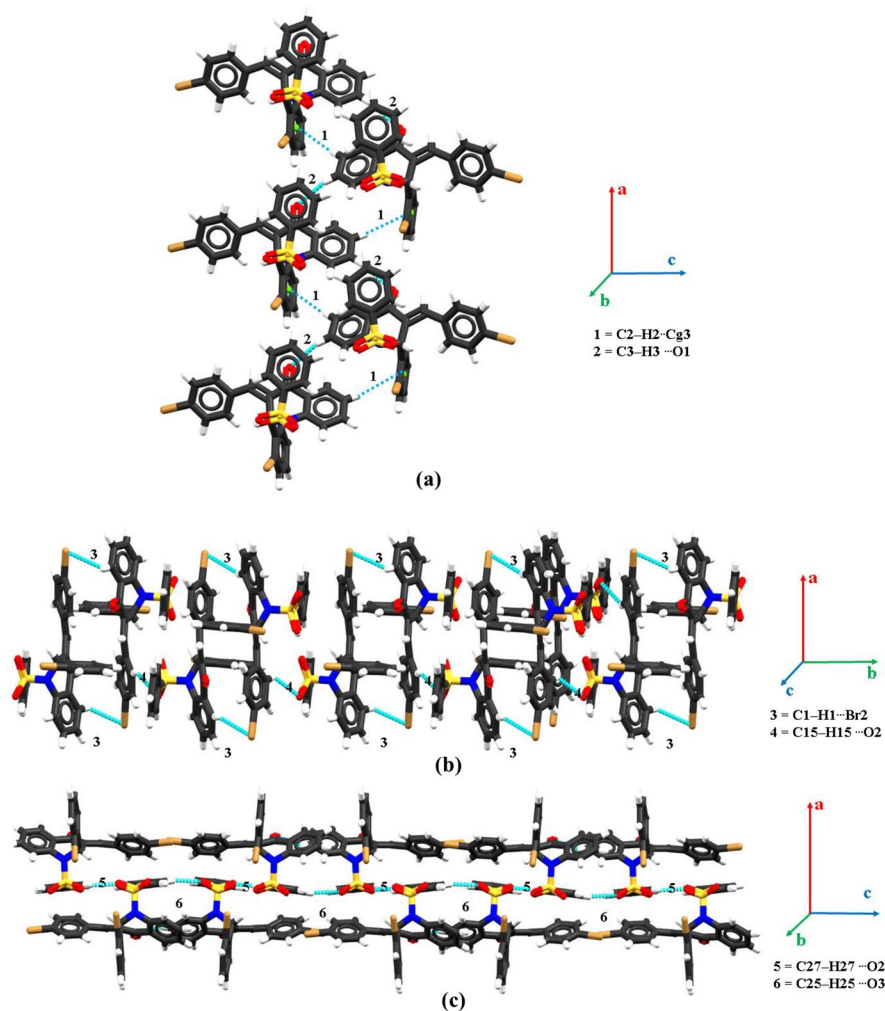


Table 2 Principal interactions for QC

D–H...A	d(D–H) Å	d(H...A) Å	d(D...A) Å	d(D–H...A) (°)	Symmetry code
C1–H1...Br2	0.949	3.041	3.782	136.02	1–x, 1–y, 1–z
C2–H2...Cg3	0.949	3.287	4.222	168.48	–1/2 + x, y, 3/2–z
C3–H3...O1	0.949	2.624	3.515	156.36	–1/2 + x, y, 3/2–z
C15–H15...O2	0.951	2.674	3.309	124.77	1/2 + x, 3/2–y, 1–z
C27–H27...O2	0.950	2.458	3.393	168.23	1/2 + x, y, 3/2–z
C25–H25...O3	0.950	2.409	3.251	147.54	1/2 + x, 3/2–y, 1–z

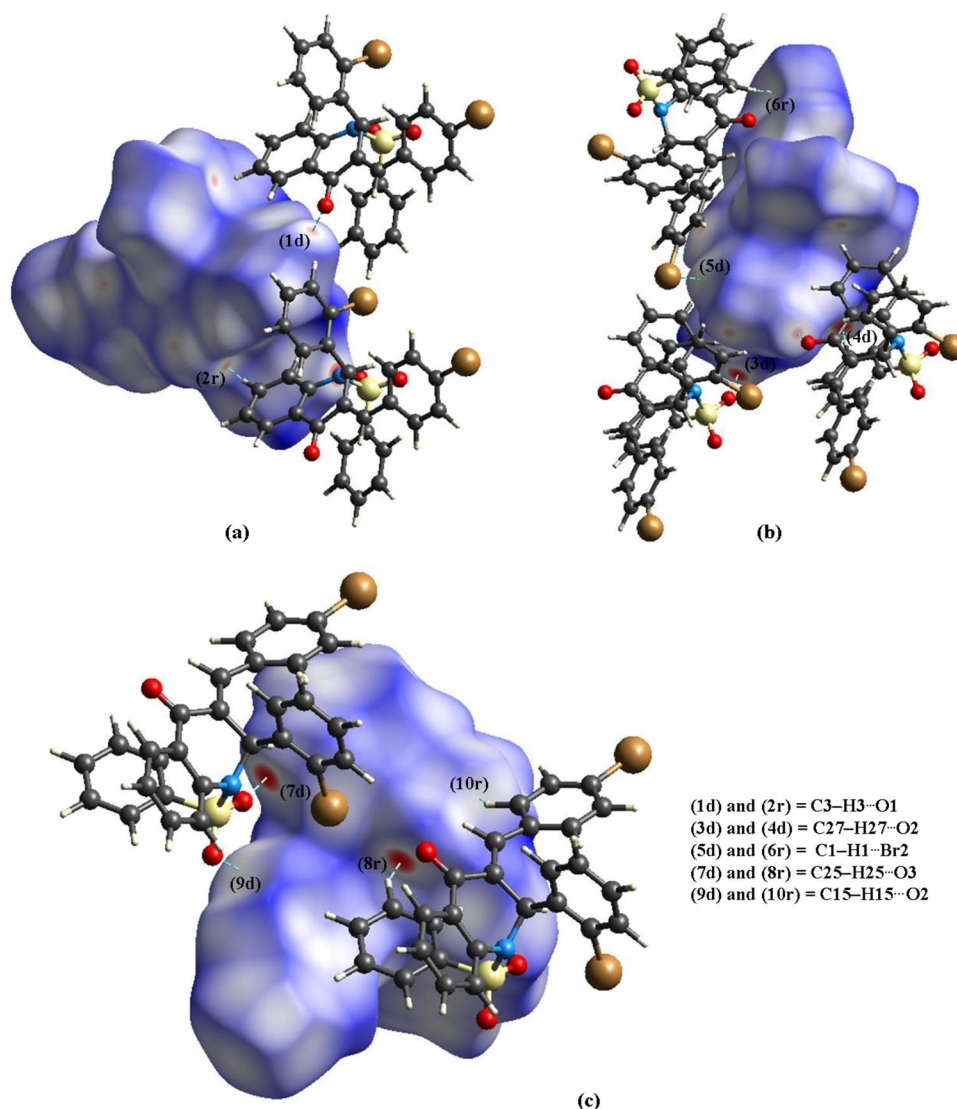
total interactions; C...H shows C–H... π interactions representing 21.6%; Br...H indicates interactions involving Br atoms representing 18.3%; and O...H contacts (16.1%) indicate the C–H...O interactions present around QC.

Theoretical analysis

The experimental values for geometric parameters were compared with theoretical and database values (Table 3). The theoretical results were obtained from optimization of QC in the gas phase, water, dichloromethane, ethanol, and

chloroform with energy minimization while the database values were obtained from the CCDC, considering mean values for 10,000 structures analyzed with Mogul [62] software. The relative differences between those values were calculated (Table S1). The theoretical results and CCDC database values are similar to the experimental values. The most considerable divergence between the experimental and theoretical values was to N1–S1 bond length; and the biggest difference (5.787%) was between the experimental and chloroform solvation C6–C7 bond length.

Fig. 4 Hirshfeld surface d_{norm} indicating interactions of QC. C3–H3...O1 interaction (a); C27–H27...O2 and C1–H1... Br2 interactions (b); C25–H25...O3 and C15–H15... O2 interactions (c)



The dihedral angles (Table 4) allowed a better understanding of the different conformations of the QC molecule in different solvents, and also present overlaps between the different conformations (Fig. 7). The conformation of the QC molecule with water solvent effect is the one that most diverges from the solid state and from the other optimizations; we can see the differences in the dihedral angles C8–C9–C10–C15 and C8–C9–C10–C1. In the benzene-sulfonamide group *tat*, we notice the greatest divergences (C5–N1–S1–C23, C16–N1–S1–C23: dihedral angles), as can be seen in Fig. 7b, f, g, h, and i (RMS: 1.766, 1.950, 1.900, 1.898, and 1.897, respectively). Additionally, the effect of the solvents ethanol, chloroform, and dichloromethane for the conformation of the QC molecule were very similar to each other (Fig. 7m, n, and o; RMS: 0.016, 0.007, and 0.009, respectively).

The representation of the HOMO and LUMO orbitals is similar for all conformations of the QC molecule (gas phase

and effect of solvents: water, dichloromethane, ethanol, and chloroform). The HOMO orbital is spread over the aromatic ring 2, Br2 atom, and part of the quinolone core, while the LUMO orbital is over the whole molecule except for aromatic ring 3 (Fig. 8). The HOMO energy characterizes the bonding orbital and ionization potential (nucleophilic character), and the LUMO energy characterizes the antibonding orbital and electron affinity (electrophilic character).

The HOMO energy calculated for gas phase is approximately -7.94 eV, LUMO is -1.85 eV, and GAP is 6.09 eV. For the effect of water solvent, the HOMO, LUMO, and GAP energy is -7.98 eV, -1.93 eV, and 6.05 eV, respectively. For dichloromethane, solvent effect is -7.99 eV, -1.98 eV, and 6.01 eV, for ethanol, solvent effect is -7.98 eV, -1.99 eV, and 5.99 , while for chloroform, solvent effect is -7.97 eV, -1.96 eV, and 5.98 eV, respectively. High GAP values suggest high kinetic stability, high excitation energies, and low chemical reactivity

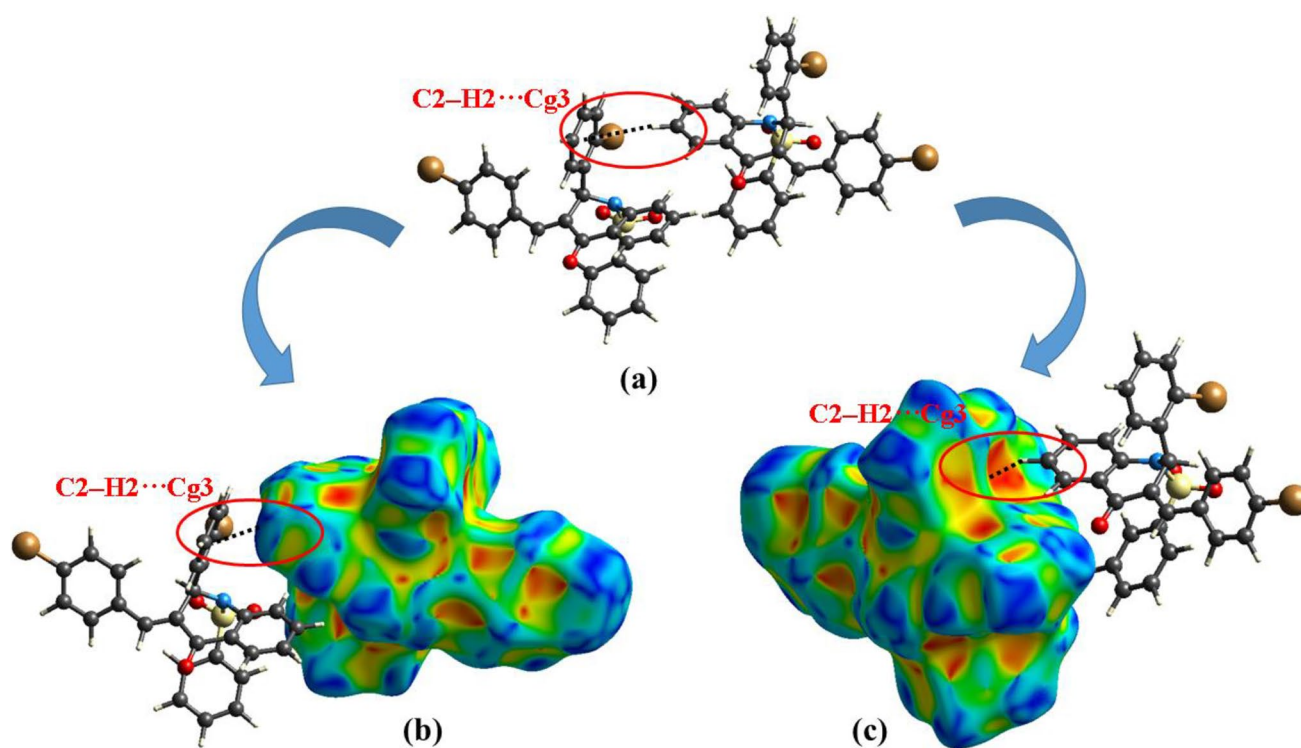


Fig. 5 Hirshfeld surface *shape index* evidencing interactions involving π -systems for QC. Representation C2-H2...Cg3 interaction without *shape index* surface (a). Representation C2-H2...Cg3 interaction

with *shape index* surface evidencing convex blue regions over C2-H2 (b). Representation C2-H2...Cg3 interaction with *shape index* surface evidencing concave red area over the aromatic ring (c)

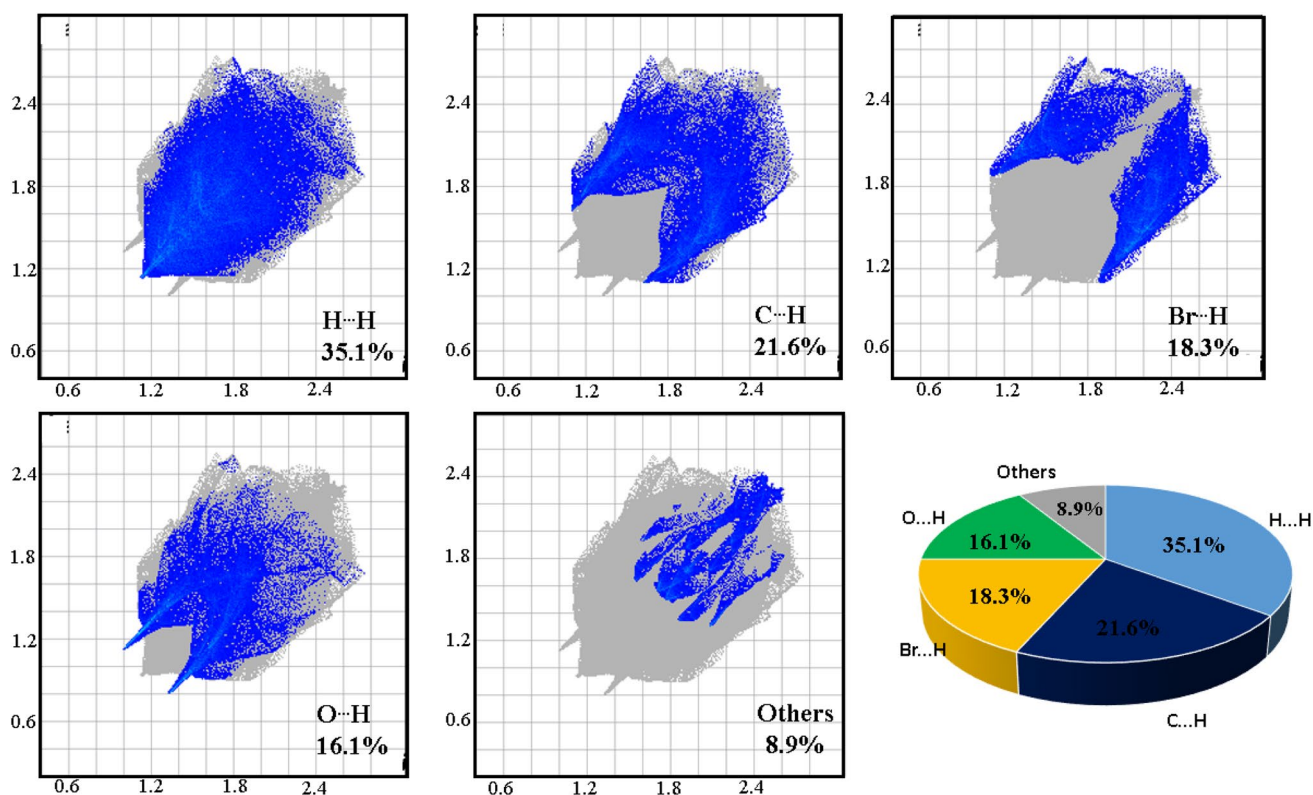


Fig. 6 Fingerprints with quantitative of the contacts for QC

Table 3 Experimental (X-ray), CCDC database, and theoretical bond lengths for QC

Atoms	X-ray (Å)	CCDC (Å)	Gas phase (Å)	Water (Å)	Dichloromethane (Å)	Ethanol (Å)	Chloroform (Å)
C1-C2	1.386	1.385	1.386	1.388	1.387	1.388	1.387
C2-C3	1.388	1.375	1.397	1.395	1.395	1.395	1.395
C3-C4	1.393	1.385	1.388	1.392	1.390	1.390	1.390
C4-C5	1.384	1.392	1.392	1.390	1.391	1.391	1.391
C5-C6	1.396	1.406	1.400	1.398	1.400	1.400	1.400
C6-C7	1.486	1.477	1.491	1.489	1.489	1.489	1.400
C7-C8	1.498	1.456	1.496	1.495	1.494	1.493	1.493
C8-C9	1.345	1.338	1.342	1.343	1.343	1.343	1.342
C9-C10	1.465	1.464	1.465	1.466	1.465	1.466	1.465
C10-C11	1.395	1.390	1.401	1.401	1.401	1.402	1.401
C11-C12	1.387	1.383	1.388	1.389	1.389	1.388	1.389
C12-C13	1.387	1.377	1.389	1.389	1.389	1.390	1.390
C13-C14	1.380	1.377	1.390	1.388	1.390	1.389	1.387
C14-C15	1.387	1.383	1.386	1.388	1.387	1.387	1.387
C15-C10	1.401	1.390	1.401	1.401	1.401	1.401	1.402
C8-C16	1.517	1.515	1.511	1.511	1.509	1.511	1.511
C16-C17	1.527	1.522	1.526	1.519	1.523	1.522	1.523
C17-C18	1.398	1.391	1.399	1.397	1.397	1.398	1.398
C18-C19	1.383	1.385	1.391	1.388	1.389	1.389	1.389
C19-C20	1.385	1.385	1.389	1.391	1.390	1.390	1.391
C20-C21	1.384	1.385	1.389	1.390	1.390	1.390	1.389
C21-C22	1.387	1.385	1.389	1.390	1.390	1.390	1.391
C22-C17	1.397	1.393	1.397	1.396	1.397	1.396	1.396
C23-C24	1.392	1.384	1.390	1.392	1.391	1.391	1.391
C24-C25	1.385	1.385	1.391	1.392	1.390	1.390	1.390
C25-C26	1.386	1.375	1.392	1.392	1.393	1.393	1.394
C26-C27	1.387	1.375	1.393	1.395	1.393	1.394	1.393
C27-C28	1.388	1.385	1.389	1.389	1.391	1.390	1.390
C28-C23	1.393	1.384	1.392	1.392	1.393	1.393	1.393
C7-O1	1.223	1.228	1.214	1.217	1.217	1.217	1.216
C13-Br2	1.897	1.898	1.877	1.880	1.879	1.880	1.879
C18-Br1	1.897	1.894	1.880	1.889	1.886	1.887	1.886
N1-C16	1.495	1.489	1.480	1.486	1.481	1.482	1.481
N1-C5	1.437	1.437	1.426	1.436	1.430	1.430	1.429
N1-S1	1.661	1.652	1.688	1.690	1.683	1.681	1.684
S1-O2	1.432	1.431	1.435	1.444	1.439	1.440	1.439
S1-O3	1.433	1.431	1.435	1.446	1.440	1.441	1.439
S1-C23	1.762	1.760	1.769	1.761	1.768	1.768	1.769

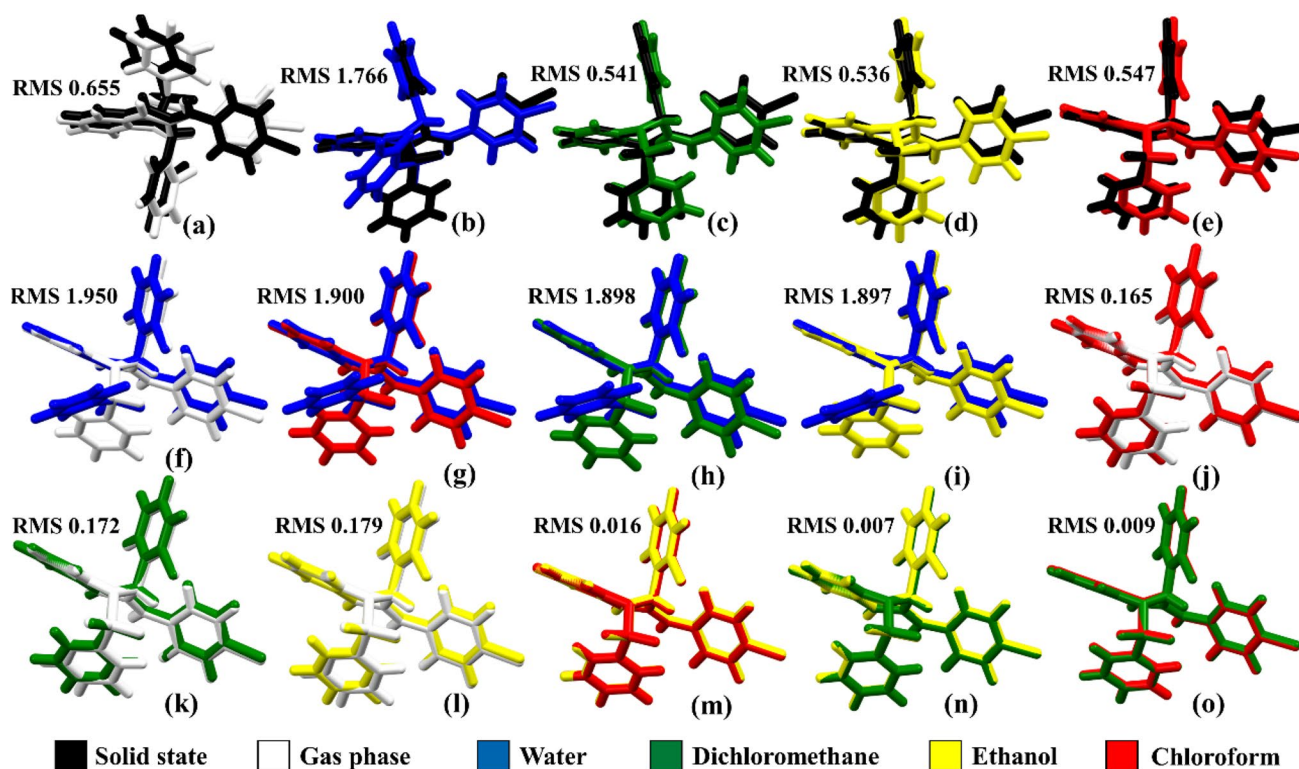
[52]. Hamama et al. [63] carried out a study with some quinolinone derivatives evaluating the antimicrobial activity and found GAP values ranging from 1.873 to 2.198 eV. Kumar et al. [64] evaluated quinolinone-appended chalcone derivative for anticancer activity, antitumor, and other therapeutic activities and found a GAP value of 2.92 eV. D'Oliveira et al. [65] evaluated different reactivity to glutathione and similar tumor cell toxicity to chalcones, and their quinolinone analogs presented the GAP values of 3.69 to 3.97 eV. Also, Khan [66] studied the antibacterial

activity of quinolinone-chalcone derivatives found 3.9 to 4.29 eV values. Furthermore, the GAP value found for QC (6.09–5.98 eV) indicates QC with greater kinetic stability than those found in the literature so far. However, Micheli et al. [67] and Raghunath [68] found GAP values for quinolinone derivatives comparable to QC.

The GAP values found for the different QC conformations are similar. The QC conformation in the gas phase is the most stable, followed by the conformation of the molecule in water solvent. According to the

Table 4 Experimental (solid state), gas phase, and effect solvents (water, dichloromethane, ethanol, and chloroform) for dihedral angles of QC

Dihedral angle (°)	Solid state	Gas phase	Water	Dichloromethane	Ethanol	Chloroform
C7-C8-C16-C17	34.50°	35.54°	35.54	35.29°	35.27°	35.27°
C8-C9-C16-C17	92.46°	92.27°	99.34°	100.48°	91.79°	91.66°
C8-C16-C17-C22	6.85	18.79°	18.79°	18.29°	18.30°	18.25°
C8-C16-C17-C18	5.57°	13.20°	13.20°	13.16°	13.14°	13.09°
N1-C16-C17-C22	28.33°	29.45°	29.45°	29.35°	29.30°	29.32°
N1-C16-C17-C18	65.37°	74.58°	74.58°	74.07°	74.08°	74.06°
C8-C9-C10-C15	154.38°	147.30°	33.01°	145.50°	145.44°	145.64°
C8-C9-C10-C11	15.16°	14.89°	152.57°	15.39°	15.46°	15.29°
C5-N1-S1-C23	52.47°	70.66°	70.66°	33.28°	62.73°	63.27°
C16-N1-S1-C23	88.40°	35.87°	35.87°	37.39°	75.46°	75.21°

**Fig. 7** Overlaps between the different conformations of QC according to the solvent effects. Overlap between solid state and gas phase (a), solid state and water (b), solid state and dichloromethane (c), solid state and ethanol (d), solid state and chloroform (e), water and gas phase (f), water and chloroform (g), water and dichloromethane (h),

water and ethanol (i), gas phase and chloroform (j), gas phase and dichloromethane (k), gas phase and ethanol (l), ethanol and chloroform (m), ethanol and dichloromethane (n), and dichloromethane and chloroform (o)

GAP values, the order of kinetic stability for QC is gas phase > water > dichloromethane > ethanol > chloroform.

The MEP map shows regions susceptible to nucleophilic or electrophilic attack. In the MEP map, red regions indicate negative sites where an electrophilic attack can occur, while blue regions indicate positive sites susceptible to nucleophilic reagents [35]. The MEP maps are similar for all QC conformations (Fig. 9), the positive sites are concentrated over hydrogen atoms, while the negative

ones are located over sulfur and oxygen atoms. Note that the region around the sulfonamide group (such as C15-H15...O2, C27-H27...O2, and C25-H25...O1) are the most susceptible to interactions with electrophiles [35]. The conformation of QC in water solvent showed the highest reactivity in the sulfonamide group (−1.81 eV), followed by the conformations in ethanol (−1.71 eV), dichloromethane (−1.66 eV), chloroform (−1.60 eV), and gas phase (−1.26 eV), respectively.

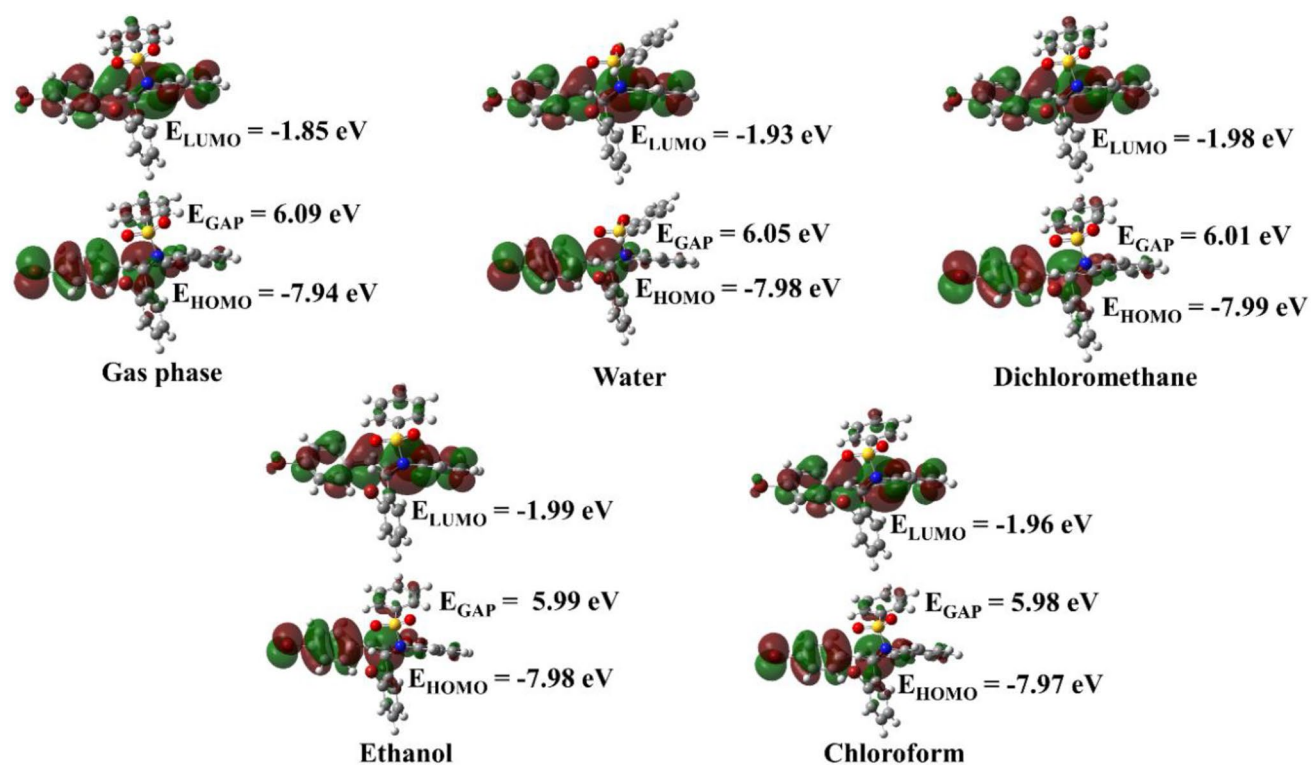


Fig. 8 Molecular orbitals HOMO and LUMO distribution and energy band-gaps for QC in different solvents

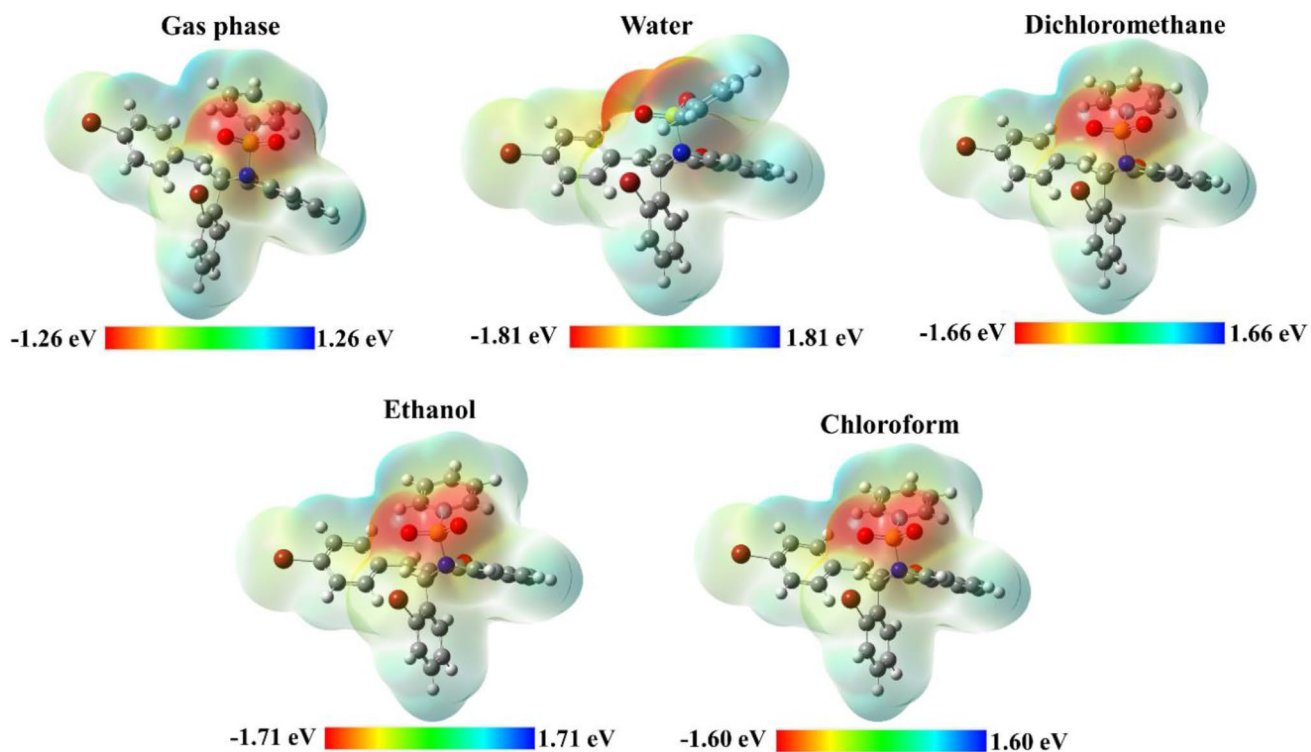


Fig. 9 MEP map for QC in different solvents

The QTAIM analysis presents parameters that contribute to characterizing an interaction. This analysis considers the electron density $\rho(r)$ in the critical point (CP), Laplacian of electron density [$\nabla^2\rho(r)$], eigenvalues of Hessian matrix (λ_1 , λ_2 , and λ_3), ellipticity of electron density (ϵ), the potential electron energy density ($V(r)$), the kinetic electron energy density ($G(r)$), and energy density ($H(r)$); these data are shown in Table 5. According to Popelier and other authors [69–71], some factors can be used to characterize an interaction, the presence of a continuous density path, and a critical point between the atoms involved in the interaction (acceptor and donor); at this critical point,

the electron density ($\rho(r)$) and the Laplacian of electron density ($\nabla^2\rho(r)$) should be in the range of 0.002–0.035 a.u. and 0.024–0.139 a.u., respectively.

The interactions described by geometric parameters and electron density were analyzed by QTAIM and all are following the expected range for electron density $\rho(r)$ (0.002–0.035 a.u.), as are the values of $\nabla^2\rho(r)$, except for the interaction C2–H2...Cg3 (0.01576 a.u.) (Table 5). All the interactions present a continuous density path and a critical point between donors and acceptors atoms (Fig. 10). The positivity values of $\nabla^2\rho$ for QC corroborate the nature of hydrogen bonds [70], and $\nabla^2\rho(r) > 0$

Table 5 Data from the topological analysis performed by the QTAIM methodology for QC. All data are in a.u.

BCP	$\rho(r)$	$\nabla^2\rho(r)$	λ_1	λ_2	λ_3	ϵ	$V(r_{bcp})$	$G(r_{bcp})$	$H(r)$	Interactions
1	0.00557	0.01576	−0.00396	−0.00279	0.02252	0.41493	−0.00262	0.00328	0.00065	C2–H2...Cg3
2	0.00644	0.02135	−0.00576	−0.00532	0.03244	0.08300	−0.00373	0.00453	0.00080	C3–H3...O1
3	0.00603	0.02144	−0.00410	−0.00260	0.02815	0.57654	−0.00305	0.00421	0.00115	C1–H1...Br2
4	0.00679	0.02852	−0.00601	−0.00485	0.03939	0.24020	−0.00443	0.00578	0.00134	C15–H15...O2
5	0.00912	0.03844	−0.00920	−0.00886	0.05651	0.03786	−0.00668	0.00814	0.00146	C27–H27...O2
6	0.00909	0.03840	−0.00917	−0.00884	0.05642	0.03817	−0.00666	0.00800	0.00140	C25–H25...O3

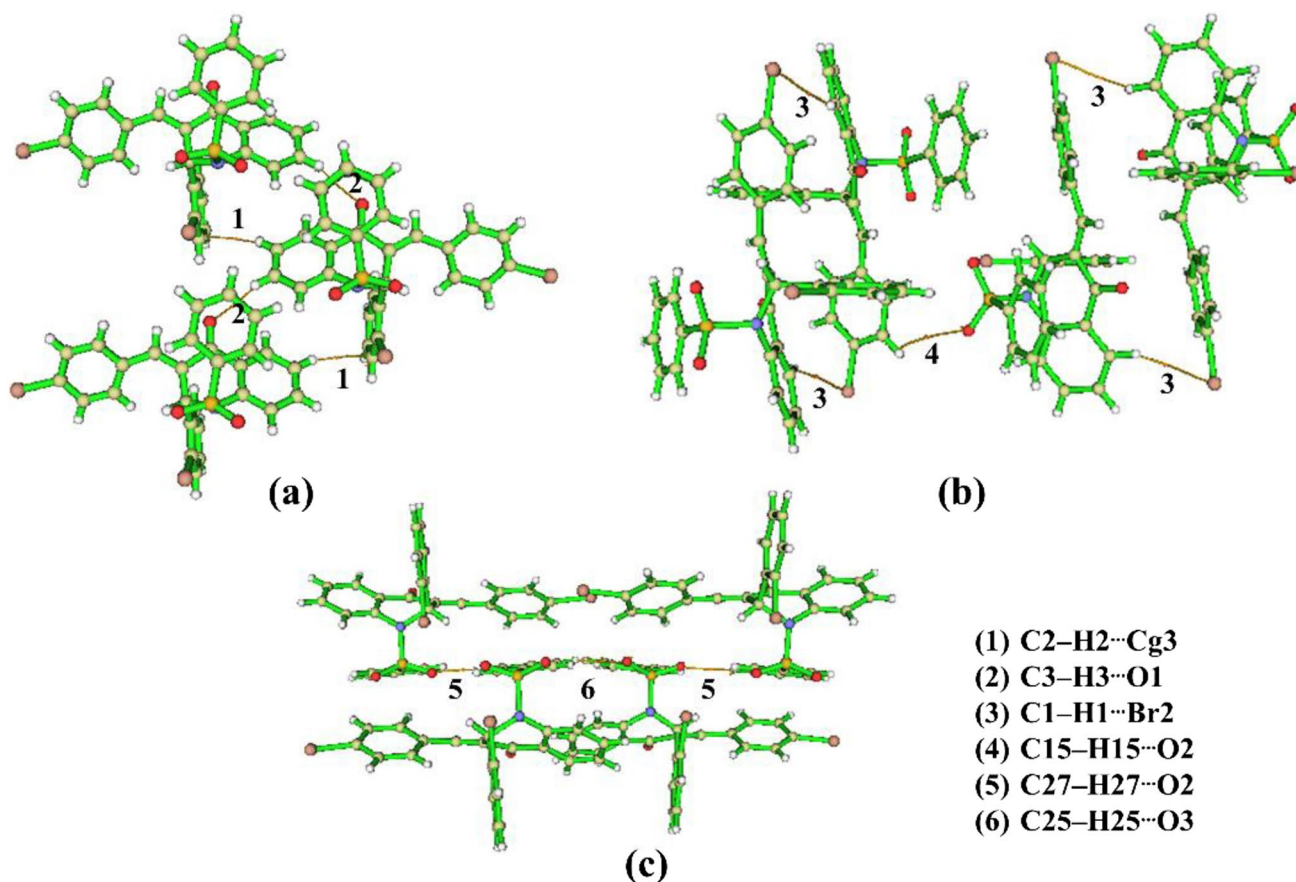


Fig. 10 Representation of critical points (CP) for QC

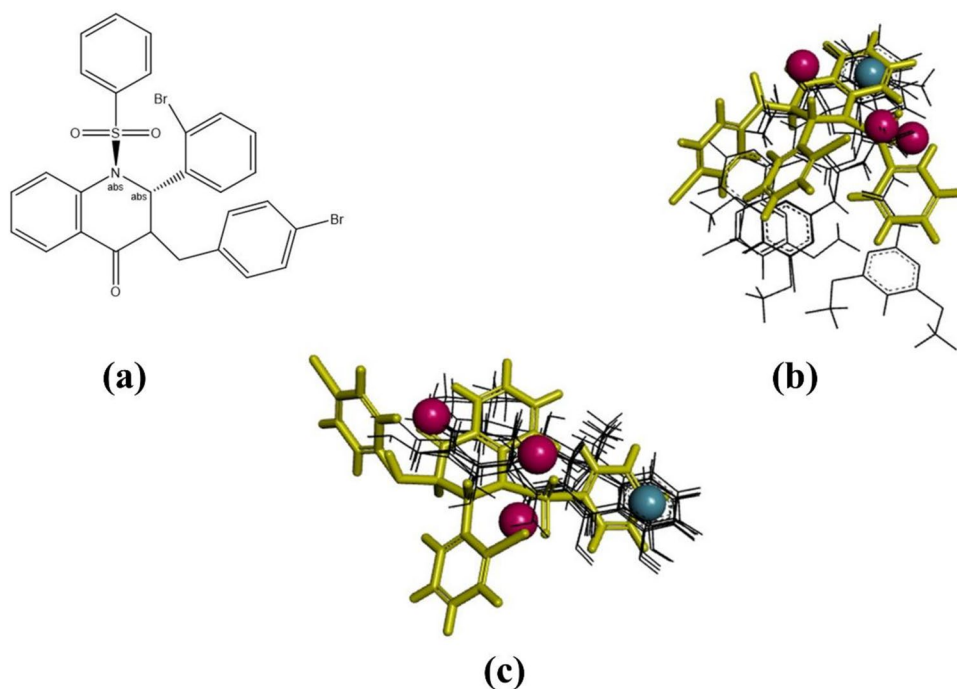
and $H(r) > 0$ indicate weak interactions with electrostatic character [53, 69]. The ellipticity ($\lambda_1/\lambda_2, 1$) can be understood as measure of the anisotropy of the curvature of the $\rho(r)$ and measure the extent to which density is preferentially accumulated, which can be used to investigate about the structural stability of a bond [71, 72]. The order of ellipticity for interactions of QC is $\epsilon(C1-H1 \cdots Br2) > \epsilon(C2-H2 \cdots Cg3) > \epsilon(C15-H15 \cdots O2) > \epsilon(C3-H3 \cdots O1) > \epsilon(C27-H27 \cdots O2) > \epsilon(C27-H27 \cdots O2)$. In terms of ellipticity, $C1-H1 \cdots Br2$, $C2-H2 \cdots Cg3$, and $C15-H15 \cdots O2$ interactions are harder to break. All these parameters are good indicators to confirm the existence of these interactions.

Pharmacophore models were tested with several categories of substances with agricultural applications from the evidence of the pesticide activity (herbicides, insecticides, fungicides, antibiotics, and fumigants) of molecules related to the quinoline compounds [9, 10, 73, 74]. The best models (with higher fit score and pharmacophore features shared between the structures) were obtained with the chlorimuron analogs and the tetracyclines (both categories with the compounds with the lowest IC_{50}) seen in Fig. 11. The model obtained with the chlorimuron analogs includes four pharmacophore features. Although there is a worldwide commercial success of chlorimuron and related compounds, the resistance of some strains and toxicity of these substances encourage a search for new alternatives [75]. Thus, QC rises as a compound with potential herbicide activity suggested by the pharmacophore results (3 points with hydrogen bond acceptors and one site with the aromatic feature) (Fig. 11b).

Figure 11c represents the pharmacophore model of QC with five tetracyclines molecules, and it can be observed that four features are shared in this set of compounds. The model with a higher fit score presented three hydrogen bond acceptors and one aromatic interaction. This result predicts QC as a potential antibiotic agent due to its spatial similarity with this antibacterial category. There is some evidence about the antibacterial activity of some related chalcone [76–78]; thus, the findings of this analysis reinforce the potential of the QC as a candidate antibacterial agent.

To further investigate the antibacterial potential of QC, and to confirm the similarity between QC and tetracycline suggested by our pharmacophoric fitting, we performed molecular docking simulations using the transcriptional regulator TtgR, which has the same multidrug recognition properties of *Pseudomonas putida* (*P. putida*) strain DOT-TIE [79]. This highly resistant *P. putida* strain achieves microbial evasion through the TtgABC efflux pump, which the main role is to extrude compounds that are harmful to the bacterial cell, such as antibiotics, flavonoids, and organic solvents. TtgABC is encoded by the gene *ttgABC*, which is efficiently downregulated by TtgR in the presence of effectors. A few examples of TtgR substrate/ effectors include chloramphenicol and tetracycline [80]. Tetracyclines are composed of a fused set of aromatic rings; and QC is structurally similar to tetracycline in that both share an aromatic core. This aromatic core is especially important for the recognition within TtgR active site: both QC and tetracycline's aromatic rings interact with the hydrophobic pocket formed by $\alpha 4$ – $\alpha 9$ in TtgR. In this context, we hypothesized that structurally

Fig. 11 Structure of QC (a), pharmacophoric fitting of QC to the chlorimuron and other 5 analogs (b), and fitting of QC to the tetracyclines (5 compounds) (c). Pharmacophore features are labeled with red (hydrogen bond acceptors) and blue (aromatic ring)



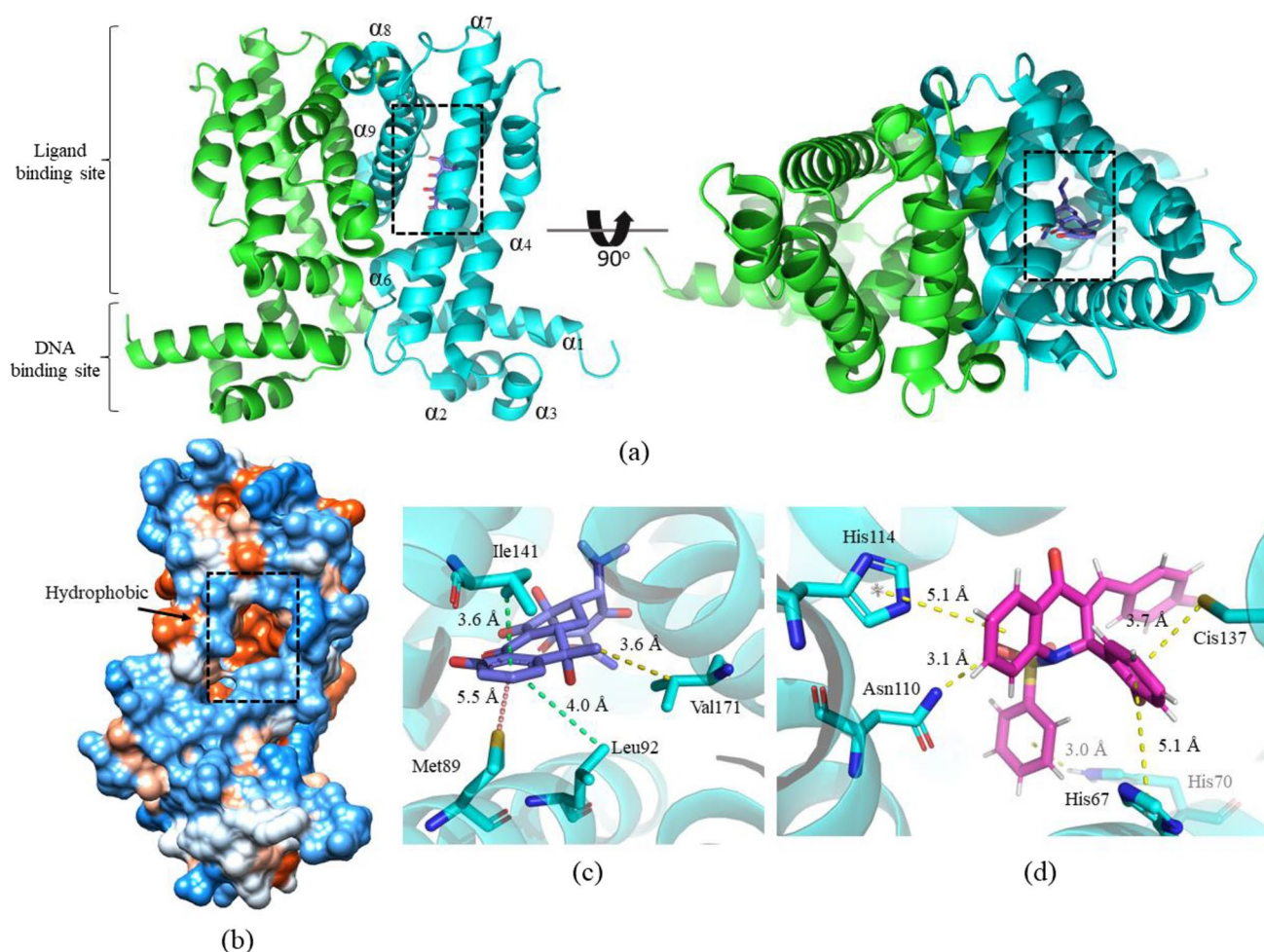


Fig. 12 Crystal structure of tetracycline complexed with homodimer TtgR, depicting the α helices and the binding domains they form (PDB 2UXO) (a); hydrophobic surface calculated using a TtgR mon-

omer showing the hydrophobic cleft formed by helices $\alpha 4$ – $\alpha 9$ (b); tetracycline (c) and QC (d) docked within the same active site

similar to tetracycline, QC would bind TtgR and indirectly inhibit TtgABC efflux pump.

Some structural features in TtgR are crucial for substrate binding and hence biological activity. TtgR is a homodimer composed primarily of α -helices, as shown in Fig. 12a, distributed in such a way to form two very distinct binding domains (ligand and DNA). The DNA binding site is formed by helices $\alpha 1$ – $\alpha 3$, while $\alpha 4$ – $\alpha 9$ compose the ligand binding sites. The tetracycline site is highly hydrophobic, which explains the relatively high binding affinity of TtgR to compounds harboring aromatic rings (Fig. 12b). To validate our docking methodology and quantify its binding affinity, we redocked the natural ligand tetracycline and compared its conformation to the native one, which yielded an RMSD of 1.41 Å. We found that tetracycline binds to TtgR with affinity -8.1 kcal/mol, interacting with Met89, Ile141, Leu92, and Val171 (Fig. 12c). Although located within the same cleft, QC interacts primarily with polar residues

His67, His70, His114, Asn110, and Cis137 (Fig. 12d). As expected, these amino acids interact with the numerous aromatic rings present in QC. The antibacterial potential of QC is evidenced in that it binds to TtgR with a higher affinity than tetracycline (-9.1 kcal/mol).

Conclusions

QC crystallized under orthorhombic space group *Pbca* and supramolecular arrangement is stabilized by C–H $\cdots$ O, C–H $\cdots$ π , and C–H $\cdots$ Br interactions. The theoretical analysis shows the electronic affinity predominates over the ionization potential characterizing electrophilic attacks on the sulfonamide region. The theoretical and CCDC results obtained are very close to crystallographic results, and the differences are due to the molecular environment between

the gas and solid phases. The theoretical gas phase model agrees well with the determined structure. In turn, the solid-state structure is in excellent agreement with previously reported similar structures. Pharmacophore analysis suggested two potential activities to QC as a candidate antibacterial and herbicide compound. By docking QC within the active site of TtgR, a transcription regulator for the efflux pump TtgABC from the highly resistant *Pseudomonas putida* (*P. putida*) strain DOT-TIE, we showed that the activation of TtgR relies upon the binding of aromatic-harboring compounds, which plays a crucial role in bacterial evasion. In this context, QC has a higher binding affinity than tetracycline, which suggests it might be a better effector for TtgR. Finally, the energy GAP indicates Kinect stability, the electrophilic activity of the sulphonyl group, and the arrangement of peripheral phenyl groups make this compound promising for biological activity.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00894-022-05140-9>.

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Author contribution Vitor S. Duarte: conceptualization, formal analysis, writing (original draft), writing (review and editing). Renata Layse G. de Paula: conceptualization, formal analysis, writing (original draft). Jean M. F. Custodio: conceptualization, revision, writing (original draft). Giulio D. C. D'Oliveira: synthesis, methodology, validation, writing (original draft), writing (review and editing). Leonardo L. Borges: methodology, validation, formal analysis, investigation, writing (original draft), writing (review and editing). Caridad Noda Pérez: synthesis, methodology, validation, writing (original draft), writing (review and editing). Pal Perjesi: conceptualization, formal analysis, writing (original draft). Allen G. Oliver: conceptualization, revision, writing (original draft). Hamilton B. Napolitano: conceptualization, investigation, resources, writing (original draft), writing (review and editing), supervision, and project administration.

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Data availability The datasets generated during and analyzed during the current study are available in the Cambridge Crystallographic Data Centre (CCDC), under the code 1,934,999 (<https://www.ccdc.cam.ac.uk/structures/>).

Declarations

Competing interests The authors declare no competing interests.

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A New Synthetic Route and Comprehensive Topological Study of a Benzimidazole Derivative

Vitor S. Duarte,^{1b}*,^{a,b} Raquel F. Naves,^{c,d} Adailton J. Bortoluzzi,^e Eduardo C. M. Faria,^{a,b}
Aline M. da Silva,^b Guilherme R. Oliveira,^c Christian G. Alonso^{1b}^c and
Hamilton B. Napolitano^{1b}^a

^aGrupo de Química Teórica e Estrutural de Anápolis, Universidade Estadual de Goiás,
75132-903 Anápolis-GO, Brazil

^bCentro de Pesquisa e Eficiência Energética, CAO A Montadora de Veículos LTDA,
75133-590 Anápolis-GO, Brazil

^cInstituto de Química, Universidade Federal de Goiás, 74690-900 Goiânia-GO, Brazil

^dInstituto Federal de Goiás, Campus Inhumas, 75402-556 Inhumas-GO, Brazil

^eDepartamento de Química, Universidade Federal de Santa Catarina,
88040-900 Florianópolis-SC, Brazil

Benzimidazole and its derivatives are molecules that have diverse biological properties, therefore we synthesized and studied a new benzimidazole to understand their physical/chemical properties. The compound was obtained through a new synthetic route, using graphite oxide, in the absence of solvent, with crystalline packaging supported by C–H...N and C–H... π interactions. According to the frontier molecular orbitals, the compound is kinetically stable while the molecular electrostatic potential map confirms the site of molecular interactions involving nitrogen atoms and the π -system. This comprehensive study on synthesis, structural description and theoretical calculations can support ongoing studies in pharmaceutical science.

Keywords: benzimidazole derivative, X-ray diffraction, supramolecular arrangement, QTAIM analysis

Introduction

Benzimidazole and its derivatives are widely studied due to their biological and clinical application. These compounds are heterocyclic formed from benzene and imidazole ring, and their structures are directly related to the planning and developing of drugs. The heteroaromatic bicyclic system of these compounds are described with biological activities, such as anti-inflammatory and anti-oxidant activity,¹⁻³ antimicrobial activities (antifungal, antibacterial, antimalarial, antiviral activity),^{4,5} potential antitumor,⁶ antiprotazoal agents,⁷ anti-ulcer, anti-hypertensive and antiparkinson,^{8,9} analgesic agents and others activities.^{5,10}

The chemical industry is an important provider of products and technologies for various pharmaceutical

sectors, and other industries such as pesticides, foods, and fuel additives. When developing new chemical compounds for industrial areas there are some desirable criteria that must be met, such as having a synthesis in less than five steps with an acceptable yield, solubility and purity.¹¹ Compounds that show a simple, low-cost, high-yield synthetic route are certainly promising as industrial products, such as the synthesis of benzimidazole derivative described in this work, which is carried out in the absence of a solvent and presents interesting aspects. In addition to the biological potential consolidated in the literature, several systemic fungicides involving benzimidazoles are marketed, such as benomyl,¹² thiophanate-methyl,^{13,14} carbendazim¹⁵ and carboxin¹⁶ while some commercial drugs involving different substituted benzimidazole derivatives also are used every day, such as thiabendazole,¹⁷ riluzole, omeprazole, lansoprazole, rabeprazole, and pantoprazole (Figure 1).

*e-mail: vitor.sduarte@seduc.go.gov.br

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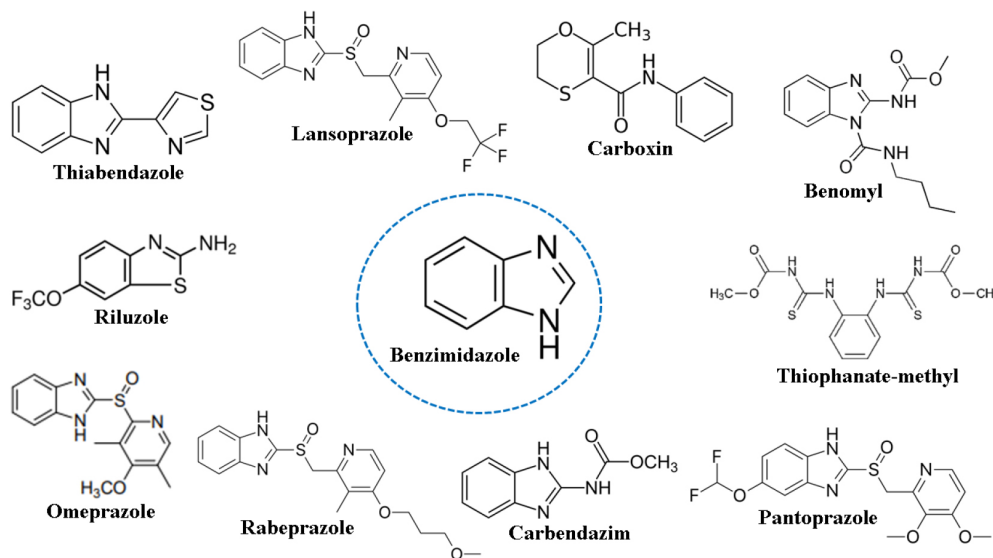


Figure 1. Benzimidazole core and some derived products.

The activity of a compound is linked to the chemical structure; therefore, studying this structure is extremely important, as well as understanding and developing more appropriate new synthetic routes. In this work we describe a new synthetic route for the 1-(2-methoxy-benzyl)-2-(2-methoxy-phenyl)-2,3-dihydro-1*H*-benzoimidazole (AM2), as well as its structural description, supramolecular arrangement analysis and theoretical calculations, to understand the physical/chemical properties of this compound and support ongoing application work in the pharmaceutical science.

Experimental

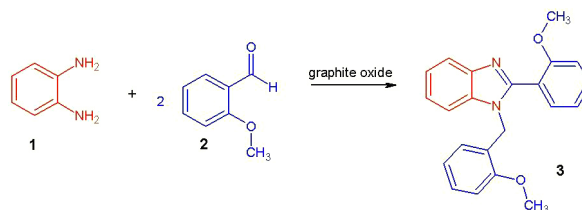
Synthesis and crystallization

In a round bottom flask, *o*-phenylenediamine (1 mmol) (**1**) and 2-methoxybenzaldehyde (2 mmol) (**2**) were stirred without solvent at 80 °C (Scheme 1). Then, 30 mg of graphite oxide was added to the mixture. The mixture was stirred for 30 min and monitored by thin layer chromatography (TLC, hexane:ethyl acetate, 3:1). After its conclusion, ethanol was added (10 mL) and the mixture was filtered by gravitation of an analytical funnel, separating the graphite oxide of the obtained product. The compost was then washed with water (5 mL) three times and subsequently recrystallized with remaining ethanol (10 mL), obtaining a white yellowish crystal.

1-(2-Methoxy-benzyl)-2-(2-methoxy-phenyl)-2,3-dihydro-1*H*-benzoimidazole (AM2)

Yield 86%; yellowish crystal; mp 153-155 °C; ¹H (500 MHz, CDCl₃) δ 7.87 (d, *J* 7.93 Hz, 1H), 7.56 (dd,

J 1.83 and 7.63 Hz, 1H), 7.47 (ddd, *J* 1.83, 7.63 and 8.24 Hz, 1H), 7.29 (ddd, *J* 1.83, 6.71 and 8.24 Hz, 1H), 7.24-7.19 (m, 3H), 7.07 (td, *J* 0.92, 7.63 and 7.63 Hz, 1H), 6.98 (d, *J* 8.24 Hz, 1H), 6.85 (d, *J* 7.63 Hz, 1H), 6.78 (td, *J* 0.92, 7.63 and 7.63 Hz, 1H), 6.72 (dd, *J* 7.63 and 1.53 Hz, 1H), 5.26 (s, 2H), 3.80 (s, 3H), 3.61 (s, 3H); ¹³C (500 MHz, CDCl₃) δ 157.6, 156.5, 154.4, 143.3, 135.5, 132.4, 131.4, 128.4, 127.7, 124.5, 122.4, 121.9, 120.8, 120.4, 119.8, 110.8, 110.7, 109.9, 55.2, 55.1, 43.5.



Scheme 1. Synthesis of AM2.

Crystallographic and Hirshfeld analysis

The model of the crystalline structure was determined by X-ray crystallography with data collected using a Bruker APEX-II CCD diffractometer (monochromator graphite Mo K α radiation and $\lambda = 0.71073$ Å). The structure was solved by the SHELXT^{18,19} software and refined with ShelXL²⁰⁻²² using full-matrix least-squares. The non-hydrogen atoms were refined with anisotropic thermal displacement parameters²¹ while hydrogen atoms were geometrically positioned and fixed according to the riding-hydrogen model with 0.98 Å for methyl groups, 0.99 Å for methylene groups and 0.95 Å for aromatic groups.²³ The molecular representations were generated by Olex2,²⁴ CrystalExplorer²⁵ and Mercury²⁶ software.

The intermolecular interactions for AM2 were analyzed using geometric parameters and confirmed by electronic density by Hirshfeld surfaces (HS) analysis using CrystalExplorer17²⁵ software. The Hirshfeld surfaces were generated from the X-ray data, representing the frontier between regions where the electron distribution is dominated by the contribution of the interior molecule and the neighboring. These surfaces are bases of the normalized contact distances (d_e : distance from the surface to the nearest atom in the molecule itself; d_i : distance from the surface to the nearest atom in another molecule).²⁷⁻²⁹ In addition, the Hirshfeld analysis allows us to understand the quantitative of the interactions and the empty space in the crystalline structure. The fingerprint is a graph constructed from the distances of d_e versus d_i and indicates the quantitative contribution of the contacts present in the molecule.³⁰ The empty spaces (voids) of the molecule were also calculated. To perform the calculations, the isosurfaces of the electron density of a procrystal equal to 0.002 a.u. were used. Said isosurface contains approximately 98% of the electrical charges of a molecule and determines the volume of the voids.^{31,32} Total crystallographic data for AM2 molecule was deposited in the Cambridge Crystallographic Data Centre (CCDC)³³ under the code 2091809.

Computational procedures

Theoretical calculations for AM2 were carried out using density functional theory (DFT)³⁴ through experimental parameters obtained from the X-ray data. The geometry was optimized in the gas phase using the Gaussian09³⁵ software. The level of theory used was M06-2X/6-311++G(d,p).³⁶⁻³⁸ This level of theory considering the electronic correlation,^{39,40} and is indicated for noncovalent interactions.^{36,41} From the results and generated wave function, the frontier molecular orbitals (FMO), the molecular electrostatic potential map (MEP) and topological analysis by quantum theory of atoms in molecules (QTAIM) were done. In order to identify the reactive regions of the AM2 molecule, the MEP calculation was performed; this map is constructed based on the potential of atomic nuclei and electrons, according to the equation:

$$V(\mathbf{r}) = \sum_{\alpha} \frac{Z_{\alpha}}{|\mathbf{r}_{\alpha} - \mathbf{r}|} - \int \frac{\rho(\mathbf{r})}{|\mathbf{r}_{\alpha} - \mathbf{r}|} d\mathbf{r} \quad (1)$$

where, Z_{α} is the charge on nucleus α , $V(\mathbf{r})$ is a potential created at a point $\mathbf{r}$ and the first term of summation is the electrostatic potential created by the nucleus. The second term is the electrostatic potential created by electrons.⁴²

The topological analysis were carried out by QTAIM methodology that is based on the mechanical-quantum concepts.⁴³⁻⁴⁶ Bader^{44,45} developed a theory that describes the atomic behavior in a molecule. In this theory, the observable properties are present in its molecular electron density $\rho(\mathbf{r})$. From this density, numerical integrations are executed with the gradient vector $\nabla\rho(\mathbf{r})$. These observables allow us to define chemical bonding as a bonding path (BP) which has a critical point (CP) that through defined parameters can indicate the existence of an interaction.^{45,47} For topological analysis of the interactions, the generated wave function was loaded into the Multiwfn⁴⁸ software.

Results and Discussion

Synthesis and solid-state description

The synthesis for AM2 occurs in the presence of different conditions, obtaining yields above 85%. Graphite oxide, a carbonaceous compound with acidic sites, is used as a catalyst for the synthesis of AM2. Thus, AM2 occurs in the absence of solvent, occurring at 80 °C, and within a time interval of 60 min. Therefore, obtaining AM2 in the presence of graphite oxide presents a simple synthetic route in the absence of solvent and being recrystallized only with ethanol. According to the geometric parameters of the unit cell, the AM2 crystallized under monoclinic space group P2₁/c with two molecules in the asymmetric unit and eight molecules in the unit cell. AM2 compound presents 2 methoxy groups in each molecule, both in the *ortho* position. All this data was obtained by X-ray diffraction and elucidated by the crystallographic methodology (Table 1) and Oak Ridge Thermal-Ellipsoid Plot (ORTEP) representation for this molecule is presented in Figure 2.

The asymmetric unit of AM2 has two molecules, however, conformer **1** does not overlap with conformer **2** (Figure 3). The conformers have a torsion in the aromatic ring regions A, A' and C, C'. Aromatic ring A from conformer **1** has a difference of 78.43° to aromatic ring A' from conformer **2**, while aromatic ring C from conformer **1** has a difference of 42.72° to aromatic ring C' from conformer **2**.

The supramolecular arrangement of AM2 is stabilized only by weak interactions, such C–H...N and C–H... π (Figure 4). However, these interactions have been described by several authors as significant in crystal packing.⁴⁹⁻⁵⁹ The interactions C18–H18...N2, C1–H1c...N2, C1'–H1a'...N2' and C3'–H3'...N2' contributing to growth of the crystal in the [001] direction, while the C5–H5...CgB' interaction contributed to [010] direction and C17–H17...CgC and

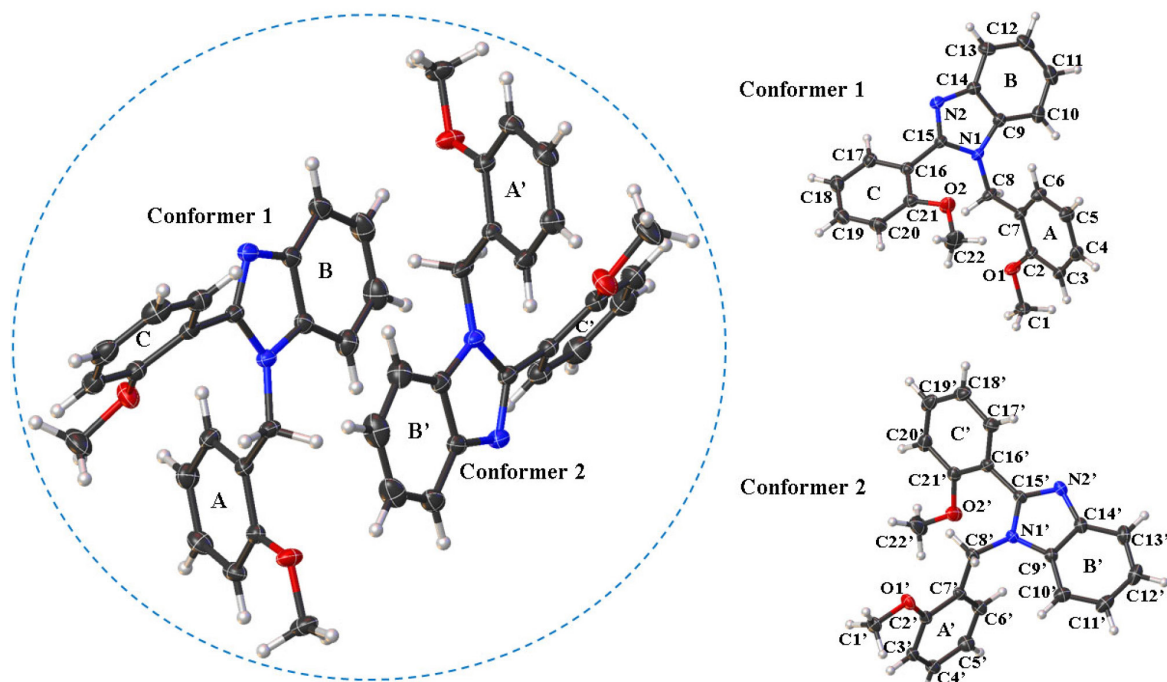


Figure 2. ORTEP representation of AM2 with ellipsoids at 50% of probability.

Table 1. Crystallographic refinement data for AM2

Molecular formula	(C ₂₂ H ₂₀ N ₂ O ₂) ₂
Formula weight / (g mol ⁻¹)	344.40
Temperature / K	150(2)
Wavelength / Å	0.71073
Radiation type	Mo Kα
Crystal system, space group, Z	monoclinic, P2 ₁ /c, 8
Unit cell dimensions / Å	a = 19.5627(17) b = 10.3557(8) c = 20.1999(18)
Unit cell dimensions / degree	α = 90 β = 118.87(2) γ = 90
Volume / Å ³	3583.3(5)
Calculated density / (g m ⁻³)	1.277
Absorption coefficient / mm ⁻¹	0.083
F(000)	1456
Refinement method	full-matrix least-squares on F ²
Goodness-of-fit on F ²	1.042
Final R indices [I > 2σ(I)]	R ₁ = 0.0521; wR ₂ = 0.1211
R indices (all data)	R ₁ = 0.0818; wR ₂ = 0.1391

Z: formula unit *per* unit cell; F(000): structure factor in the zeroth-order case; F²: squared structure factor; R₁: R-value; I > 2σ(I): observed reflection criteria; wR₂: R-value for F².

C1–H1b...CgC interactions contributed to [010] and [100] directions. The data of these interactions is shown in Table 2.

The interactions of AM2 were characterized from the geometric parameters with X-ray data and confirmed from

the electronic density by HS analysis. The interactions involving H...N are shown in Figure 4a and confirmed by HS dnorm (Figure 4b). In this surface, red spots indicate the regions where interactions can occur. Represented intermolecular contacts are smaller than the sum of van der Waal radius (vdW). According to the geometric parameters the C18–H18...N2 and C3'–H3'...N2' interactions present the shorter distances [d(H...A), d(D...A) Å] and the HS dnorm analysis of the regions (1) and (4) indicate stronger interactions.

The C–H...π interactions presented in AM2 also contributed to crystal packing, despite their weak nature (1.0–2.5 kcal mol⁻¹).^{60–64} These interactions were described by geometric parameters and confirmed by HS shape index (Figure 5), in which blue convex regions on C–H atoms and red concave regions on aromatic rings systems indicate the location of these interactions.^{28,29} In the Figure 5a the C17–H17...CgC and C1–H1b...CgB' interactions are confirmed by blue convex region over the atoms C17–H17 while red concave region over aromatic ring CgC. Additionally, Figure 5b evidences the C5–H5...CgC interaction with blue convex region over the atoms C5–H5 and red concave region over aromatic ring CgB'.

From the characterization of the interactions present for the stability of AM2, we performed the percentage quantification of the contribution of these interactions. For this analysis, the fingerprint is able to indicate the percentage of each interaction presented in the molecule. In the 2D-fingerprint plot for the AM2 (Figure 6a), the presence

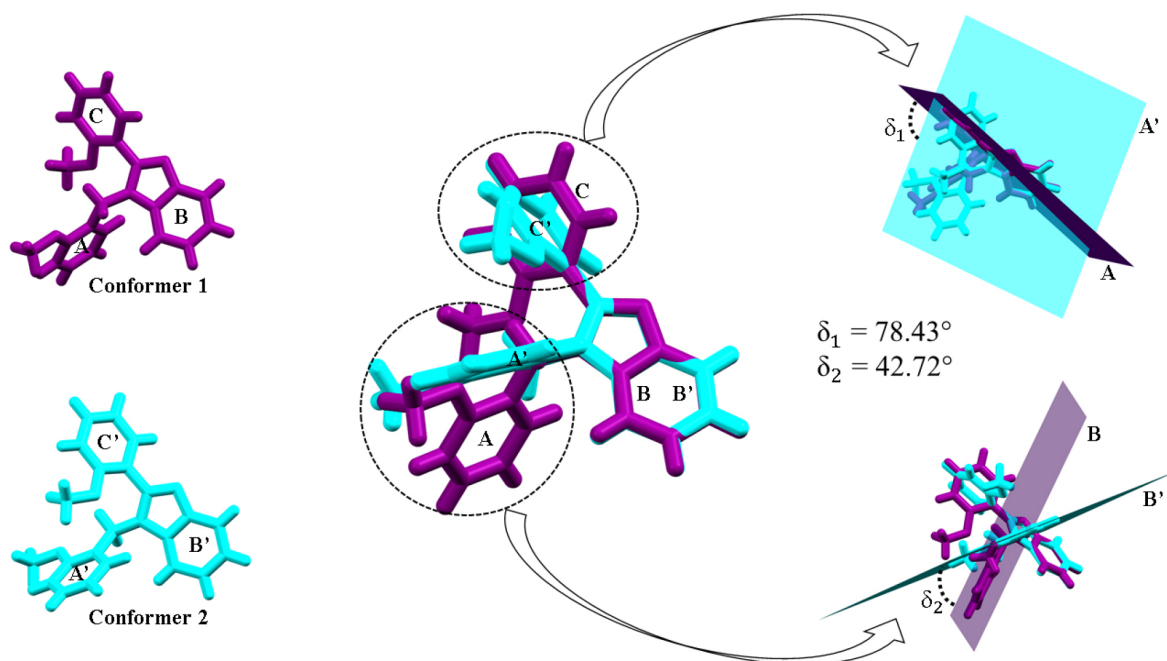


Figure 3. Overlap between conformers 1 and 2 of AM2.

Table 2. Observed interactions for AM2

D-H...A	d(D-H) / Å	d(H...A) / Å	d(D...A) / Å	d(D-H...A) / degree	Symmetry code
C3'-H3'...N2'	0.950	2.586	3.459	152.95	x, 1/2 - y, 1/2 + z
C1'-H1a'...N2'	0.980	2.657	3.407	133.63	x, 1/2 - y, 1/2 + z
C18-H18...N2	0.950	2.568	3.451	154.73	x, 3/2 - y, 1/2 + z
C1-H1c...N2	0.980	2.742	3.522	136.91	x, 3/2 - y, 1/2 + z
C1-H1b...CgB'	0.980	3.253	4.221	169.99	-x, 1-y, 1-z
C5-H5...CgC	0.950	3.310	3.886	121.06	x, 3/2 - y, 1/2 + z
C17-H17...CgC	0.950	3.616	4.373	138.52	-x, -1/2 + y, 1/2 - z

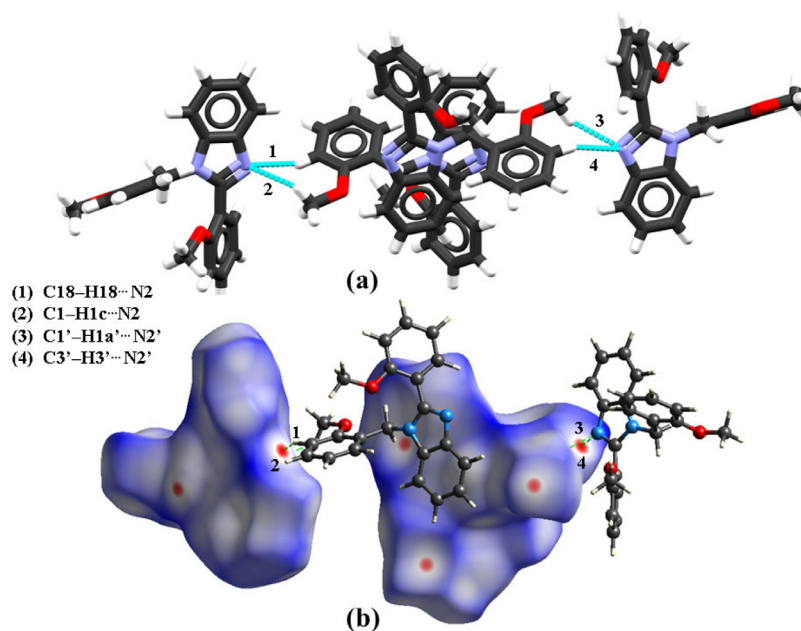


Figure 4. Representation of the interactions presents in AM2.

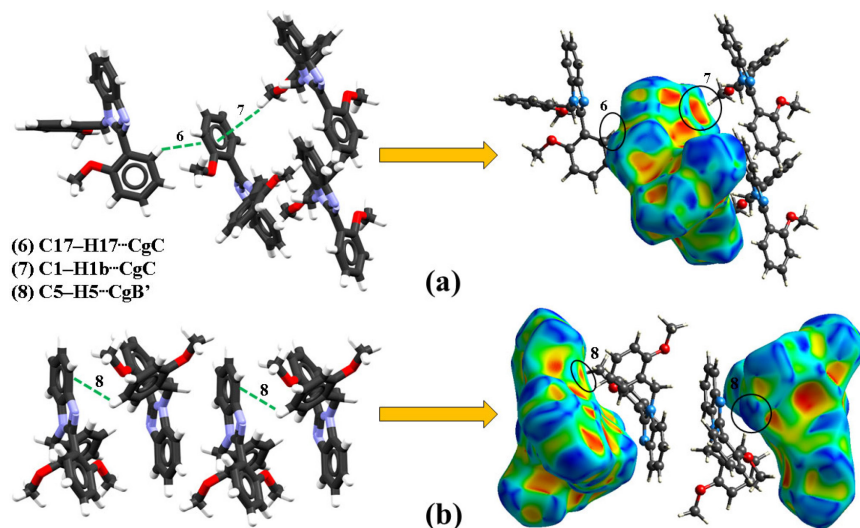


Figure 5. HS shape index of the C-H... π interactions presented in AM2.

of pseudo-mirrored peaks in region 1.0(d_e , d_i)-1.2(d_e , d_i) indicate contacts involving hydrogens (H...H) representing 62.1% of contacts in AM2. Additionally, 1.4(d_e) with 1.0(d_i) and 1.4(d_i) with 1.0(d_i) indicate C-H...N interactions (H...N) corresponding to 6.4% whereas C-H... π interactions, which are represented by H...C, are 26.9% of the interactions. These interactions represented 95.4% of the total structural stability of AM2. The packing of the crystalline structure presents eight molecules in the unit cell. Figure 6b shows the packing of the unit cell and the voids. These voids correspond to the empty space existing in the crystalline structure and were calculated from the electronic density of the spherical atom model. The calculated volume of the voids was 439.11 Å³, corresponding to approximately 12.25% of the unit cell. Note that there is little empty space in AM2; there are no large cavities, and the electron-density iso-surfaces are not completely closed around the

components, being open in the regions that molecular interactions are found, e.g., C-H...N and C-H... π .

Molecular modeling analysis

The highest occupied molecular orbital (HOMO) orbital for AM2 is located on aromatic rings B and C (conformer **1**) or B' and C' (conformer **2**) while lowest unoccupied molecular orbital (LUMO) orbital is located close to the aromatic ring A (conformer **1**) and aromatic ring A' (conformer **2**) (Figure 7). The LUMO orbitals are characterizing π^* antibonding, their energies are negative confirmed that these regions are electrophilic subject to accept electrons in a chemical reaction, while HOMO orbital characterizing nonbonding orbital, which is characteristic of the nucleophilic region.^{65,66} The GAP energy, defined as $GAP = E_{LUMO} - E_{HOMO}$, is an important

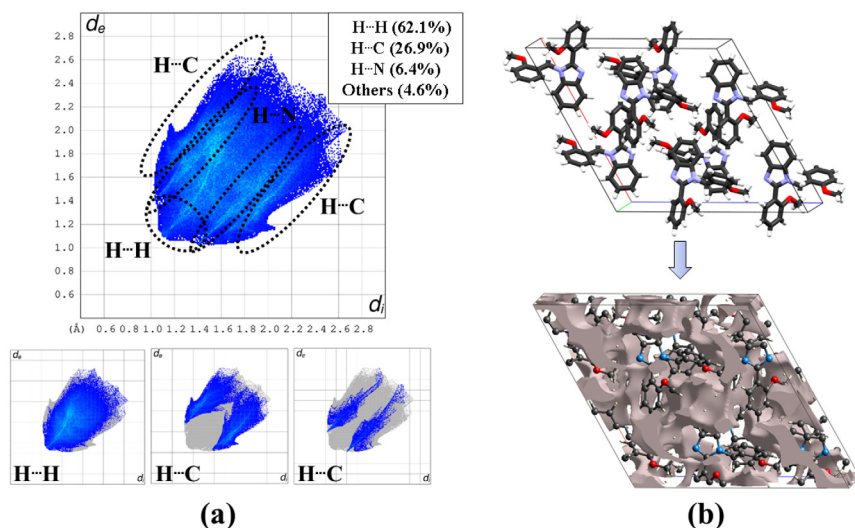


Figure 6. Fingerprint with quantitative of the contacts for AM2 (a). Packing of the unit cell and the voids presents in AM2 (b).

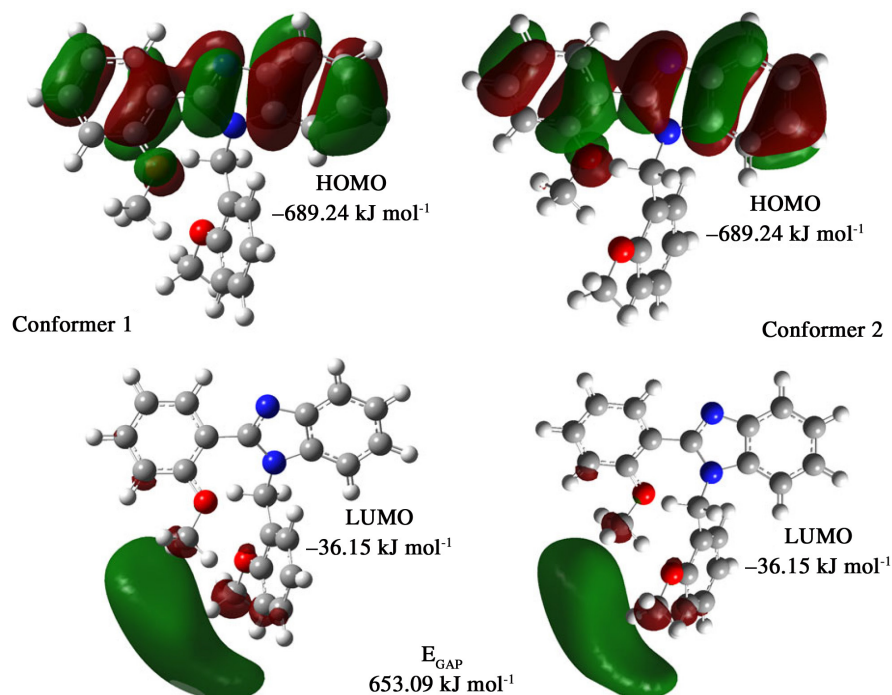


Figure 7. Frontier molecular orbitals (HOMO/LUMO) for AM2.

indicator of the kinetic stability and chemical reactivity of the molecule.⁶⁶ High GAP values suggest high kinetic stability and high excitation energies, whereas low GAP values suggest high chemical reactivity.⁶⁶ The energy GAP calculated for AM2 is 653.09 kJ mol⁻¹. According to said parameter, in comparison with same class molecules,⁶⁷⁻⁸¹ AM2 is presented kinetically stable.

In the MEP map (Figure 8) blue colors (positive values) indicate regions susceptible to electrophilic attacks due to the low electron density while red colors (negative values) indicate regions susceptible to nucleophilic attack due to the high electron density.^{42,82,83} On the N2 and N2' atoms, conformer **1** and **2**, respectively, the MEP energy is about -160 kJ mol⁻¹ for both. According to this interpretation, the nitrogen sites of AM2 susceptible to nucleophilic

attack, correspond to the C3'-H3'...N2', C1'-H1a'...N2', C18-H18...N2 and C1-H1c...N2 interactions described by geometrical parameters and electronic density. The aromatic rings B and C (conformer **1**) and B' and C' (conformer **2**) have MEP energy at about -8.53 kJ mol⁻¹ (aromatic rings B and B') and -7.74 kJ mol⁻¹ (aromatic rings C and C') which corresponds to the locations of the C1-H1b...CgB', C5-H5...CgC and C17-H17...CgC interactions. The regions of nucleophilic attack can be ranked as follows: N2 and N2' > aromatic ring B and B' > aromatic ring C and C'.

The QTAIM analysis provided insights of the C-H...N interactions investigating the properties of bonding critical point (BCP). These properties are electron density $\rho(\mathbf{r})$ at critical point, Laplacian of electron density $\nabla^2\rho(\mathbf{r})$,

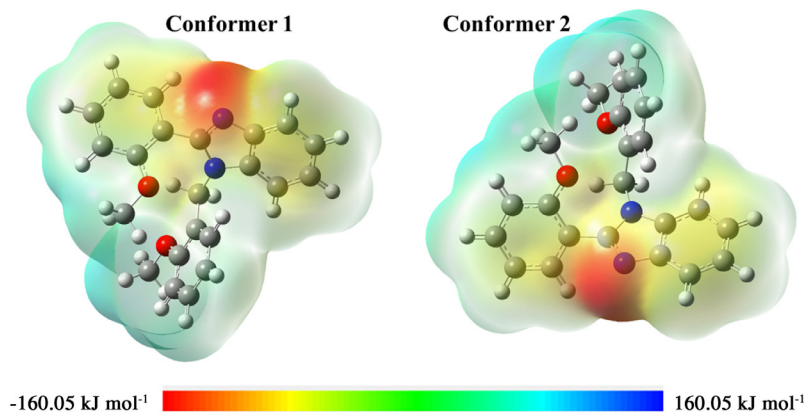


Figure 8. MEP map for AM2.

eigenvalues of Hessian matrix (λ_1 , λ_2 and λ_3), ellipticity of electron density (ε), potential electron energy density $V(\mathbf{r})$, kinetic electron energy density $G(\mathbf{r})$ and energy density $H(\mathbf{r})$, as shown in Table 3. QTAIM analysis has been used to describe a series of interactions (dihydrogen bonding,⁸⁴⁻⁸⁸ C–H...O interactions⁸⁹⁻⁹³ and classical hydrogen bondings,⁹⁴⁻⁹⁷ halogen bondings,⁹⁸⁻¹⁰⁵ π -systems interactions,¹⁰⁶⁻¹⁰⁸ interactions involving Se atoms^{109,110} and C–H...N interactions).¹¹¹⁻¹¹⁶ According to Popelier and Koch^{84,90} and others authors^{117,118} some criteria in the QTAIM analysis are necessary to characterize an interaction, such as a continuous density path with a critical point (CP) between acceptor and donor atoms, electron density $\rho(\mathbf{r})$ in the critical point in range of 0.002-0.035 a.u. and $\nabla^2\rho(\mathbf{r})$ in range of 0.024-0.139 a.u. All the C–H...N interactions of AM2 analyzed have a continuous density path between donor and acceptor atoms, as well as the presence of a CP between them (Figure 9). The values of $\rho(\mathbf{r})$ in the CP for all interactions are in the expected range, as are the values of values of $\nabla^2\rho(\mathbf{r})$, except for interaction C1'–H1a'...N2' (0.02045 a.u.), which has a slight deviation.

The indicators $\nabla^2\rho(\mathbf{r}) > 0$ and $H(\mathbf{r}) > 0$ suggest that the analyzed interactions are weak interactions with closed-shell character.^{46,118} The ellipticity ($\varepsilon = \lambda_1/\lambda_2 - 1$) is defined as a measure of the anisotropy of the curvature of the $\rho(\mathbf{r})$ and the extent to which the charge is preferentially accumulated, and can be used to investigate about the structural stability of a bond.^{90,119} The order of

ellipticity for these interactions is $\varepsilon(\text{C1}'\text{--H1a}'\cdots\text{N2}') > \varepsilon(\text{C1}\text{--H1c}\cdots\text{N2}) > \varepsilon(\text{C18}\text{--H18}\cdots\text{N2}) > \varepsilon(\text{C3}'\text{--H3}'\cdots\text{N2}')$. In terms of ellipticity C1'–H1a'...N2' and C18–H18...N2 interactions are harder to be broken than C18–H18...N2 and C3'–H3'...N2'. All these characteristics and parameters contribute to confirm the existence of these interactions.

Structure comparison

In the literature, we find a polymorph (Mol-2)¹²⁰ and the same structural form (Mol-1)¹²¹ for AM2. Figure 10 shows the comparison between the 3 molecules. The polymorph (Mol-2) has a different conformation, with one molecule in the asymmetric unit and four in the unit cell, besides different unit cell parameters. The cell angles for Mol-2 are $\alpha = 90^\circ$, $\beta = 91.06(10)^\circ$ and $\gamma = 90^\circ$, note that, these angles are very different from the AM2 molecule, the β angle (91.06°) of Mol-2 is close to 90° , almost characterizing Mol-2 in a different crystalline system, such as the orthorhombic ($a \neq b \neq c$; $\alpha = \beta = \gamma = 90^\circ$). In addition, the packaging of the Mol-2 polymorph differs greatly from the AM2 packaging, driven by different interactions and the empty spaces (voids) between the molecules is similar, around 12%.

The graphite oxide was used as a catalyst for the synthesis of AM2 whereas it is Mol-1 and Mol-2 molecules. The reaction takes place in the absence of catalyst, but uses methanol, dichloromethane and triethylamine as solvent.

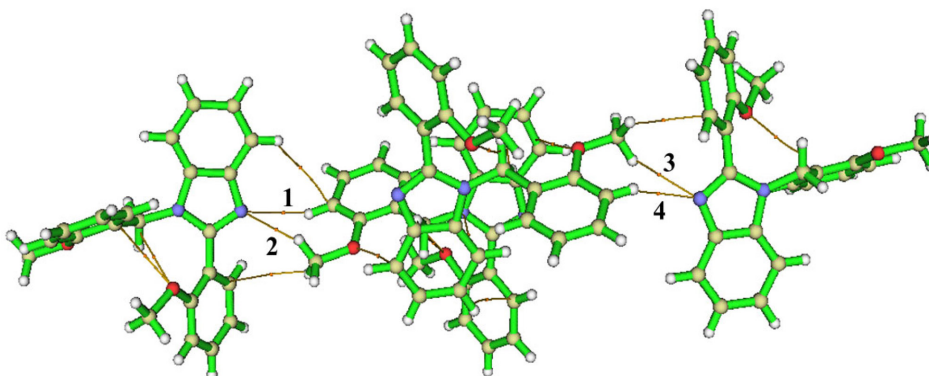


Figure 9. Critical points for C–H...N interactions of AM2.

Table 3. Data from the topological analysis performed by the QTAIM methodology for AM2

BCP	$\rho(\mathbf{r})$ / a.u.	$\nabla^2\rho(\mathbf{r})$ / a.u.	λ_1 / a.u.	λ_2 / a.u.	λ_3 / a.u.	ε / a.u.	$V(\mathbf{r}_{\text{bcp}})$ / a.u.	$G(\mathbf{r}_{\text{cp}})$ / a.u.	$H(\mathbf{r})$ / a.u.	Interactions
1	0.00864	0.02686	−0.00723	−0.00692	0.04101	0.04499	−0.00443	0.00557	0.00114	C18–H18...N2
2	0.00824	0.02507	−0.00677	−0.00605	0.03790	0.11841	−0.00438	0.00532	0.00094	C1–H1c...N2
3	0.00698	0.02045	−0.00545	−0.00486	0.03077	0.12092	−0.00368	0.00439	0.00071	C1'–H1a'...N2'
4	0.00900	0.02810	−0.00766	−0.00736	0.04313	0.04036	−0.00459	0.00580	0.00121	C3'–H3'...N2'

QTAIM: quantum theory of atoms in molecules; a.u.: atomic units (Hartree atomic units). A hartree is equal to 2625.5 kJ mol^{−1}, 627.5 kcal mol^{−1}, 27.211 eV, and 219474.6 cm^{−1}. BCP: bonding critical point; $\rho(\mathbf{r})$: electron density at critical point; $\nabla^2\rho(\mathbf{r})$: Laplacian of electron density; λ_1 , λ_2 and λ_3 : eigenvalues of Hessian matrix; ε : ellipticity of electron density; $V(\mathbf{r})$: potential electron energy density; $G(\mathbf{r})$: kinetic electron energy density; $H(\mathbf{r})$: energy density.

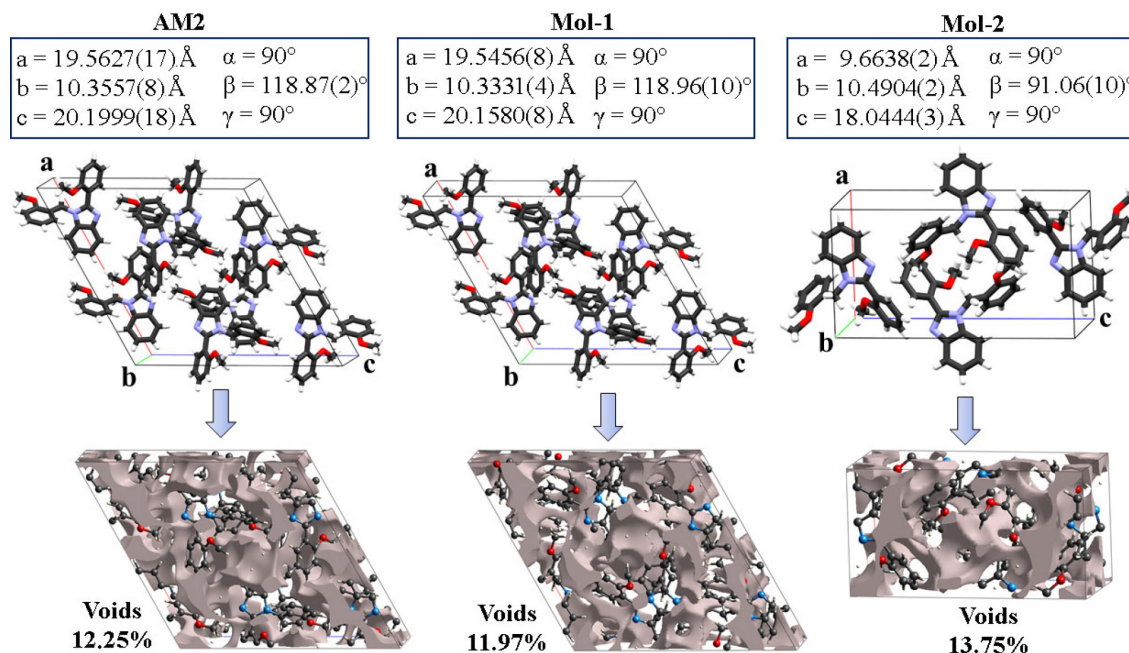


Figure 10. Comparison between AM2, Mol-1 and Mol-2.

The AM2 synthesis occurs in the absence of solvent within a time interval of 60 min, while molecules Mol-1 and Mol-2 use solvent and were obtained during a minimum interval of 3 h. The AM2 synthetic route in the presence of graphite oxide is simple and environmentally viable-considering it occurs (i) in a shorter reaction time, (ii) in the absence of solvents and (iii) in the presence of ethanol only when recrystallized.

Conclusions

The AM2 compound was obtained through a new synthetic route, by using graphite oxide in the absence of solvent, occurring at 80 °C, and within a time interval of 60 min. AM2 crystallized in monoclinic space group $P2_1/c$ with two molecules in the asymmetric unit, and its supramolecular arrangement is supported by C–H $\cdots$ N and C–H $\cdots$ π interactions. These interactions described by geometric parameters, were confirmed by electron density and QTAIM topological analysis. Molecular orbitals indicated kinetic stability and the potential map confirmed the interaction sites. All these descriptions corroborate to understand this class of molecule and contribute to future application studies on pharmaceutical industry. Also, the described interactions observed unto supramolecular arrangement can be explored in the context of biological activities, as well as in the identification of the active sites responsible for electrophilic (or nucleophilic) attacks. Finally, these comprehensive structural aspects can be linked on structure-property relations in the biological scope.

Supplementary Information

Crystallographic data (excluding structure factors) for the structures in this work were deposited in the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 2091809. Copies of the data can be obtained, free of charge, via <https://www.ccdc.cam.ac.uk/structures/>.

Supplementary information (^1H NMR spectrum and ^{13}C NMR spectrum of compound AM2) is available free of charge at <http://jbcs.sbq.org.br> as PDF file.

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Author Contributions

V. S. Duarte and H. B. Napolitano were responsible for conceptualization, investigation, data curation and project administration; R. F. Naves, G. R. Oliveira and C. G. Alonso for experimental syntheses and characterization of substances; A. J. Bortoluzzi for investigation, X-ray crystallography data treatment, software and validation; E. C. M. Faria, A. M. da Silva

for conceptualization, visualization and formal analysis funding acquisition. All authors were responsible for writing original draft and writing-review and editing.

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Insights on sustainable fuels: a new benzimidazole derivative with potential as a diesel-biodiesel blend additive

Vitor S. Duarte^{a,b}, Raquel F. Naves^{d,e}, Adailton J. Bortoluzzi^c, Eduardo C. M. Faria^{a,b}, Aline M. da Silva^b, Vânia Mori^f, Christian G. Alonso^d, Guilherme R. Oliveira^d and Hamilton B. Napolitano^a 

^aGrupo de Química Teórica e Estrutural de Anápolis, Universidade Estadual de Goiás, Anápolis, GO, Brasil; ^bCentro de Pesquisa e Eficiência Energética, CAO Montadora de Veículos LTDA, Anápolis, GO, Brasil; ^cDepartamento de Química, Universidade Federal de Santa Catarina, Florianópolis, SC, Brasil; ^dInstituto de Química, Universidade Federal de Goiás, Goiânia, GO, Brasil; ^eInstituto Federal de Goiás, Inhumas, GO, Brasil; ^fInstituto Nacional de Tecnologia, Rio de Janeiro, RJ, Brasil

ABSTRACT

Biodiesel is an important fuel in the energy industry with recurrent durability and stability problems. The use of molecular-based technologies to preserve the physicochemical properties of diesel-biodiesel blend is a promising path on additive studies. To minimize oxidative stability problems and get insights into the additive structural features, we evaluated a new benzimidazole derivative as a potential additive for diesel-biodiesel blends. In the study, an extensive structural description and supramolecular topological analysis, besides theoretical calculations to understand specific physicochemical properties related to oxidative stability when added to biofuel, were carried out. Also, the synthesis of the title compound in the presence of graphite oxide shows a sustainable synthetic route, and the supramolecular arrangement has only C–H...O and C–H... π interactions that are related to antibacterial and antioxidant activity. The new benzimidazole derivative structure has two alkoxy groups in the *para* position of the aromatic ring acting as electron-donating substituents – desirable conformations for antioxidant activity. The energy of 640.99 kJ/mol in the Frontier Molecular Orbitals indicates high kinetic stability and the oxidative stability in the diesel-biodiesel blend (B20) was 26.3 h (better than commercial additives). The obtained results indicate the potential of benzimidazole derivative as a diesel-biodiesel blend additive.

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1. Introduction

The natural resources shortage is a current problem close related to crisis that permeates the world economic system, with an uncertain future consequences due to the depletion of many essential resources for sustainable life [1, 2]. The economic system is essentially dependent on large extraction of natural resources [3, 4] – over 80% of the used energy comes from fossil fuels (petroleum, mineral coal and natural gas) [5, 6]. The human development combined with population growth lead to imminent natural resource scarcity [7–10]. The demand for new energy sources that are clean and renewable as an alternative for fossil fuels is growing – like biofuel studies [11, 12]. Biodiesel can be obtained from both animal and plant sources [11, 12] and has a low rate of pollutants emission and lower toxicity when compared to fossil fuels [13, 14]. This biofuel is biodegradable and can be used in diesel cycle engines without major adaptations [15]. The lower energy availability and less stability hinder the use of such biofuels [16–19]. Nevertheless, the use of additives [20, 21] that preserve the oxidative stability on diesel-biodiesel mixtures [22–24] make this sustainable biofuel workable [25, 26].

Biodiesel has problems due to the microorganism proliferations (*fungi* and *bacteria*) that cause oxidation [16, 17, 27–30]; consequently, compounds with antimicrobial or

antioxidant properties are desirable as additives [14, 31]. Considering that benzimidazoles constitute a class of organic molecules formed from benzene and an imidazole ring, they are widely used as antimicrobial [32–34] and antioxidant properties [35–37]. Moreover, several systemic fungicides with benzimidazoles are available on the market, such as carboxin [38], benomyl [39], carbendazim [40] and thiophanate-methyl [41–43]. Since benzimidazole antioxidant and antimicrobial properties are already described [33, 35–37], the application as an additive for diesel-biodiesel mixtures is promising scientific topic. Therefore, this work suggests a possible new application of the benzimidazole class as potential additives to diesel-biodiesel mixtures.

In this work, we carried out the synthesis, the structural description and topological analysis of the interactions that contribute to the supramolecular arrangement for a new benzimidazole derivative 1-(4-ethoxy-benzyl)-2-(4-ethoxy-phenyl)-1H-benzimidazole (BZD). In addition, we performed theoretical calculations to understand physicochemical properties and Rancimat test to analyze the oxidative stability when added to diesel-biodiesel mixtures. The synthesis of BZD was carried out in the presence of graphite oxide under satisfactory conditions (in the absence of solvent) being a chemically interesting synthetic

CONTACT Vitor S. Duarte  vitor.sduarte@seduc.go.gov.br; Hamilton B. Napolitano  hbnapolitano@gmail.com  Grupo de Química Teórica e Estrutural de Anápolis, Universidade Estadual de Goiás, Anápolis, GO, Brasil

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Figure 1. Experimental setup for synthesis and crystallization of BZD.

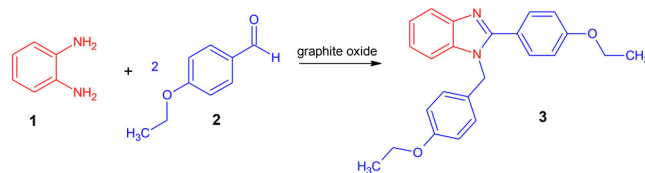
route. The BZD supramolecular arrangement is supported only by weak interactions, and the alkoxy groups in the aromatic ring *para* position function as electron-donating substituents. Also, these structural features can be linked with antioxidant activity based on oxidative stability analysis (suggesting a kind of structure-activity relationship) [44–48]. Finally, theoretical calculations indicated that the molecule regions most susceptible to interactions are in agreement with the experimental results and the Frontier Molecular Orbitals (suggesting high kinetic stability).

2. Experimental and computational procedures

2.1. Synthesis and crystallization

In a round-bottom flask, *o*-phenylenediamine (1 mmol) (**1**) and 4-ethoxybenzaldehyde (2 mmol) (**2**) were stirred without solvent at 80 °C (Figure 1). Then, 30 mg of graphite oxide was added to this mixture. The mixture was stirred for 30 min and monitored by Thin-Layer Chromatography (TLC) (hexane: ethyl acetate, 3:1). Upon completion, ethanol (10 ml) was added and the mixture was gravity filtered in an analytical funnel, separating the graphite oxide from the product obtained. The compound was washed with water (5 ml) three times and then recrystallized from hot ethanol (10 ml) to obtain a yellowish white crystal (**3**) (Scheme 1). Table S1 (Supplementary material) shows some chemical properties of compounds used on synthesis.

1-(4-ethoxy-benzyl)-2-(4-ethoxy-phenyl)-1H-benzimidazole (BZD): yield: 84%; Mp: 143–147 °C, ¹H (CDCl₃, 500 MHz): δ 7.86 (d, *J* 7.93 Hz, 1H), 7.64 (d, *J* 8.54, 2H), 7.33–7.28 (m, 1H), 7.24–7.23 (m, 2H), 7.04 (d, *J* 8.54 Hz, 2H), 6.97 (d, *J* 8.54 Hz, 2H), 6.86 (d, *J* 8.54 Hz, 2H), 5.39 (s, 2H), 4.09 (dd, *J* 7.02 and 14.4 Hz, 2H, CH₂), 4.02 (dd, *J* 7.02 and 14.4 Hz, 2H, CH₂), 1.46 (t, *J* 7.02 Hz, 3H, CH₃), 1.42 (t, *J* 7.02 Hz, 3H, CH₃). ¹³C (CDCl₃, 500 MHz): δ 160.32, 158.50, 154.19, 143.11, 136.09, 130.72, 128.33, 127.73, 122.52, 114.95, 114.69, 110.46, 63.60, 47.93, 14.83. FT-IR (KBr cm⁻¹): 3458, 2972, 2867, 1623, 1474, 1388, 1252, 1172, 1049, 920, 834, 735.



Scheme 1. Synthesis of BZD.

2.2. Structural and topological analysis

The structural model for BZD was determined using crystallographic analysis. The X-ray diffraction data were obtained using a Bruker Apex-II CCD diffractometer with monochromator graphite MoK α radiation and $\lambda = 0.71073$ Å. The structure was solved by the ShelXT [49, 50] software and refined with ShelXL [51, 52] using full-matrix least-squares on the Olex2 platform [53]. The non-hydrogen atoms were refined with anisotropic thermal displacement parameters [54], while hydrogen atoms were geometrically positioned and fixed according to the riding-hydrogen model with 0.99, 0.98, and 0.95 Å for the methylene, methyl, and aromatic groups, respectively [55].

The intermolecular interactions were analyzed using geometric parameters by Mercury [56] software, also by electronic density by Hirshfeld Surfaces (HS) analysis, and confirmed by Quantum Theory of Atoms in Molecules (QTAIM). The HS were generated from the X-ray data using CrystalExplorer17 [57]. These surfaces represent the electron distribution of the molecule with the neighborhood and are related to the normalized contact distances (distance external to the surface (d_e) – distance from the surface to the nearest atom in the molecule itself and distance internal to the surface (d_i) – distance from the surface to the nearest atom in another molecule) [58–60]. The 2D fingerprint is a graph constructed from d_e versus d_i distribution and indicates the quantitative of the contacts present in the molecule [61].

Additionally, the topological QTAIM analysis considers parameters of quantum mechanics and carries out the execution of numerical integrations with the gradient vector [$\nabla\rho(\mathbf{r})$] [62, 63]. The atomic behavior in a molecule can be analyzed from some observable properties of electron density [$\rho(\mathbf{r})$] [64, 65]. These observables allow the definition of chemical bonding as a Bonding Path (BP) between atoms that have a Critical Point (CP) between them. The M06-2X/6-311++G theory level was used to generate the wave function, which was analyzed by Multiwfn software [66]. All crystallographic data for the BZD molecule were deposited in the Cambridge Crystallographic Data Centre (CCDC) [67] under the code CCDC 2157066 [https://www.ccdc.cam.ac.uk/structures/?].

2.3. Theoretical calculations

The theoretical analysis for BZD was performed using density functional theory (DFT) from the optimization of experimental parameters obtained by X-ray diffraction. These experimental data describe the geometric parameters of the molecule and were optimized in the gas phase by the Gaussian09 software [68]. For this, the M06-2X/6-311++G(d,p) theory level was used [69–71], because this level is suitable for small organic molecules, and is recommended for noncovalent interactions [69, 72–74] considering

Table 1. Crystal data and structure refinement for BZD.

Parameter	C ₁₈ H ₁₈ O ₄
Molecular weight	372.45 g/mol
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system, space group, Z	monoclinic, P2 ₁ /n, 4
Unit cell dimensions	$a = 12.1548(15)$ Å $\alpha = 90^\circ$ $b = 10.2480(12)$ Å $\beta = 99.321(2)^\circ$ $c = 15.643(2)$ Å $\gamma = 90^\circ$
Volume	1922.8(4) Å ³
Density (calculated)	1.287 Mg/m ³
Absorption coefficient	0.082 mm ⁻¹
Crystal size	0.240 × 0.180 × 0.160 mm ³
<i>F</i> (000)	792
Refinement method	Full-matrix least-squares on <i>F</i> ²
Goodness-of-fit on <i>F</i> ²	1.004
Final <i>R</i> indices [<i>I</i> ≥ 2σ(<i>I</i>)]	<i>R</i> ₁ = 0.0500, <i>wR</i> ₂ = 0.1155
<i>R</i> indices (all data)	<i>R</i> ₁ = 0.0903, <i>wR</i> ₂ = 0.1366

the electronic correlation, and presents satisfactory results [73, 74].

The generated wave function was used to determine some properties, such as the Frontier Molecular Orbitals (FMO) and the Molecular Electrostatic Potential (MEP). The Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) [75, 76] indicate the reactivity and kinetic stability of the molecule [76–78]. The MEP map describes the reactive regions of a molecule and this map is constructed through Equation 1.

$$V(\mathbf{r}) = \sum_{\alpha} \frac{Z_{\mathbf{A}}}{|\mathbf{r}_{\alpha} - \mathbf{r}_{\mathbf{A}}|} - \int \frac{\rho(\mathbf{r})}{r_{\alpha} - r} d\mathbf{r} \quad (1)$$

where *V*(**r**) is the potential created at point **r**, the first term in the summation represents the electrostatic potential created in the nucleus and the second term is the electrostatic potential created by the electrons as a function of electron density. *Z*_A is the charge on the nucleus **A** at a distance **R**_A. *ρ*(**r**) is the electron density function of the molecule and *V*(**r**) is a physical property that can be measured experimentally by diffraction methods [79].

2.4. Oxidation stability test

The Rancimat test is a method of accelerated oxidation used to determine the oxidative properties of Fatty Acid Methyl Esters (FAME) used as biofuels in their pure form or as additives for mineral diesel. This test is performed according to standard EN 15751 [80] following all requirements. The test is carried out with the sample heated to a temperature of 110 °C. A stream of pure air provides oxygen forming peroxides in an oxidation reaction. Peroxides break down to form aldehydes, ketones, and carboxylic acids. The sample and air are directed into an airtight container filled with deionized water and equipped with a conductivity electrode, then measuring equipment detects the end of the induction period [81, 82]. The result of stability oxidation by the Rancimat method is commonly determined in hours, reported as the Oxidation Stability Index (OSI) or more usually, the Induction Period (IP). For analysis of BZD, Metrohm 873 model equipment was used in following the requirements of the EN 15751: 2014 standard [80].

3. Results and discussion

3.1. Synthesis and molecular modeling analysis

The synthesis to obtain the BZD compound occurred under satisfactory conditions, with a yield above 80%. Thus, the compound was synthesized using graphite oxide, a carbonaceous compound, with acidic sites, in the absence of solvent, occurring at 80 °C and within a time interval of 60 min. Therefore, obtaining BZD in the presence of graphite oxide presents environmentally correct conditions, occurring in a good reaction time, in the absence of solvent, and recrystallized only with ethanol. The BZD compound is a new benzimidazole derivative, which crystallizes in the centrosymmetric monoclinic P2₁/n space group, with one independent molecule in the asymmetric unit (Table 1). BZD compound shows three aromatic rings and two OCH₂CH₃ (alkoxy) groups in the *para* position of the aromatic rings A and C (Figure 2).

The supramolecular arrangement of BZD is stabilized only by weak interaction of type C–H...O and C–H... π (Table 2). However, these interactions have been described by several authors as significant for the stability of the supramolecular arrangement [83–94]. Furthermore, some works indicate that C–H... π interactions can be related to optimization and facilitation of some biological activities [95–97] – as well as in a protein-binding process that can be related to protein engineering, drug design, or a specific biological activity [98–100], or even in materials engineering [101]. Additionally, C–H...O interactions represent pharmaceutical relevance with the architecture of new drugs [102] and are present in RNA recognition of small molecules that can contribute to drug discovery [103]. C–H...O interactions also contribute to conformational stability in a system with binding proteins as important antibacterial targets [104] and stabilization of complexes related to antioxidant activity [105].

The C21–H21...O2 interaction contributes to the growth of the crystal in the (100) and (001) direction, and the C23–H23b...CgB and C18–H18...CgC interactions contribute to (010) and (001) directions, while C11–H11...CgC contributes to the (010) direction (Figure 3). According to the geometric parameters of the C21–H21...O2 and C11–H11...CgC interactions have smaller distances between the donor and acceptor atoms [*d*(D...A)Å] involved in the interactions: 2.694 and 2.691, respectively. Angles are also closer to 180° (this directional angle value could characterize a stronger interaction): 170.52° for C21–H21...O2 and 151.61° for C11–H11...CgC.

The interactions observed from X-ray data were analyzed from the electronic density by HS analysis. Interaction C21–H21...O2 was analyzed by normalized contact distance (*d*_{norm}), the red spots in the HS *d*_{norm} indicate intermolecular contacts smaller than the sum of van der Waal (vdW) radii of the atoms [58, 60] (Figure 4a). In this interaction, region (r) indicated the acceptor atom site of the molecular interaction while region (d) indicated the donor site. The HS Shape index was used to evidence the C–H... π interactions present in BZD (Figure 4b and c). On this surface, concave red regions over aromatic ring systems and convex blue regions over C–H atoms indicate the interactions involving the π -systems [59, 60]. Despite their weak nature (1.0–2.5 kcal/mol) [106–110], the C–H... π

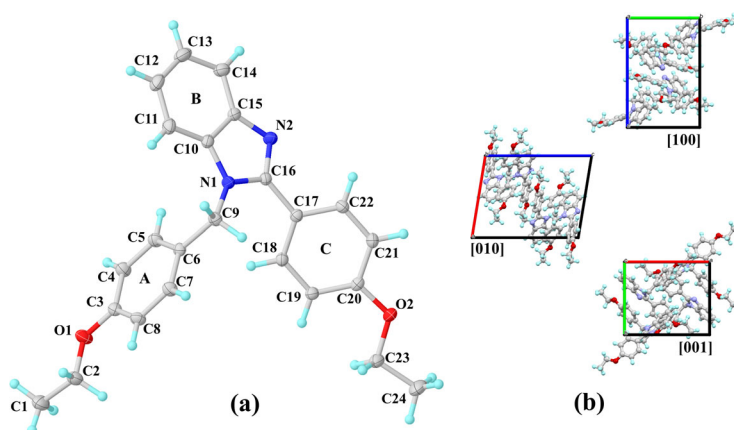


Figure 2. Oak Ridge Thermal-Ellipsoid Plot (ORTEP) representation of BZD with ellipsoids at 50% of probability (a). Molecular packing in the unit cell for BZD (b).

Table 2. Main intermolecular interactions of BZD.

D-H...A	d(D-H)Å	d(H...A)Å	d(D...A)Å	d(D-H...A)(°)	Symmetry code
C21-H21...O2	0.950	2.694	3.635	170.52	1-x,y,1-z
C11-H11...CgC	0.950	2.691	3.556	151.61	1.5-x,1/2+y,1.5-z
C18-H18...CgC	0.950	3.340	3.616	99.26	1-x,1-y,1-z
C23-H23b...CgB	0.990	3.252	4.003	133.89	1-x,1-y,1-z

interactions are important building blocks in supramolecular arrangement, due to the multifunctionality of these non-covalent interactions with different functional groups [111–114]. In Figure 4b and c, the C11–H11...CgC, C18–H18...CgC and C23–H23b...CgB interactions are confirmed and contributed to crystal packing.

The supramolecular arrangement of BZD is constructed by C–H...O and C–H... π interactions and, with the aid of 2D fingerprint, we performed the percentage quantification of each interaction presented (Figure 5). The presence of pseudo-mirrored peaks in the region 1.0–1.2 (*de*, *di*) is indicative of weak contacts involving hydrogens (H...H), which represent 60.4% of contacts present in BZD; this percentage is high because BZD is an organic molecule and has many hydrogen atoms. C–H... π interactions (H...C) represent 22.8% of contacts present in BZD, while C–H...O interactions (H...O) represent 6.5% of contacts. After H...H, the largest number of interactions observed in the BZD solid state is C–H... π type (about 90% of the total for structural stability of BZD while other interactions represent about 10%).

QTAIM analysis has been used to describe dihydrogen bonding [115–119], classical hydrogen bondings [120–123] and C–H...O interactions [124–128] through the investigation of the properties of Bonding Critical Point (BCP). Table 3 are shown the properties: electron density [$\rho(\mathbf{r})$], Laplacian of electron density [$\nabla^2\rho(\mathbf{r})$], eigenvalues of Hessian matrix (λ_1 , λ_2 , and λ_3), the ellipticity of electron density (ϵ), the potential electron energy density [$V(\mathbf{r})$], the kinetic electron energy density [$G(\mathbf{r})$] and energy density [$H(\mathbf{r})$].

The C21–H21...O2 interaction present in BZD was confirmed according to some criteria suggested by Popelier and Koch [115, 125]. According to these criteria, a continuous density path with a Critical Point (CP) is necessary between acceptor and donor atoms involved in the interaction, and in this CP an [$\rho(\mathbf{r})$] in range of 0.002–0.035a.u and $\nabla^2\rho(\mathbf{r})$ in the range of 0.024–0.139a.u. The

C21–H21...O2 interaction has a continuous density path between donor and acceptor atom and the presence of a CP between them (Figure 6). The values of [$\rho(\mathbf{r})$] and [$\nabla^2\rho(\mathbf{r})$] in the critical point are in the expected range (0.00726 and 0.02401, respectively).

The positive value of [$\nabla^2\rho(\mathbf{r})$] and small value of [$\rho(\mathbf{r})$] suggest a hydrogen bond [115], according to the C21–H21...O2 interaction. Additionally, the character of interaction can be measured by some indicators, such as [$\nabla^2\rho(\mathbf{r})$] < 0 and [$H(\mathbf{r})$] < 0 for strong interactions with covalent character, [$\nabla^2\rho(\mathbf{r})$] > 0 and [$H(\mathbf{r})$] < 0 for medium strength and [$\nabla^2\rho(\mathbf{r})$] > 0 and [$H(\mathbf{r})$] > 0 for weak interactions with electrostatic character [129, 130]. According to these parameters, the C21–H21...O2 interaction agrees with the electrostatic character. All these results are good indicators and confirm the existence of the C21–H21...O2 interaction described by geometric parameters and HS.

3.2. Chemical structure of BZD as an antioxidant

The arrangement of the HOMO and LUMO orbitals over the BZD molecule is similar, as both are over aromatic rings B and C (Figure 7). The HOMO orbital for BZD characterizes the π orbital (bonding orbital) and ionization potential (nucleophilic character), while the LUMO orbital characterizes the π^* orbitals (antibonding orbital) and electron affinity (electrophilic character). The energy calculated for these orbitals is 676.09 kJ/mol for HOMO and –35.10 for LUMO, and the energy gap ($E_{gap} = E_{LUMO} - E_{HOMO}$) between these orbitals is 640.99 kJ/mol. The energy gap can be an important indicator of some proprieties because high gap values suggest high kinetic stability, high excitation energies, and low chemical reactivity [77]. Some studies with Benzimidazole and derivatives show the potential of these molecules for application in materials science, and the gap values found are lower than that of BZD. Hayakawa *et al.* (2008) [131] carried out a study with triphenylamine-

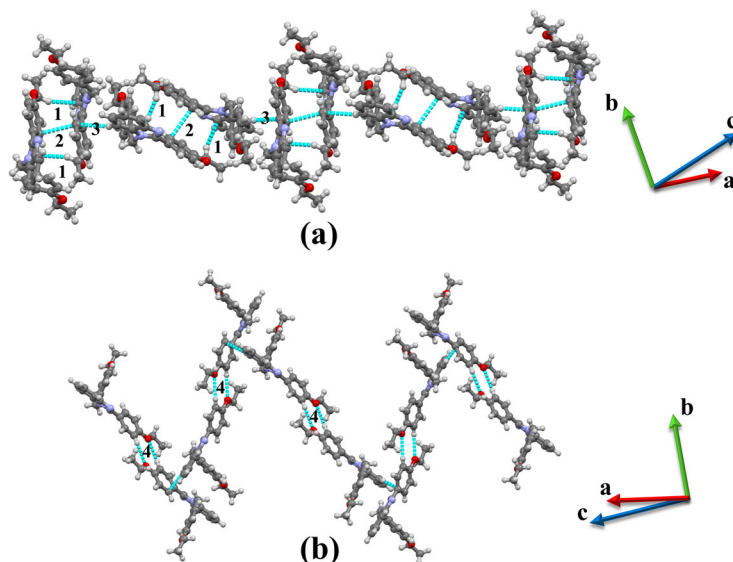


Figure 3. Intermolecular interactions observed in BZD packing. Interactions: (1) C23–H23b...CgB; (2) C18–H18...CgC; (3) C11–H11...CgC (a) and (4) C21–H21...O2.

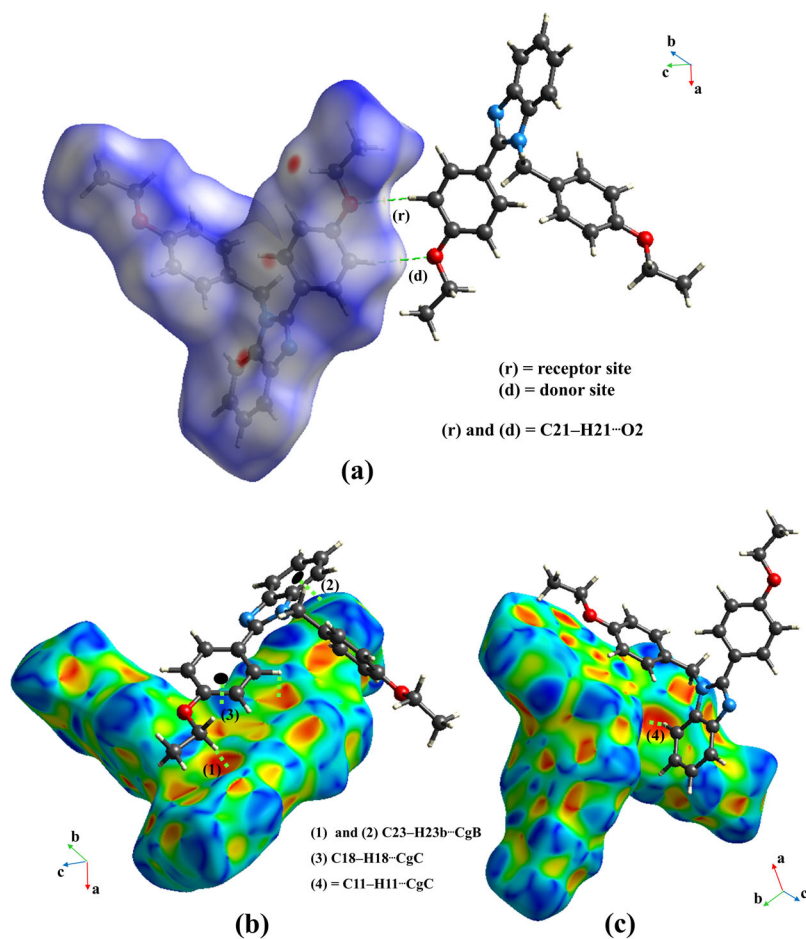


Figure 4. HS d_{norm} of the C–H...O interactions of BZD (a); HS shape index of the C–H... π interactions of BZD (b) and (c).

benzimidazole derivatives for organic light-emitting diodes with gap values of 3.73 eV and 3.65 eV.

Huang *et al.* (2012) [132] evaluated benzimidazole–carbazole for blue and white electrophosphorescence applications and found gap values ranging from 2.3 to 2.4 eV. Additionally, Mary *et al.* (2014) [133] evaluated the non-linear optical activity of a chlorinated benzimidazole with gap values of 3.916 eV, while Tercan & Dayan (2019) [134] analyzed a series of Ru(II) complexes bearing benzimidazole type ligands for photophysical properties and Dye-

Sensitized Solar Cell (DSSC) Applications with gap values ranging from 1.82 to 1.97 eV. Considering biological activities, several studies show gap values similar and smaller than those of BZD. Niamien *et al.* (2012) [135] analyzed the inhibiting effect of some benzimidazole derivatives that had gap values of 5.122 eV, 5.300 eV, and 5.394 eV, while Fatma *et al.* (2008) [136] presented new benzimidazole analogs as antiviral agents, with gap values ranging from 7.216 to 8.415 eV. For antioxidant and antimicrobial activities, Mishra *et al.* (2019) [137] studied a series of novel azo

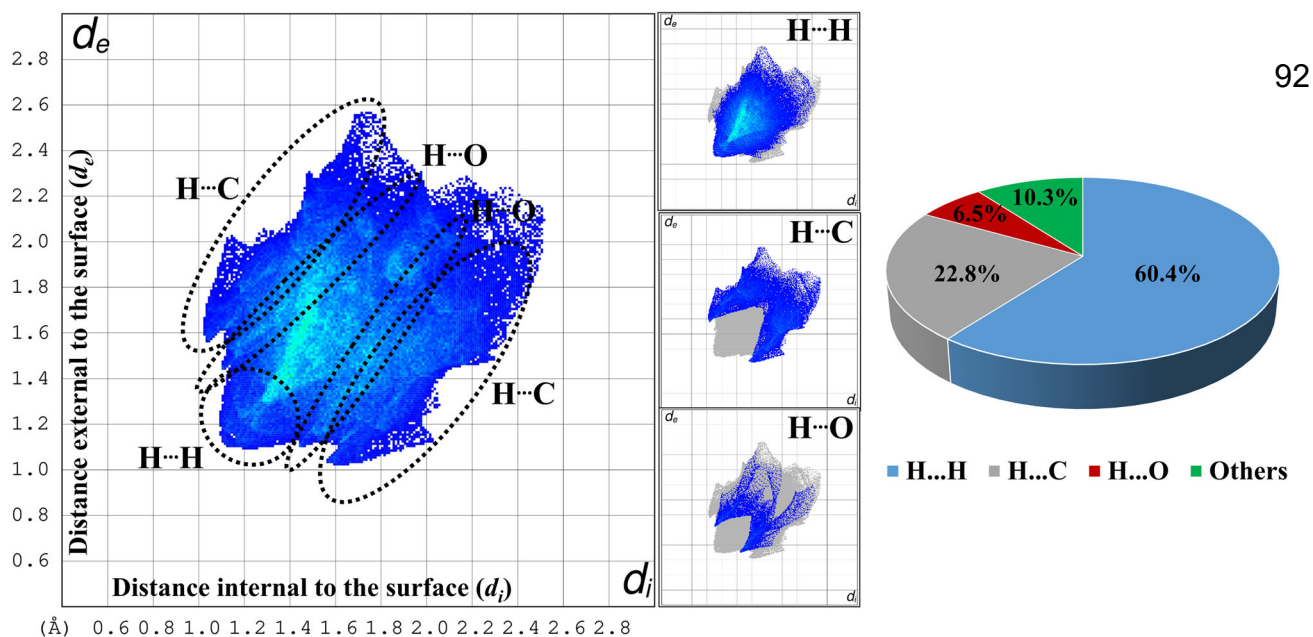


Figure 5. 2D fingerprint with quantitative descriptions of the observed contacts of BZD. (d_e) axis is the distance from the surface to the nearest atom in the molecule itself. (d_i) axis is the distance from the surface to the nearest atom in another molecule.

Table 3. Parameters from the topological analysis carried out by the QTAIM methodology for BZD. The data are in atomic units (a.u.).

CP	$\rho(r)$	$\nabla^2\rho(r)$	λ_1	λ_2	λ_3	ε	$V(r)$	$G(r)$	$H(r)$	Interactions
1	0.00726	0.02401	-0.00656	-0.00631	0.03646	0.03967	-0.00428	0.00509	0.00080	C21-H21...O2
2	0.00726	0.02401	-0.00656	-0.00631	0.03646	0.03967	-0.00428	0.00509	0.00080	C21-H21...O2

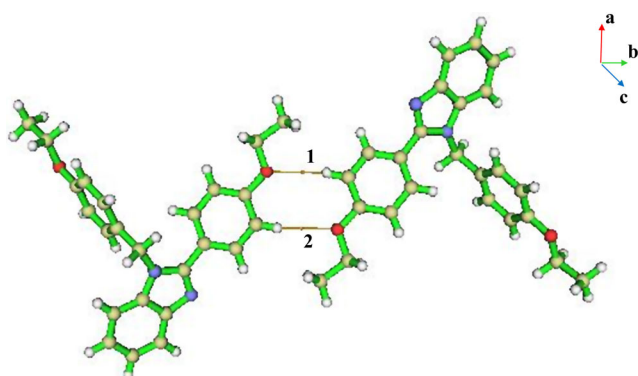


Figure 6. CP for C21-H21...O2 interaction of BZD.

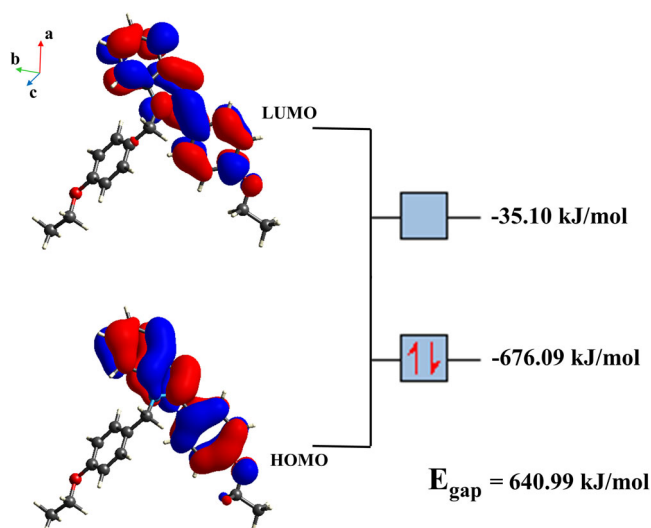


Figure 7. FMO, LUMO and HOMO and respective energies for BZD.

linked substituted benzimidazole for antimicrobial activity and found gap values ranging from 2.83 to 3.06 eV. Mohi (2020) [138] tested new benzimidazole derivatives against fungi and bacteria, revealing their potential for antimicrobial activity; these compounds have gap values ranging from 2.22 to 3.31 eV. Marinescu *et al.* (2020) [139] also showed the potential of new benzimidazole mannich bases with antimicrobial activity – however, they found slightly higher gap values (8.62 to 10.06 eV). Arshad *et al.* (2020) evaluated a benzimidazole analogue with antioxidant potential and found a gap value of 3.58 eV, while Prabu *et al.* (2019) [140] evaluated benzimidazole carboxamide derivatives (4.537 eV and 4.707 eV). Finally, Shatokhin *et al.* (2022) [141] performed a study with several substituted benzimidazoles for antioxidant activities and found gap values ranging from 4.010 to 4.240 eV. Notably, several current works indicate the antioxidant and antimicrobial activity of compounds from the benzimidazole class with gap values lower than those found for BZD. The gap value found for BZD (6.643 eV) indicates BZD with greater kinetic stability than those found in the literature.

In the MEP analysis, we identified regions with lower and higher electron density distribution. In the MEP (Figure 8), blue colors indicate positive electrostatic potential, revealing the regions most susceptible to nucleophilic attack, while red colors indicate negative electrostatic potential with a high electron density, revealing the regions most susceptible to electrophilic attacks [79, 142, 143]. On the O and N-atoms and aromatic rings B and C, the high electron density is presented. These regions indicate greater potential for electrophilic attacks and agree with the regions of the interactions described for this molecule. In addition, on H-atoms and aromatic ring A, regions with positive electrostatic potential are presented. The sites

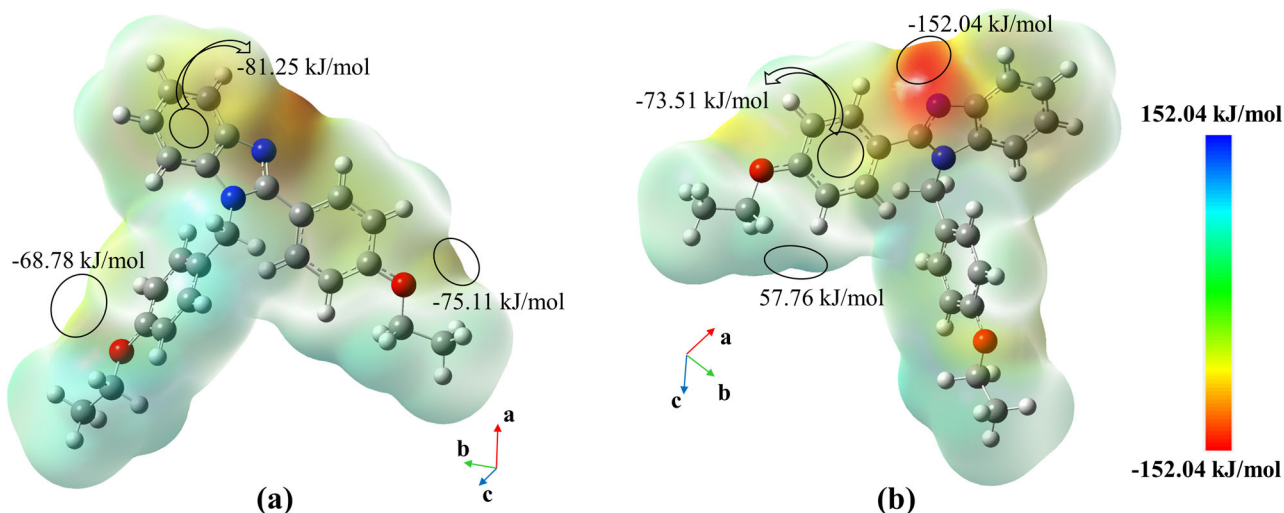


Figure 8. MEP map for BZD.

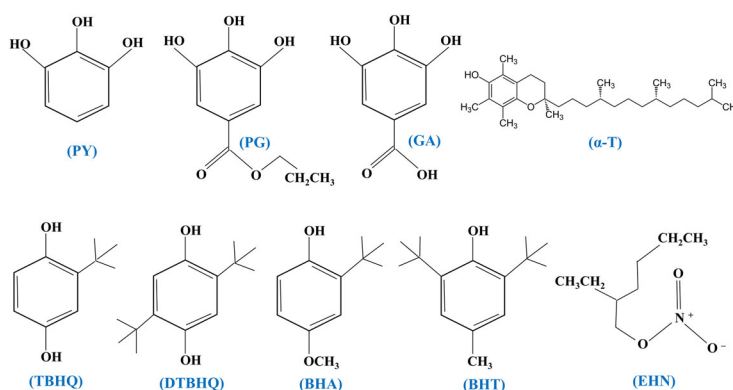


Figure 9. Chemical structures of some antioxidants.

of nucleophilic/electrophilic attacks for BZD can be ranked as follows: N2 > aromatic ring B > O2 > aromatic ring C > O1 > H-atoms.

An antioxidant is a compound that can be natural [144–147] or synthetic [15, 27] and that delays, controls or inhibits the auto-oxidation processes in other chemical products, and its molecular structure differs according to the need for the product to be applied. For biofuels, substituted phenolic compounds and secondary aromatic amines are the most common compounds currently in use (Figure 9). Antioxidants are used as a reducing agent, donating electrons or hydrogen to free radicals to neutralize the oxidation reaction (hydrogen is released from active NH or OH groups and donated to free radicals) – (primary antioxidants) [148]. Phenols used as antioxidants (Figure 9) have OH groups that can donate electrons or hydrogens, and some of these additives have groups similar to the structure of BZD, groups that could donate electrons or hydrogen as a reducing agent.

The secondary antioxidants can replenish hydrogen or decompose the hydroperoxides in a reaction [149]. The chemical structure of an antioxidant can be obtained through a hybrid or bifunctional structure, such as hydroxyl benzimidazoles (hydroxyls with benzimidazoles) that have interesting chemical groups (OH and NH), which can be effective in scavenging free radicals due to hydrogen donation to the peroxy radicals [15]. Electron-donating substituents such as alkyl or alkoxy at the *para* or *ortho* positions of the aromatic ring are desirable structural conformations for antioxidant activity [15]. BZD is a compound of the

benzimidazole class and has two alkoxy groups at the *para* position of the aromatic ring. These structural parameters make BZD an interesting functional structure as a diesel-biodiesel blend additive.

3.3. Biofuel antioxidant additive analysis

Biodiesel is of interest because it reduces emissions of CO₂ and atmospheric pollutants. This fuel can be obtained from various mixtures of animal and vegetable origin, such as biodiesel from soy [150], frying oil [150], waste vegetable oil [151], castor bean [152], peanut [153], fish [154], rubber seed [155], chicken fat [156], watermelon crude oil [157], among others [158–162]. For Rancimat oxidative tests, we used a diesel-biodiesel blend (B20), where B20 refers to the percentage by volume of the biodiesel added to diesel (20% biodiesel + 80% diesel). The biodiesel used has the composition of 60% soybean oil, 37% palm oil, 2% bovine fat, and 1% pork fat. The BZD compound was used as an additive for B20 (0.5 mg/mL or 500 ppm), being mixed with the fuel by manual process. After adding BZD to B20 by manual process, this fuel was stored for 140 days in High-Density Polyethylene (HDPE) tanks (material used in some vehicle fuel tanks).

The Rancimat tests were performed in triplicate, and the average of the results showed that after 140 days the fuel had oxidative stability of 26.3 h (Table 4). In Brazil there is still no legislation in force that establishes the minimum oxidation stability limit at 110 °C for diesel-biodiesel blend;

Table 4. Rancimat results for 140 days, oxidation stability at 110 °C (triplicate oxidative stability tests) for BZD. In addition, literature results for diesel-biodiesel mixtures.

Fuel	Additive	Additive concentration	Induction Period – IP (h)				Standard deviation	Measurement Uncertainty (h)
			Result 1	Result 2	Result 3	Average		
B20	BZD	500ppm	26.95	26.26	25.68	26.3	0.636	1.3
Fuel/Additive concentration	Canola oil methyl ester – B20/500 ppm							İleri & Koçar (2013) [163] İleri & Koçar (2014) [164]
Additive	EHN	BHT	BHA	TBHQ	DTBHQ	PG	PY	
IP (h)	7	7.2	19.4	18.5	–	–	–	
Fuel/Additive concentration	Croton megalocarpus – B20/100 ppm							Osawa <i>et al.</i> (2016) [165]
Additive	EHN	BHT	BHA	TBHQ	DTBHQ	PG	PY	
IP (h)	–	–	19.5	–	–	22.5	23	
Fuel/Additive concentration	Soybean oil – B20/200 ppm							Center (2011) [166] Tang <i>et al.</i> (2008) [167]
Additive	α -T	BHT	BHA	TBHQ	DTBHQ	PG	PY	
IP (h)	<12	≈21	≈21	≈26	≈17	≈28	34.49	
Fuel/Additive concentration	Palm methyl ester – B20/1000 ppm							Rizwanul <i>et al.</i> (2014) [168]
Additive	α -T	BHT	BHA	TBHQ	DTBHQ	PG	PY	
IP (h)	–	29.6	30.9	–	–	–	–	
Fuel/Additive concentration	Rice bran – B20/1000 ppm							Alagu <i>et al.</i> (2018) [169]
Additive	α -T	BHT	BHA	TBHQ	DTBHQ	PG	PY	
IP (h)	–	28	35	–	–	–	–	
Fuel/Additive concentration	Calophyllum inophyllum – B20/2000 ppm							Rizwanul <i>et al.</i> (2014) [170]
Additive	α -T	BHT	BHA	TBHQ	DTBHQ	PG	PY	
IP (h)	–	25.28	22.27	28.38	–	–	–	
Fuel/Additive concentration	Used frying oil – B100/500 ppm							Mittelbach & Schober (2003) [27]
Additive	α -T	BHT	BHA	TBHQ	DTBHQ	PG	PY	
IP (h)	–	≈8	≈11	≈18	–	≈27	≈28	
Fuel/Additive concentration	Cottonseed oil – B100/500 ppm							Tang <i>et al.</i> (2011) [166] Tang <i>et al.</i> (2008) [167]
Additive	α -T	BHT	BHA	TBHQ	DTBHQ	PG	PY	
IP (h)	≈6	≈8	≈8	≈20	12.5	≈12.5	≈19	
Fuel/Additive concentration	Poultry fat – B100/500 ppm							Tang <i>et al.</i> (2011) [166] Tang <i>et al.</i> (2008) [167]
Additive	α -T	BHT	BHA	TBHQ	DTBHQ	PG	PY	
IP (h)	≈1	<4	<9	<1.5	<1	<3	≈9	
Fuel/Additive concentration	Yellow grease – B100/500 ppm							Tang <i>et al.</i> (2011) [166] Tang <i>et al.</i> (2008) [167]
Additive	α -T	BHT	BHA	TBHQ	DTBHQ	PG	PY	
IP (h)	≈2	≈3	≈3	≈3.5	≈3	≈7	≈13	
Fuel/Additive concentration	Jatropha oil – B100/500 ppm							Agarwal <i>et al.</i> (2015) [171]
Additive	α -T	BHT	BHA	TBHQ	DTBHQ	PG	PY	
IP (h)	–	≈5	≈6	≈4	–	≈15	≈25	
Fuel/Additive concentration	Croton Oil – B100/500 ppm							Kivevele <i>et al.</i> (2011) [172]
Additive	α -T	BHT	BHA	TBHQ	DTBHQ	PG	PY	
IP (h)	–	–	≈5.48	–	–	≈15.2	≈15.7	
Fuel/Additive concentration	Pongamia (karanja) – B100/500 ppm							Obadiah <i>et al.</i> (2012) [173]
Additive	GA	BHT	BHA	TBHQ	DTBHQ	PG	PY	
IP (h)	0.67	0.80	0.76	0.86	–	–	2.86	
Fuel/Additive concentration	Pongamia (karanja) – B100/2000 ppm							Obadiah <i>et al.</i> (2012) [173]
Additive	GA	BHT	BHA	TBHQ	DTBHQ	PG	PY	
IP (h)	0.82	3.14	2.96	2.91	–	–	25.02	
Fuel/Additive concentration	Pongamia (karanja) – B100/3000 ppm							Obadiah <i>et al.</i> (2012) [173]
Additive	GA	BHT	BHA	TBHQ	DTBHQ	PG	PY	
IP (h)	0.88	4.88	5.02	6.19	–	–	34.35	

however, according to Brazilian Resolution ANP 798/2019 [174], the minimum oxidation stability limit for biodiesel to be sold is 12 h for 60 days. According to the European Committee of Standardization, the minimum biodiesel oxidation stability required is 6 h at 110 °C (EN 14214) [175], but, since 2018, there has been a movement by groups of vehicle manufacturers, additive manufacturers, distributors, and vehicle components industries aiming to establish a minimum limit of 20 h in the Rancimat test. This means that fuel must meet this requirement when it is delivered to the final consumer. However, there is still no official regulation defining a limit for this property. Currently, the additives most used for fuels and biofuels are Butylated Hydroxytoluene (BHT), Butylated Hydroxyanisole (BHA), Tertiary Butyl Hydroquinone (TBHQ), Ditert-butylhydroquinone (DTBHQ), Propyl Gallate (PG), Pyrogallol (PY), α -Tocopherol (α -T), 2-Ethylhexyl Nitrate (EHN) and Gallic Acid (GA). Due to the great variety of diesel-biodiesel

mixtures (additives and concentrations used), the values of oxidative stability can be diverse – however, results above 20 or near 30 h are acceptable. Table 4 shows values of the effects of antioxidants on biofuels and the effect of the BZD molecule on a B20.

In similar conditions, İleri & Koçar (2014) [164] tested some commercial additives in a B20 fuel (a biofuel made from Canola oil methyl ester). They used the same concentration of additives in the fuel as BZD (500 ppm). The oxidative stability values found for the commercial additives were: BHA (19.4 h) > TBHQ (18.5 h) > BHT (7.2 h) > EHN (7 h). It should be noted that in our tests we found an oxidative stability value of 26.3 h using BZD as an additive, and this value is higher than those found for these commercial additives and above 20 h, which is desirable. We emphasize that the composition of biodiesel is also a factor that influences oxidative stability [15]. Therefore, in Table 4 we showed several types of biofuels, additives, and

concentrations, and the data show that few additives in biofuels have stability for more than 30 h. Obadijah *et al.* (2012) [173] showed that for a biofuel made from karanja the concentration of the additive directly influences the stability, obtaining acceptable values for the PY additive only with a concentration of 3000 ppm (Table 4).

The biofuel used in the tests is a majority blend of soybean oil and palm oil. Tang *et al.* (2008) [167] used a B20 with biofuel made from soybean oil while Rizwanul *et al.* (2014) [168] used a B20 with biofuel made from palm oil in their studies. Tang found good values for oxidative stability with a concentration of 200 ppm of PG and PY additives, while the other additives presented similar or inferior results to BZD. Fattah Pedro used a B20 (palm oil) and found values similar to those found for BZD. The two commercial additives tested showed values around 30 h: BHA (30.9) > BHT (29.6), but the concentration of additive used was twice that of BZD, 1000 ppm of BHT and BHA against 500 ppm of BZD.

Some works indicate the oxidative stability for different blends of diesel/biodiesel (B30, B40, B50). Chakraborty & Baruah (2012) [176] investigated the oxidation stability of *Terminalia belerica* biodiesel using the 500 ppm additive concentration for a B30 blend; and the oxidative stability values for BHT and TBHQ after 12 weeks were less than 25 h. Jain & Sharma (2011) [177] in an oxidation stability study of *Jatropha curcas* biodiesel found for a B30 blend, with 500 ppm additives concentration, the values of PY (≈ 31 h) > PG (≈ 28 h) > TBHQ (23 h) > BHT (≈ 21 h) > BHA (≈ 21 h). In this study, the values for a B40 blend are shown [PY (≈ 30 h) > PG (≈ 25 h) > BHT (≈ 18 h) > BHA (≈ 16 h) > TBHQ (≈ 16 h)]. Rawat *et al.* (2014) [178] using *Karanja* (*Pongamia Pinnata*) biodiesel blends (B40), found values lower than 20 h of oxidative stability with the additives BHT, BHA, TBHQ, PG, and PY. For a B50 blend of *Jatropha curcas* biodiesel, for 500 ppm additive concentration, Jain & Sharma (2011) [177] found the oxidative stability values of PY (≈ 28 h) > PG (≈ 24 h) > BHT (≈ 17 h) > BHA (≈ 15 h) > TBHQ (≈ 11 h). Similar values were found by Osawa *et al.* (2016) [165] for a B50 blend of *Croton megalocarpus* biodiesel. Several conditions can change the effect of additives on the oxidative stability of fuels; we have seen that few additives show stability that lasts longer than 30 h. It should be noted that the value of 26.3 h found for BZD is above the desired value of 20 h, resembling commercial additives and, in some cases, presenting better oxidative stability values than commercial additives, so we consider the value found to be adequate and promising for other studies of this class of molecule.

4. Conclusions

The BZD compound is promising from a structural, physico-chemical, and experimental perspective. The supramolecular arrangement of BZD is supported only by weak interactions of the C–H...O and C–H... π type and the energy of the FMO indicated high kinetic stability. The values found for oxidative stability in the diesel-biodiesel blend (B20) were 26.3 h. The molecule was applied in B20 with a contraction that can be considered low when compared to other additives that need a higher concentration to be efficient. Even *in natura*, without any type of

processing in low concentration, BZD showed good results that suggest BZD is a compound with potential for application as a new additive for biofuels. In addition, it provides support for other studies of this class of molecule, regarding this type of application, and paves the way of new studies for different diesel-biodiesel blends.

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Conflicts of interest

There are no conflicts of interest to declare.

ORCID

Hamilton B. Napolitano  <http://orcid.org/0000-0002-6047-9995>

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PAPER

Arylsulfonamide chalcones as alternatives for fuel additives: antioxidant activity and machine learning protocol studies†

Vitor S. Duarte,^{*a} Igor D. Borges,^{ab} Giulio D. C. d'Oliveira,^c Eduardo C. M. Faria,^{ab} Leonardo R. de Almeida,^a Valter H. Carvalho-Silva,^{id a} Caridad Noda-Pérez^c and Hamilton B. Napolitano^{id *a}

Biodiesel is a promising fuel with the potential to reduce some negative aspects of fossil fuels, such as the emission of pollutants and greenhouse gases (GHGs), the scarcity of natural resources and market instability. To amplify its low durability and stability the use of technologies based on molecular compounds that reduce the oxidation rate of biodiesel and preserve its physical–chemical properties is very common and necessary throughout the world. To reduce oxidative stability problems of diesel–biodiesel blends, arylsulfonamide chalcones were evaluated as potential additives for B20 blends. In this study, comprehensive structural, computational, and experimental analyses were undertaken to understand the antioxidant potential of these compounds as possible additives. The supramolecular arrangements were stabilized by weak molecular interactions (C–H...O and C–H... π), which are related to antioxidant and antibacterial action, and groups can act as electron-donating substituents. The energy range of 593.1–570.2 kJ mol^{−1} in the frontier molecular orbitals indicates high structural stability, due particularly to sulfonamide groups which enable electrophilic attack. Furthermore, the Fukui function aligned with kinetics parameters, obtained using machine learning protocols, provided information to clarify and expand the comprehension of chalcone antioxidant features mediated by free-radical capture. The heat of combustion indicated good energy availability (6530.5–7306.5 kcal kg^{−1}), close to those of conventional fuels. In addition, the oxidative stability of the diesel–biodiesel blend (B20) remained at around 27 hours, after 140 days of storage, which is better than for some commercial additives. We hope that this comprehensive study will support the understanding of chalcone-based compounds as alternatives to fuel additives.

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1. Introduction

For several years, leaders from around the world have been discussing actions to face climate change challenges. The United Nations Conference on Climate Change (COP27)^{1,2} has discussed solutions to environmental problems, such as reducing conventional and greenhouse gas (GHG) pollutant emissions, as well as the energy crisis, which is considered a global emergency.^{3,4} The synergism of fossil fuels and renewable fuels represents a sustainable option that can reduce the emission of pollutants and provide an alternative energy matrix.^{5–7} Biodiesel is an example of a renewable and promising biofuel that can

be obtained from renewable biomass sources.⁸ Although the production of biofuels generates GHG emissions during some stages of their production, a study of the renewable fuel standard (RFS) program adopted by the US Environmental Protection Agency (EPA) indicated that, within a 30-year time period, many biofuels could generate GHG emissions lower than gasoline.⁹

The stability of biodiesel is a critical factor in its production, storage, and commercialization^{10–12} because the mixture of methyl or ethyl esters in biodiesel are rich in unsaturated bonds and contain polar oxygenated groups. Its molecular structure makes it more susceptible to oxidative, thermal or microbiological degradation compared with other fossil fuels.^{13,14} Biodiesel has a more pronounced hygroscopic character, retaining more water in the fuel, and promoting the proliferation of microorganisms.^{15–17} Accordingly, the addition of biodiesel to diesel (as in blends) affects the stability of the final product, reducing the efficiency of the fuel.^{10,17} Recent parametrization has authorized a certain percentage of biodiesel in diesel, of which 10–20% of biodiesel in diesel is the most

^a Grupo de Química Teórica e Estrutural de Anápolis, Universidade Estadual de Goiás, Anápolis, GO, Brazil. E-mail: vitor.sduarte@seduc.go.gov.br, hbnapolitano@gmail.com

^b Centro de Pesquisa e Eficiência Energética, CAO Montadora de Veículos LTDA, Anápolis, GO, Brazil

^c Instituto de Química, Universidade Federal de Goiás, Goiânia, GO, Brazil

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common mixture (B10–B20 blends), according to the legislation of each country.^{18–22}

Regional climatic conditions also affect the quality of the product, in addition to the basic raw materials (corn, soy, palm, animal fat, residues, *etc.*) used for biodiesel production.^{23–25} The low oxidative stability of biodiesel causes a greater propensity to degradation, and the storage of this fuel for long periods can make it unsuitable for use, which can generate residues or sediments that damage engines,^{26,27} consequently generating maintenance for shorter periods, causing greater costs and resistance from the automotive industry.²⁸ Therefore, the use of compounds – so-called additives – that delay biodiesel oxidation and preserve its properties is rising as a great need throughout the world.^{29–33}

Chalcones are organic compounds and a class of intermediate flavonoids with a keto carbonyl group and one α,β -unsaturated bond that are obtained from natural^{34,35} or synthetic sources.^{36,37} The molecular structure of these molecules presents interesting characteristics that are driven by substituent groups, and these molecules are described in the literature as having miscellaneous applications.^{38–41} The ability to prevent free-radical-induced oxidative damage is related to their potential antioxidant activity, and the antiproliferation of microorganism action for this class of molecules means that chalcones are used in several areas, such as drugs,^{40,42–44} food preservatives,^{45,46} and recently in studies as additives for biofuels.^{42,47–51} The structure–activity relationship of a molecule is often favored by substitution with bioactive chemical groups, which can potentiate the molecular activity.^{52–54} The sulfonamide group is an example of a chemical group that is reported in the literature to have several biological properties, including antimicrobial^{55–57} and antioxidant activities.^{58–61} Therefore, the replacement of this group in chalcone molecules can be structurally innovative toward antioxidant activities.^{62–64}

Here, this paper presents a comprehensive structural analysis, investigating the structure–activity relationship supported by density functional theory (DFT) calculations, to clarify the structural stability and the molecular regioselectivity of chalcones. From a kinetic perspective, machine learning (ML) protocols were used to clarify and expand our understanding of groups related to the oxidant activity of five arylsulfonamide chalcones. Finally, an experimental study was performed for these molecules, to assess the heat of combustion, as well as an accelerated oxidative stability analysis (using the Rancimat method) to connect the calculated theoretical properties with the antioxidant potential and behavior of these molecules when used as possible additives for a diesel–biodiesel blend (B20).

2. Computational and experimental procedures

2.1. Molecular modeling analysis

Five arylsulfonamide chalcone compounds were synthesized according to the reactions described by d'Oliveira and coauthors:⁶⁵ **Chal01**,⁶⁶ **Chal02**,⁶⁷ **Chal03**,⁶⁸ **Chal04**⁶⁶ and **Chal05**⁶⁹

(Fig. 1), and their crystallographic data were obtained from the Cambridge Crystallographic Data Centre (CCDC) under codes: 1904244, 1850083, 1868826, 1949070 and 1904245, respectively. The structural description, molecular representation and comparisons between the structures were generated using Olex2,⁷⁰ Ortep,⁷¹ and Mercury software.^{72,73} The initial analysis of the intermolecular interactions for the arylsulfonamide chalcone compounds was performed based on their electronic density through the Hirshfeld surface (HS) analysis and 2D fingerprint plots using CrystalExplorer17 software.⁷⁴ The HSs are generated considering the neighborhood pattern of the molecule and the contact distances between the atoms: d_e (distance from the surface to the nearest atom in the molecule itself) and d_i (distance from the surface to the nearest atom in another molecule).^{75–77} The 2D fingerprint plots are plotted from the d_e versus d_i distribution and provide a quantitative analysis of the contacts present in the molecule.⁷⁸

Theoretical analyses of the arylsulfonamide chalcones compounds was performed using DFT.⁷⁹ The experimental geometric parameters of the crystallographic data were optimized in the gas phase through Gaussian09 software⁸⁰ using the M06-2X/6-311++G(d,p)^{81–83} level of theory. This functional is recommended for non-covalent interactions,^{84,85} has a relatively small computational cost, and presents satisfactory results, besides considering the electronic correlation.^{86,87} From the wave function generated, the frontier molecular orbitals (FMOs) were calculated: these orbitals are the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO).^{88,89} In addition, the molecular electrostatic potential (MEP) map was also generated to identify the regions with the highest and lowest electron density and thus characterize the most reactive sites. The local electrophilicity of the molecules was determined *via* the Fukui function^{90,91}

$$f(r) = \left[\frac{\partial \rho(r)}{\partial N} \right]_{\nu}, \quad (1)$$

where N is the number of electrons present in the system, and the constant term ν in the partial derivative is the external potential. The Multiwfn package program⁹² was used to study

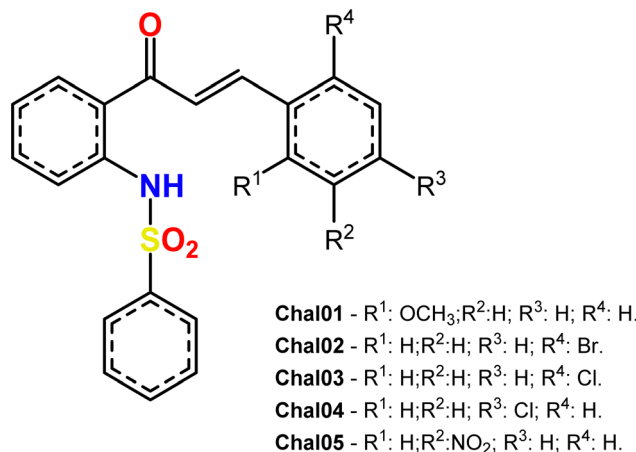


Fig. 1 Structure of the arylsulfonamide chalcones (**Chal01**–**Chal05**).

the Fukui functions. From the Fukui function, it was possible to predict the possible molecular regions in which the arylsulfonamide chalcones act as antioxidant agents.

2.2. Heat of combustion

The heat of combustion is the amount of heat released by burning a known quantity of the sample, which is transferred to a calorimetric system comprising a known quantity of water at a temperature in the range of 18–25 °C with an accuracy of ± 1 °C during a series of measurements. The sample burn releases heat that promotes a temperature change in the initially added water. Finally, the ratio of the released energy to the added sample mass represents the calorific value. The bomb calorimeter (IKA C200 model) was used according to the ASTM D4809 standard.⁹³

2.3. Storage stability test

The storage stability of S10 diesel containing a 20% volume of biodiesel (*i.e.*, 20% biodiesel + 80% diesel), which is called a B20 blend, was verified. The composition of the biodiesel used is mostly soy-derived (60% soybean oil, 37% palm oil, 2% bovine fat and 1% pork fat). To the B20 fuel was added **Chal01**, **Chal02**, **Chal03**, **Chal04** and **Chal05**, respectively, where a concentration of 500 ppm was used for each sample. The B20 fuel was stored in high-density polyethylene (HDPE) tanks in an external environment for 140 days; HDPE is used in some vehicle fuel tanks. After the storage period, the oxidation stability was measured according to the accelerated Rancimat method with all tests performed in triplicate.

2.4. Oxidation stability tests

Oxidation stability testing of the biodiesel fuel was carried out using the Rancimat method according to the requirements described in the EN 15751 standard.⁹⁴ In this procedure, heating the sample at 110 °C with a constant flow of purified air (at 10 L h⁻¹) supplies oxygen to the medium, promoting a slow oxidation reaction that forms peroxide products which, due to the high temperature, dissociate and form volatile carboxylic acids.⁹⁵ Flitsch *et al.* (2014)⁹⁶ identified these volatile products using gas chromatographic techniques during the Rancimat accelerated oxidation test. The fatty acid oxidation reaction produces formic and acetic acids, methyl esters and epoxides. These compounds are carried by the passage of air into a measuring vessel containing demineralized or distilled water, where the oxidation products are monitored using a conductivity meter.⁹⁷ The result is given as the period from the beginning of the test until an inflexion point in the conductivity is recorded, which is known as the induction period (IP; in units of hours).⁹⁸ In this work, a Metrohm 873 model Biodiesel Rancimat system was used following the requirements of the EN 15751: 2014 standard.⁹⁴

2.5. Machine learning procedures

The oxidation reactions promoted by free-radical compounds were simulated using pySiRC,⁹⁹ a machine-learning computational platform. The hydroxyl radical ($\bullet$ OH) – an archetypal

system of degradation reactions – was selected to mimic the oxidation effect promoted by the radical attack. Simulations were carried out using the Morgan and MACCS fingerprint as a structural descriptor and the XGBoost ML algorithm to predict the reaction rate constant of oxidative attack promoted by hydroxyl radicals on the compounds in the B20 blends.¹⁰⁰

The parameters were calculated for the major compounds of diesel (represented by the C₁₀H₂₀ molecule), biodiesel (BD; as represented by methyl 9-octadecenoate (M9OD; C₁₉H₃₈O₂, 19.98%)), methyl palmitate (MPAL; C₁₇H₃₄O₂, 12.87%), the methyl 8,11-octadecenoate (M8OD; C₁₉H₃₄O₂, 10.22%) fatty acid methyl ester,¹⁰¹ and the aforementioned molecules (**Chal01**–**Chal05**). For comparison, the kinetic parameters of other additive compounds reported by Hosseinzadeh-Bandbafha and co-authors¹⁰² were also estimated, *i.e.*, butylated hydroxytoluene (BHT), *tert*-butyl hydroquinone (TBHQ), butylated hydroxyanisole (BHA), propyl gallate (PG), pyrogallol (PY) and gallic acid (GA).

4. Results and discussions

4.1. Molecular modeling description

The five arylsulfonamide chalcones are structurally similar: all have the chalcone nucleus in which a sulfonamide group is attached to the aromatic ring 1 in the *ortho* position; however, all structures have different substituents on the aromatic ring 2 (Fig. 2). **Chal01** has a methoxy group attached to the aromatic ring 2 in the *ortho* position; **Chal02** has a Br atom attached to the aromatic ring 2 in the *ortho* position, whereas **Chal03** has a Cl atom at the *ortho* position and **Chal04** has a Cl atom at the *para* position. Finally, **Chal05** has a nitro group at the *meta* position of the aromatic ring 2. All compounds crystallized in the monoclinic crystal system with one independent molecule in the asymmetric unit (*Z'*) and four molecules in the unit cell (*Z*), except for **Chal04**, which crystallized in the triclinic crystal system with one independent molecule in the asymmetric unit and two molecules in the unit cell (Table S1, ESI[†]).

The 2D fingerprint plots (Fig. 3) help us to understand the percentage of each type of intermolecular interaction present in the molecule. For the analyzed molecules the values (d_i , d_e) $\approx$ (1.0, 1.4) correspond to an H-bond distance of ~ 2.4 Å, which can be attributed to weak hydrogen bonds.¹⁰³ As all compounds are organic molecules, contacts involving hydrogen atoms (H $\cdots$ H) represent a large percentage for all the structures [**Chal01** (44.2%), **Chal02** (36.3%), **Chal03** (37.1%), **Chal04** (35.1%) and **Chal05** (27.6%)] (Table 1). C $\cdots$ C indicates contacts involving aromatics ($\pi\cdots\pi$), which is low for all structures. The H $\cdots$ O contacts for these molecules indicate intermolecular interactions of the C–H $\cdots$ O=C and C–H $\cdots$ O=S type, and show significant representations in all of them, as well as H $\cdots$ C contacts which indicate C–H $\cdots\pi$ interactions. The supramolecular arrangement for the five structures is supported only by weak interactions of the C–H $\cdots$ O and C–H $\cdots\pi$ type, for **Chal03** and **Chal04** that have Cl atoms, C–H $\cdots$ Cl (H $\cdots$ Cl) contacts are also present and contribute to the stability

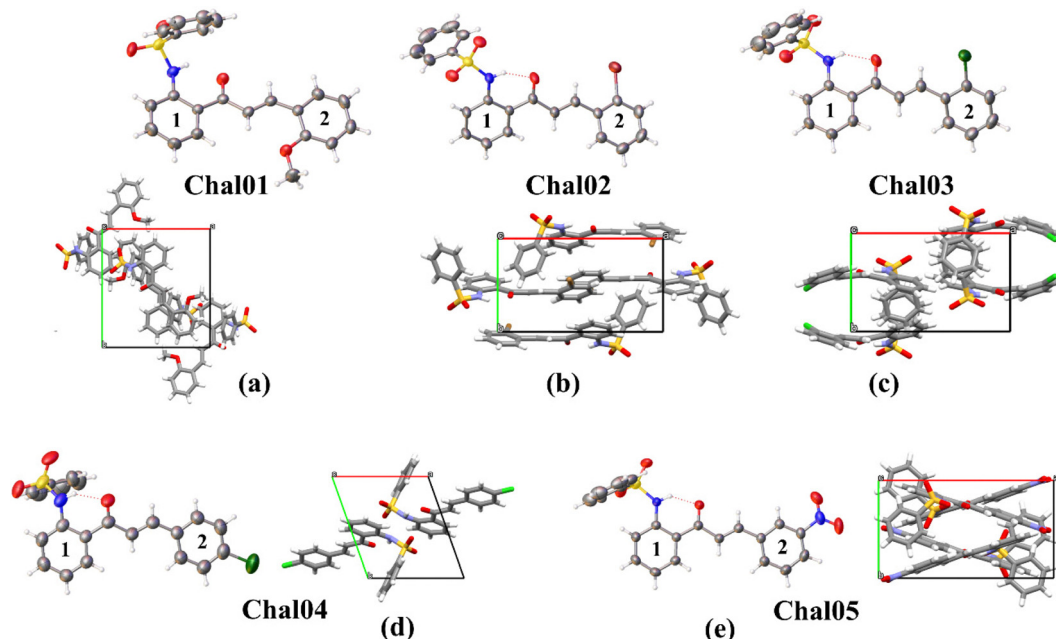


Fig. 2 ORTEP representations with ellipsoids at 50% probability, and molecular packing in the unit cell along the "c" axis for the **Chal01–Chal05** compounds.

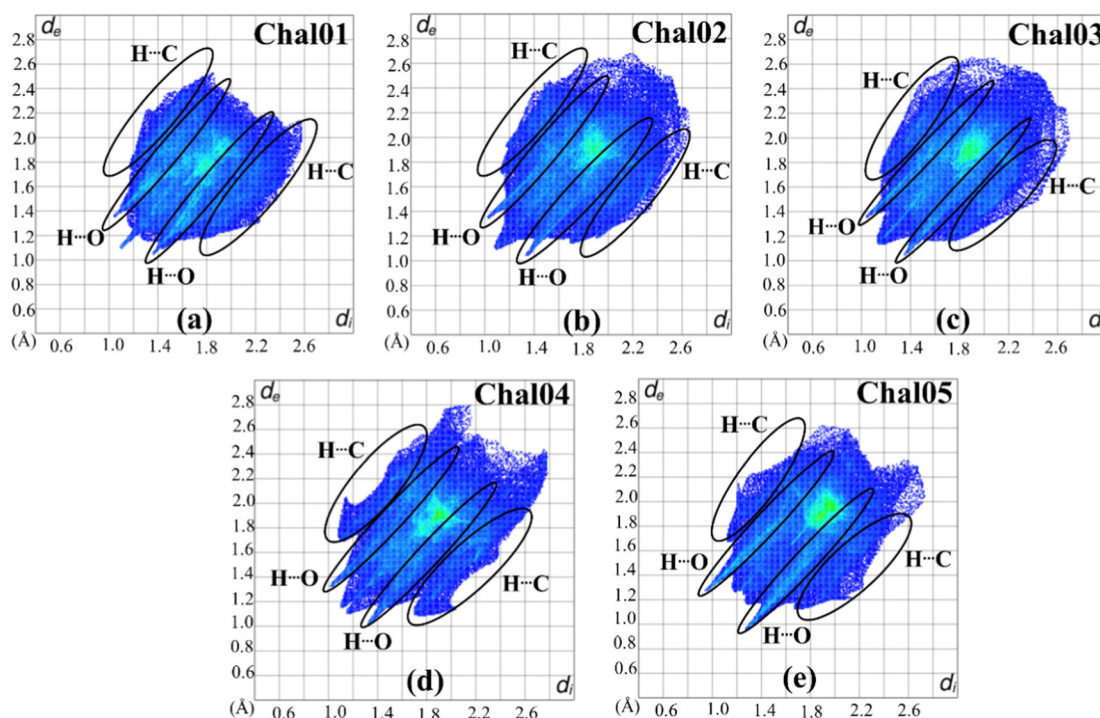


Fig. 3 2D fingerprint plots for the **Chal01–Chal05** compounds.

of the supramolecular arrangement (Fig. S1, ESI†). In addition, for **Chal02**, which has a Br atom, C–H...Br (H...Br) contacts are present in the supramolecular arrangement.

An overlap analysis of the structures shows conformational divergences between them, despite being part of the same class

of molecules and all having an aryl sulfonamide group attached to aromatic ring 1, and due to the different substituents present on aromatic ring 2, different conformations can be noted. The overlap was performed using the chalcone core as a reference for anchoring, and the root mean square (RMS) between the

Table 1 Percentage of interactions present in the arylsulfonamide chalcone compounds

	H...H (%)	H...O (%)	H...C (%)	C...C (%)	H...Cl (%)	H...Br (%)	Others (%)
Chal01	44.2	21.6	24.6	7.4	—	—	2.2
Chal02	36.3	19.9	19.3	8.5	—	8.4	7.6
Chal03	37.1	19.9	19.1	8.6	7.6	—	7.7
Chal04	35.1	19.6	18.1	9.9	12.8	—	4.5
Chal05	27.6	36.5	20.5	9.4	—	—	6

overlaps was calculated for this configuration. The structures that showed the most similar conformations were **Chal01** and **Chal05** (RMS: 0.118), and **Chal03** and **Chal05** (RMS: 0.350), where these structures showed a small divergence in the overlap in the aromatic ring of the sulfonamide group (Fig. 4d and c). The structures **Chal03** and **Chal04** have a difference in the molecular structure only for the Cl atom, which in **Chal03** is at the *ortho* position and in **Chal04** is at the *para* position of aromatic ring 2. This change in the position of the Cl atom substituent indicates a divergence of 174.97° between the aryl groups attached to the sulfonamide (RMS: 0.393), as shown in Fig. 4a. Another interesting overlap is between **Chal02** and **Chal03**, where the molecular structure between them diverges from the Br atom substituent for **Chal02** and the Cl atom for **Chal03**, which are both in the same position. This change in the molecular structure shows a divergence of 153.51° between the aryl groups and a divergence in aromatic ring 2 of 56.91° , with an RMS of 0.716 (Fig. 4b). Small differences, such as the position of a substituent or different substituents in the same position, can corroborate different conformations of the molecule, different interactions, and supramolecular arrangements.^{104–108}

The HOMO and LUMO arrangements for the molecules are shown in Fig. 5. The distribution of the LUMO is similar for all

molecules, although the HOMO configuration shows greater differences among molecules. The energy difference (E_{GAP}) between these orbitals is used as an indicator of some properties of the molecule, such as the structural stability and chemical reactivity.¹⁰⁹ The E_{GAP} values for the arylsulfonamide chalcones are **Chal01** (592 kJ mol^{-1}), **Chal02** ($586.5 \text{ kJ mol}^{-1}$), **Chal03** ($585.1 \text{ kJ mol}^{-1}$), **Chal04** ($593.1 \text{ kJ mol}^{-1}$) and **Chal05** ($570.2 \text{ kJ mol}^{-1}$).

These values suggest that **Chal04**, which has a chlorine atom at the *para* position of aromatic ring 2, has the highest structural stability, while **Chal05**, which has a nitro group, has the lowest, with the overall order **Chal04** > **Chal01** > **Chal02** > **Chal03** > **Chal05**. The HOMOs for the arylsulfonamide chalcones characterize the bonding orbitals with ionization potential (nucleophilic), while the LUMOs characterize the antibonding orbitals with electron affinity (electrophilic). The MEP map analysis shows that the sulfonamide group of all the molecules has a high electron density, suggesting that these regions are more susceptible to electrophilic attack, as well as the nitro group region of **Chal05**. In parallel, the blue colors in the MEP maps indicate regions that are most susceptible to nucleophilic attack (Fig. 5).

To determine the local electrophilicity, the Fukui function was used to predict the regions of nucleophilic, $f^+ = [\partial \rho(r)/\partial N]_{v(r)}^+$, electrophilic, $f^- = [\partial \rho(r)/\partial N]_{v(r)}^-$ and radical attack, $f^0 = [\partial \rho(r)/\partial N]_{v(r)}^0$. During the biodiesel degradation process, the sites of unsaturation in the fatty acid methyl ester chain are prone to attack by free radicals involved in oxidative chain reactions.¹¹⁰ Consequently, the biodiesel chemical composition is altered, leading to the formation of aldehydes, alcohols, and short-chain carboxylic acids,¹¹¹ which in turn causes an increase in insoluble sediments, acidity, and viscosity, making the fuel unsuitable for use.^{111,112} At trace concentrations (typically 500

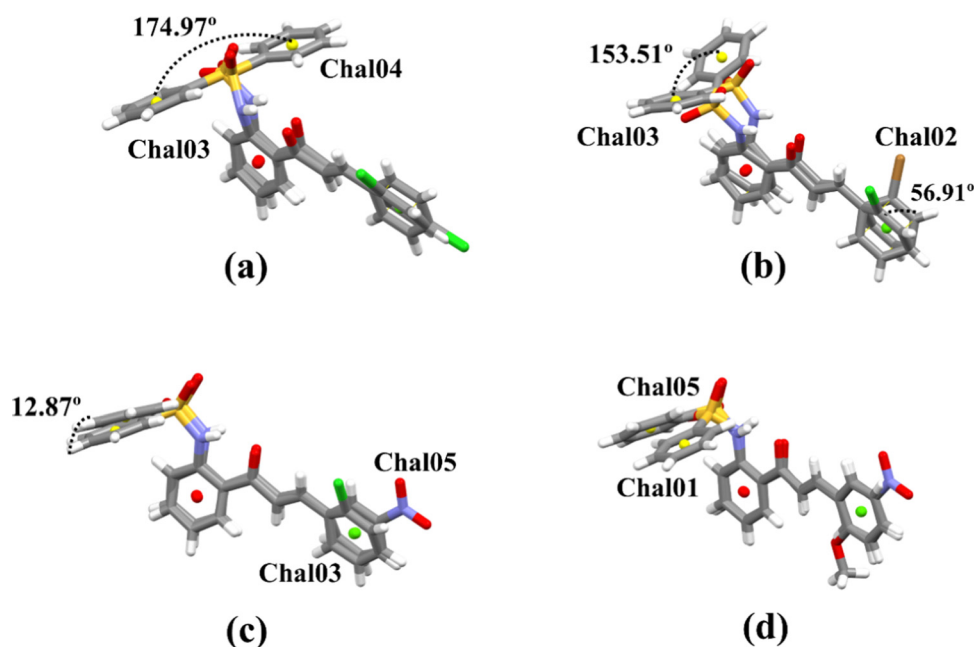


Fig. 4 Overlap between arylsulfonamide chalcone compounds: **Chal03** and **Chal04** (a), **Chal02** and **Chal03** (b), **Chal03** and **Chal05** (c) and **Chal01** and **Chal05** (d).

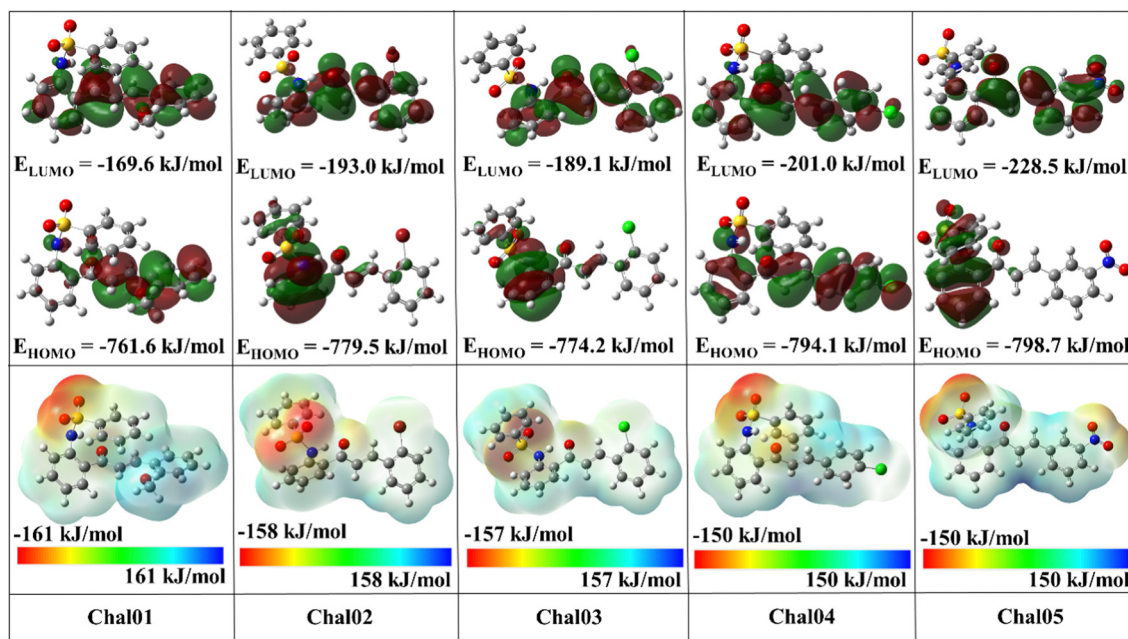


Fig. 5 FMO (top rows) and MEP map (bottom row) representations of **Chal01–Chal05**.

ppm), antioxidant additives are effective for scavenging the free radicals involved in oxidative reactions.¹¹³ The isosurfaces obtained from the f^+ , f^- , and f^0 functions (Fig. 6) enable us to observe that, in the five arylsulfonamide chalcones, the charge density is high in the carbonyl group, as well as in the C_β atom, leaving these regions susceptible to nucleophilic attack (f^-).

According to the isosurfaces generated by the f^- function, electrophilic attack can occur on the N atom of the **Chal02**, **Chal03** and **Chal05** sulfonamide portion. For **Chal01** and **Chal04**, this will occur on the C_α atom, while the $-OCH_3$ group in **Chal01** is susceptible to electrophilic attack, and for **Chal04** the C bonded the Cl atom is susceptible to electrophilic attack. The delocalized π electrons present in the C_α – C_β bond of the aliphatic portion of the chalcones resonate with the π electrons of the respective rings. This mesomeric effect, produced by the O atom of the carbonyl group, minimizes the charge density on the C_α atom, making this an electrophilic region for the **Chal01** and **Chal04** molecules.

For the isosurfaces produced by the f^0 function, for molecules **Chal01** and **Chal04**, the atoms in the keto-vinylene group $-(CO)-CH=CH-$ are favorable to the capture of free radicals produced in these processes, explaining the antioxidant character of chalcones,³⁸ whereas for **Chal02**, **Chal03** and **Chal05**, they showed that the N atom and the carbonyl O and C atoms are susceptible to radical attack. The oxidation of the diesel-biodiesel blend is thus mitigated by the additive compounds, which act as a barrier to protect the blend.¹¹²

4.2. Antioxidant additive analysis

Q10 The use of biofuels has increased dramatically throughout the world, and the production of biofuels has grown by about 10-fold over the past 20 years (2000–2019); in 2019, world

production of biofuels was 2 773 000 barrels per day, of which total biodiesel production was about 28%, at 795 000 barrels per day.^{114,115} As mentioned, biodiesel is interesting due to its renewable character, the reduction of atmospheric pollutants and the diversity of its production (corn,¹¹⁶ soy,^{117,118} waste vegetable and frying oil,^{117,119} chicken fat,¹²⁰ cotton,¹²¹ palm,^{122,123} and other sources^{124–131}). The Rancimat test results were similar for all arylsulfonamide chalcones, with values of around 27 hours; however, the fuel with the added **Chal04** molecule showed the best result (28.56 h), while the fuel with **Chal02** added had the lowest result, at 26.07 h (Table 2). These oxidative stability values of around 27 h for the fuel are very interesting; according to the European Committee of Standardization, the minimum biodiesel oxidation stability required is 8 h at 110 °C (EN14214:2012).¹³² However, since 2018, there has been a movement by groups of distributors, additive manufacturers and vehicle components industries to establish a minimum limit of 20 h. In Brazil, which is one of the major biodiesel producers, according to Brazilian Resolution ANP 798/2019¹³³ (for a 60 day period), the minimum oxidation stability limit for biodiesel is 12 h.

In the literature for studies on B20 blends with commercial additives, it was found that there is an induction period variation for different concentrations of additives used (Table 3). Furthermore, several conditions can affect the additive effects on the oxidative stability of fuels, such as the composition of the biodiesel. Noting that few additives reach or exceed the stability value of 30 h, the values found for arylsulfonamide chalcones **Chal01–Chal05** are therefore prodigious, where our additive samples were used without any type of processing, thus resembling commercial additives. However, we emphasize that the presence of sulfur and nitrogen atoms

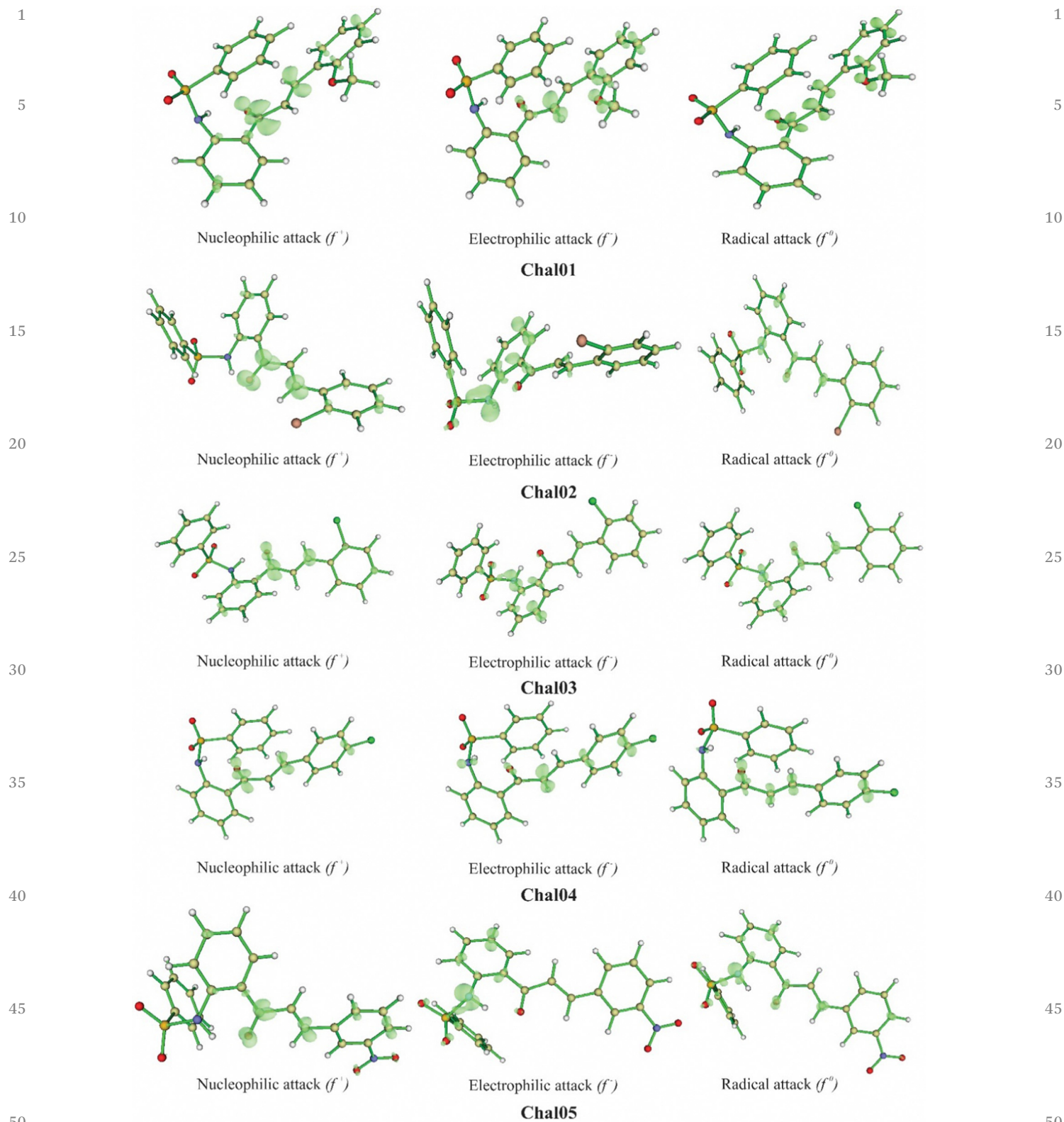


Fig. 6 Isosurfaces of the f^+ , f^- , and f^0 functions indicating the nucleophilic, electrophilic, and radical attack regions, respectively, for the **Chal01–Chal05** molecules, calculated at a value of 0.5.

might present a problem due to the formation of sulfur and nitrogen oxides during combustion; the amount of these elements must be monitored to ensure that they do not exceed regulatory limits. Such elements must be carefully evaluated,

Table 2 Oxidative stability from **Chal01–Chal05** compounds acting as additives on diesel–biodiesel blends

Compound	Result 1 (h)	Result 2 (h)	Result 3 (h)	Average (h)	Standard deviation (h)	Measurement uncertainty (h)
Chal01	26.88	27.43	27.99	27.43	0.555	0.9
Chal02	26.32	26.05	25.83	26.07	0.245	0.9
Chal03	29.04	27.84	27.77	28.22	0.714	0.9
Chal04	27.54	28.9	29.23	28.56	0.896	1.3
Chal05	26.94	28.26	27.74	27.65	0.665	1.3

particularly for less polluting fuels (such as biofuels). The development of a new additive should be guided by a set of analyses (and not just a specific analysis type), and experimental tests must be carried out to demonstrate the meaningful pros and cons. Although arylsulfonamide chalcones have some challenges, these chalcone-based compounds are promising for future insights on fuel additives.

The oxidative stability of biodiesel and its low energy availability are problems associated with this fuel, so additives that preserve its stability and present promising energy availability can be interesting. The heat of combustion analysis for the arylsulfonamide chalcone samples was carried out and presented the following values: **Chal01** (7306.5 kcal kg⁻¹), **Chal02** (6530.5 kcal kg⁻¹), **Chal03** (6803.5 kcal kg⁻¹), **Chal04** (6704.8 kcal kg⁻¹) and **Chal05** (6891.8 kcal kg⁻¹) (Table 4). These heat of combustion values found for the arylsulfonamide chalcones can be considered close to those of conventional fuels, which have good energy availability. The heat of combustion is related to the amount of energy released in the oxidation of a fuel, and high values are associated with a better fuel performance, so an additive that also has good energy availability is desirable.

4.3. Machine learning analysis

The reaction rate constant (k_{OH}) reveals an important kinetic parameter to evaluate the efficiency of the degradation of a compound *via* hydroxyl radical attack: a high value indicates faster oxidation. For this discussion, we considered the highest percentage values within the applicability domain (AD%) of the ML model (XGBoost) and molecular descriptor; in this case, the AD% using the MACCS fingerprint for all tested molecules was above 60%, with 62.71% for **Chal05** being the lowest. This indicates a more accurate prediction for the MACCS fingerprint than using the Morgan fingerprint for these molecules within the training set of this tool. The values of k_{OH} , presented in

Table 4 Heat of combustion from **Chal01–Chal05** compounds and some conventional fuels

Compound	Heat of combustion (kcal kg ⁻¹)	Compound	Heat of combustion (kcal kg ⁻¹)
Chal01	7306.5	Ethanol	8504.1
Chal02	6530.5	Diesel B0 ^{117,119,126,142,143}	9646.9–10 824.4
Chal03	6803.5	BD-B100 (soy) ¹¹⁷	8698.7
Chal04	6704.8	BD-B10 (soy) ¹⁴⁴	9577.7
Chal05	6891.8	BD-B100 (methyl palm) ¹²⁷	8526.7
Gasoline	9768.5	BD-B100 (waste oil) ¹¹⁹	9052.2
Butanol	8504.1	BD-B100 (frying oil) ¹¹⁷	8646.2

Table 5, are for the majority compounds of diesel (represented by C₁₀H₂₀ molecule) $1.14 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$, and biodiesel (the fatty acid methyl ester) represented by methyl 9-octadecenoate (M9OD) $5.94 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, methyl palmitate (MPAL) $4.98 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ and methyl 8,11-octadecenoate (M8OD) $5.94 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$. The arylsulfonamide chalcones in this study present k_{OH} values of $1.06 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$ (**Chal01**), $3.63 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ (**Chal02**), $1.94 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ (for **Chal03** and **Chal04**) and $8.17 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ (**Chal05**), and for **Chal01** and **Chal05** the oxidation potential is higher than the values obtained for the reference molecules of both diesel and all BDs (Table 5).

The k_{OH} values were also obtained for additive compounds as mentioned above, with the higher values in ascending order for TBHQ $7.63 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, PY $1.02 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$, and PG $1.22 \times 10^{10} \text{ M}^{-1} \text{ s}^{-1}$; by contrast, close values for BHT $4.34 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ and BHA $4.31 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$, alongside $1.48 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ for GA, showed a lower oxidative potential (Table 5). Thus, the constants obtained for GA, **Chal03/Chal04**, **Chal02**,

Table 3 Oxidative stability for some commercial additives in B20 and B100 blends. The concentration of additive in the blend is shown in the table in parts per million (ppm). The induction period (IP) is shown in hours (h)

	BHA	BHT	TBHQ	PG	PY	GA	EHN	Ref.
IP (h) [B20/100 ppm]	19.5	—	—	—	—	—	—	Osawa <i>et al.</i> (2016) ¹³⁴
IP (h) [B20/200 ppm]	21	21	—	—	—	—	—	Tang <i>et al.</i> (2008) ¹³⁵
IP (h) [B20/500 ppm]	19.4	7.2	18.5	—	—	—	7	İleri and Koçar (2014) ¹³⁶
IP (h) [B20/1000 ppm]	30.9	29.6	—	—	—	—	—	Rizwanul <i>et al.</i> (2014) ¹³⁷
IP (h) [B20/1000 ppm]	35	28	—	—	—	—	—	Alagu <i>et al.</i> (2018) ¹³⁸
IP (h) [B20/2000 ppm]	22.2	25.2	28.38	—	—	—	—	Rizwanul <i>et al.</i> (2014) ¹³⁹
IP (h) [B100/500 ppm]	11	8	18	27	28	—	—	Mittelbach and Schober (2003) ²⁹
IP (h) [B100/500 ppm]	6	5	4	15	25	—	—	Agarwal <i>et al.</i> (2015) ¹⁴⁰
IP (h) [B100/2000 ppm]	—	3.14	2.91	—	25	0.8	—	Obadijah <i>et al.</i> (2012) ¹⁴¹

*Values found in the literature according to the references.

Table 5 Reaction rate (k_{OH}) for arylsulfonamide chalcone compounds **Chal01**–**Chal05**, and other additives.¹⁰² The values were obtained using the ML model XGBoost and were separated into two types of molecular fingerprints, Morgan and MACCS. Diesel and biodiesel (BD)¹⁰¹ are represented by their majority compound, respectively. AD is the % of similarity within the applicability domain

Molecule	Reaction rate constant (k_{OH}) ($\text{M}^{-1} \text{s}^{-1}$)			
	Morgan	AD (%)	MACCS	AD (%)
Diesel ($\text{C}_{10}\text{H}_{20}$)	6.05×10^9	50	1.14×10^{10}	76.92
BD M9OD ($\text{C}_{19}\text{H}_{38}\text{O}_2$)	19.98% 5.90×10^9	48.21	5.94×10^9	85
BD MPAL ($\text{C}_{17}\text{H}_{34}\text{O}_2$)	12.87% 5.70×10^9	58.7	4.98×10^9	89.47
BD M8OD ($\text{C}_{19}\text{H}_{34}\text{O}_2$)	10.22% 5.90×10^9	40.32	5.94×10^9	85
Chal01 ($\text{C}_{22}\text{H}_{19}\text{O}_4\text{NS}$)	4.60×10^{10}	20.29	1.06×10^{10}	70.31
Chal02 ($\text{C}_{21}\text{H}_{16}\text{O}_3\text{NSBr}$)	8.47×10^9	21.54	3.63×10^9	66.67
Chal03 ($\text{C}_{21}\text{H}_{16}\text{O}_3\text{NSCl}$)	1.28×10^{10}	21.54	1.94×10^9	66.67
Chal04 ($\text{C}_{21}\text{H}_{16}\text{O}_3\text{NSCl}$)	1.28×10^{10}	21.88	1.94×10^9	66.67
Chal05 ($\text{C}_{21}\text{H}_{16}\text{O}_5\text{N}_2\text{S}$)	1.24×10^{10}	24	8.17×10^9	62.71
BHT ($\text{C}_{15}\text{H}_{24}\text{O}$)	4.16×10^9	100	4.34×10^9	100
TBHQ ($\text{C}_{10}\text{H}_{14}\text{O}_2$)	7.57×10^9	100	7.63×10^9	100
BHA ($\text{C}_{22}\text{H}_{32}\text{O}_4$)	7.27×10^9	66.67	4.31×10^9	77.78
PG ($\text{C}_{10}\text{H}_{12}\text{O}_5$)	1.11×10^{10}	100	1.22×10^{10}	100
PY ($\text{C}_6\text{H}_6\text{O}_3$)	7.06×10^9	40.74	1.02×10^{10}	100
GA ($\text{C}_7\text{H}_6\text{O}_5$)	4.09×10^9	40.62	1.48×10^9	100

BHT and BHA are even slightly below the reference molecules. These values suggest that oxidative degradation in arylsulfonamide chalcones **Chal01** and **Chal05** (**Chal01** > **Chal05**) has a higher oxidation potential than in the diesel and biodiesel reference compounds, which is consistent with the results obtained experimentally *via* the accelerated Rancimat method. When compared with the existing additives, such oxidative rates are generally of the same order, but the higher than $6 \times 10^9 \text{ M}^{-1} \text{s}^{-1}$ values for **Chal01** and **Chal05** indicate that arylsulfonamide chalcones could retard the degradation of biodiesel, and be suitable sources for enhancement of the oxidative stability.

5. Conclusions

Environmental concerns are present in all sectors of society on nowadays. In this context, it will be crucial to intensify biofuel participation in the global energetic matrix for the reduction of pollutant emissions and fossil fuel dependency. Despite offering several advantages for its use, biodiesel is more susceptible to degradation than petroleum diesel, thus demanding the application of additives that can increase the shelf-life of this biofuel. Arylsulfonamide chalcones are promising from both theoretical and experimental perspectives regarding their molecular structure, which supports their antioxidant activity. Their supramolecular arrangements are stabilized only by weak interactions that support electron-donation with the contribution of antioxidant and antibacterial properties. FMO energy analysis indicated the structural stability and antioxidant power of five arylsulfonamide chalcones, and showed the sites where nucleophilic, electrophilic, and radical attack could occur during chemical processes; in addition the MEP map showed the sulfonamide group sites with greater reactivity.

Heat of combustion testing showed a promising energy availability for these compounds, which is close to those of conventional fuels, and the oxidative stability of B20 blends with added arylsulfonamide chalcone compounds was around 27 hours. Fukui indices and machine learning protocols indicated the following order of oxidative degradation potentiality: **Chal01** > **Chal05** > **Chal02** > **Chal03/Chal04**. These arylsulfonamide chalcones, in particular **Chal01** and **Chal05**, have a higher oxidation potential than the diesel and BD reference compounds (consistent with Rancimat analysis).

The Global Health Innovative Technology Fund has established criteria for potential molecular compounds with some biological activity, such as (1) synthesis in ≤ 5 steps, (2) a purity of >90%, (3) adequate yield and (4) satisfactory solubility.¹⁴⁵ Arylsulfonamide chalcones are compounds that satisfy these criteria, with a synthesis in ≤ 5 steps with solubility in polar and non-polar solvents and with high purity.^{146,147} In addition, it is important to consider (1) the cost, (2) availability, (3) sustainability, and (4) the potential formation of nitrogen and sulfur oxides during combustion. Although arylsulfonamide chalcones have some challenges, further research on chalcone-based compounds will inform the applicability of chalcones as biofuel additives, as well as their comparison with existing antioxidants. Finally, the structural parameters and physicochemical properties herein provide insights for future synthesis and molecular-based studies on the development of new additive strategies.

Conflicts of interest

There are no conflicts of interest to declare.

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5. CONSIDERAÇÕES FINAIS

O estudo estrutural, teórico e experimental das chalconas e dos benzimidazóis indicou o potencial antioxidante dessas classes de compostos, sugerindo-as como possíveis aditivos para misturas envolvendo biocombustíveis, como o biodiesel. Os resultados obtidos e publicados nos periódicos científicos corroboram com os objetivos propostos nessa tese. Primeiramente, o estudo do estado da arte permitiu direcionar alguns compostos interessantes a serem estudados, então a elucidação estrutural pela metodologia cristalográfica dos raios X permitiu o conhecimento de parâmetros estruturais relacionados a atividades e propriedades físico-químicas que foram melhor determinadas com os estudos teóricos envolvendo DFT, orbitais moleculares, Mapa de potencial eletrostático e topologia QTAIM. A análise estrutural para os compostos da tese indicou que os arranjos supramoleculares que são estabilizados apenas por interações fracas corroboram para doação de elétrons que podem contribuir com as propriedades antioxidantes e antibacterianas. Posteriormente com o auxílio da análise de farmacóforo, apontamos que uma quinolinona chalcona com um grupo sulfonamida apresenta aceitadores de ligação de hidrogênio e uma interação aromática para os compostos chlorimuron e tetraciclinas. Este resultado evidenciou um potencial antibacteriano que foi confirmado por meio de simulações de docking molecular com o regulador transcricional.

A quinolinona chalcona, estruturalmente semelhante à tetraciclina, que é composta por um conjunto fundido de anéis aromáticos, foi utilizada como base para a análise, uma vez que ambos os compostos compartilham um núcleo aromático essencial para o reconhecimento no sítio ativo de TtgR. Então, tanto a quinolinona chalcona quanto os anéis aromáticos de tetraciclina interagem com o bolso hidrofóbico formado por $\alpha 4$ - $\alpha 9$ em TtgR.²⁵ Neste contexto, o estudo permitiu inferir que, devido à sua semelhança estrutural com a tetraciclina, a quinolinona chalcona seria capaz de se ligar ao TtgR e, conseqüentemente, inibir a bomba de efluxo TtgABC. Algumas características estruturais do TtgR são cruciais para a ligação do substrato e, portanto, para a atividade biológica. Os resultados mostraram que a ligação de compostos aromáticos, desempenha um papel crucial na evasão bacteriana.

²⁵ O TtgR é um regulador transcricional que controla a expressão de genes em bactérias, sendo que o bolso hidrofóbico formado por $\alpha 4$ - $\alpha 9$ em TtgR é uma região específica na sua estrutura molecular que é importante para sua função regulatória. Essa região é formada pelas regiões alfa-4 até alfa-9 da proteína TtgR. O bolso hidrofóbico é responsável por reconhecer e se ligar a moléculas específicas, como compostos orgânicos hidrofóbicos, que atuam como ligantes do TtgR e induzem sua atividade regulatória que tem implicações em processos biológicos como a resistência bacteriana a antibióticos e a adaptação a ambientes hostis.

Posteriormente, com os índices de Fukui e os protocolos de aprendizado de máquina, investigou-se parâmetros relacionados com as atividades antimicrobianas e antioxidantes, como demonstrado para as quinolinonas chalconas que apresentaram um potencial de estabilidade oxidativa superior em comparação com as referências de diesel e biodiesel, o que é coerente com os resultados experimentais obtidos por meio do método Rancimat. Os resultados de estabilidade oxidativa (Rancimat) indicaram que o combustível aditivado com as moléculas da classe dos benzimidazóis e com moléculas da classe chalconas apresentaram estabilidade oxidativa superior a muitos aditivos comerciais, as moléculas testadas experimentalmente obtiveram um período de indução de 26,07 – 28,56 h. Por conseguinte, o teste de poder calorífico mostrou boa disponibilidade energética para as moléculas da classe chalcona analisadas. Dessa maneira, essa tese contribuiu para o estudo de novos aditivos para biocombustíveis e misturas, ressaltando os aspectos: o entendimento entre estrutura e atividade, o uso de cálculos teóricos e algoritmos de aprendizado de máquina (*machine learning*) que indicaram corretamente as atividades antioxidantes, visto que, houve uma validação experimental. Essa tese também mostra que o entendimento estrutural de moléculas, é uma ótima ferramenta de partida no planejamento e desenvolvimento de compostos antioxidantes para combustíveis. Cabe destacar ainda o pioneirismo deste trabalho, que pode subsidiar novos estudos a partir das classes de moléculas citadas, como aditivos para combustíveis.

Finalmente, em termos de produção científica, fui coautor em diversos artigos que permitiram o crescimento acadêmico e profissional. Os artigos estão dispostos em áreas como: Biocombustíveis (BORGES, FARIA, *et al.*, 2022, FARIA, DUARTE, *et al.*, 2020, MOREIRA, FARIA, *et al.*, 2022b, SALLUM, DUARTE, *et al.*, 2022, VIEIRA, BORGES, *et al.*, 2023), Saúde (FARIA, DUARTE, *et al.*, 2021b, WENCESLAU, DE PAULA, *et al.*, 2021), Síntese e Análise estrutural (DE PAULA, CARVALHO, *et al.*, 2020, SILVA, Marianna C., DUARTE, *et al.*, 2021, TERNAVISK, DUARTE, *et al.*, 2020), Meio ambiente e Produtos naturais (TEIXEIRA, DUARTE, *et al.*, 2019, SILVA, DUARTE, *et al.*, 2023) e Materiais óticos (DE PAULA, DUARTE, *et al.*, 2019, RIBEIRO, DE PAULA, *et al.*, 2020).

6. REFERÊNCIAS

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7. ANEXOS

7.1 Anexo I

Pedido nacional de patente no INPI [BR 10 2022 006539 0]

BRASIL

Acesso à informação

Participe

Serviços

Legislação

Canais

Instituto Nacional da

Propriedade Industrial

Ministério da Economia

Consulta à Base de Dados do INPI

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Depósito de pedido nacional de Patente

(21) Nº do Pedido: BR 10 2022 006539 0

(22) Data do Depósito: 05/04/2022

(43) Data da Publicação: -

(47) Data da Concessão: -

(71) Nome do Depositante: UNIVERSIDADE ESTADUAL DE GOIÁS (UEG) (BR/GO) / CAO A MONTADORA DE VEÍCULOS LTDA (BR/GO)

Anuidades ?

Petições ?

Serviço	Pgo	Protocolo	Data	Imagens	Cliente	Delivery	Data
Serviços							
206	✓	870220068256	02/08/2022	- - -	UNIVERSIDADE ESTADUAL DE GOIÁS (UEG)		-
206	✓	870220050540	08/06/2022	- - -	UNIVERSIDADE ESTADUAL DE GOIÁS (UEG)		-
200	✓	870220029232	05/04/2022	- - -	UNIVERSIDADE ESTADUAL DE GOIÁS (UEG)		-

Anuidade

Outros

Publicações ?

RPI	Data RPI	Despacho	Img	Complemento do Despacho
2693	16/08/2022	2.1		- Teor da exigência disponível no parecer (pdf) - acesse: Buscaweb no Portal do INPI. Prazo para cumprimento - 30 (Trinta) dias corridos contados do 1º dia útil após essa publicação (não confunda o prazo de 30 dias, com 1 mês (Trinta) dias corridos contados do 1º dia útil após essa publicação (não confunda o prazo de 30 dias, com 1 mês ou com 31 dias). Protocole a petição de cumprimento - Guia de Recolhimento da União (GRU) de código 206 (Cumprimento de exigência formal preliminar) + documentos corrigidos, de acordo com o parecer. O pedido com exigência não cumprida ou cumprida fora do prazo não será aceito e terá sua numeração anulada.
2687	05/07/2022	2.5		- Teor da exigência disponível no parecer (pdf) - acesse: Buscaweb no Portal do INPI. Prazo para cumprimento - 30 (Trinta) dias corridos contados do 1º dia útil após essa publicação (não confunda o prazo de 30 dias, com 1 mês (Trinta) dias corridos contados do 1º dia útil após essa publicação (não confunda o prazo de 30 dias, com 1 mês ou com 31 dias). Protocole a petição de cumprimento - Guia de Recolhimento da União (GRU) de código 206 (Cumprimento de exigência formal preliminar) + documentos corrigidos, de acordo com o parecer. O pedido com exigência não cumprida ou cumprida fora do prazo não será aceito e terá sua numeração anulada.
2679	10/05/2022	2.5		- Teor da exigência disponível no parecer (pdf) - acesse: Buscaweb no Portal do INPI. Prazo para cumprimento - 30 (Trinta) dias corridos contados do 1º dia útil após essa publicação (não confunda o prazo de 30 dias, com 1 mês (Trinta) dias corridos contados do 1º dia útil após essa publicação (não confunda o prazo de 30 dias, com 1 mês ou com 31 dias). Protocole a petição de cumprimento - Guia de Recolhimento da União (GRU) de código 206 (Cumprimento de exigência formal preliminar) + documentos corrigidos, de acordo com o parecer. O pedido com exigência não cumprida ou cumprida fora do prazo não será aceito e terá sua numeração anulada.
2676	19/04/2022	2.10	-	- Número de Protocolo '870220029232' em 05/04/2022 14:49 (WB)

Dados atualizados até 28/02/2023 - Nº da Revista: 2721

Documentos Publicados

Rua Mayrink Veiga, 9 - Centro - RJ - CEP: 20090-910



7.2 ANEXO II

Pedido nacional de patente no INPI [BR 10 2023 006206 7]

BRASIL

Acesso à informação

Participe

Serviços

Legislação

Canais

Instituto Nacional da
Propriedade Industrial
Ministério da Economia

Consulta à Base de Dados do INPI

[Início | Ajuda?]

» Consultar por: [Base Patentes](#) | [Finalizar Sessão](#)1/1

Depósito de pedido nacional de Patente

(21) Nº do Pedido: BR 10 2023 006206 7

(22) Data do Depósito: 03/04/2023

(43) Data da Publicação: -

(47) Data da Concessão: -

(71) Nome do Depositante: UNIVERSIDADE ESTADUAL DE GOIÁS (UEG) (BR/GO) / CAO A MONTADORA DE VEÍCULOS LTDA (BR/GO)

Anuidades ?

Petições ?

Serviço	Pgo	Protocolo	Data	Imagens	Cliente	Delivery	Data
Serviços							
200	✓	870230027779	03/04/2023	- - -	UNIVERSIDADE ESTADUAL DE GOIÁS (UEG)		-
Anuidade							
Outros							

Publicações ?

RPI	Data RPI	Despacho	Img	Complemento do Despacho
2727	11/04/2023	2.10	- -	Número de Protocolo '870230027779' em 03/04/2023 11:35 (WB)

Dados atualizados até 25/04/2023 - Nº da Revista: 2729

Documentos Publicados

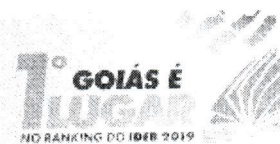
Rua Mayrink Veiga, 9 - Centro - RJ - CEP: 20090-910

7.3 ANEXO III

Acordo de cooperação nº 001/2021/2021-UEG/CAOA

18/03/2021

SEI/GOVERNADORIA - 000019202772 - Acordo de Cooperação

Universidade
Estadual de
GoiásESTADO DE GOIÁS
UNIVERSIDADE ESTADUAL DE GOIÁS - UEG

Acordo de Cooperação nº 001/2021/2021 - UEG

Processo nº 202000020010717

**ACORDO DE COOPERAÇÃO QUE ENTRE SI CELEBRAM A
UNIVERSIDADE ESTADUAL DE GOIÁS - UEG E A CAO
MONTADORA DE VEÍCULOS - LTDA, VISANDO AO
ESTABELECIMENTO DE COOPERAÇÃO PARA O
DESENVOLVIMENTO DE ATIVIDADES CONJUNTAS.**

UNIVERSIDADE ESTADUAL DE GOIÁS - UEG, pessoa jurídica de direito público interno, instituição de ensino, pesquisa e extensão, criada pela Lei nº 13.456/1999, transformada em autarquia estadual por força da Lei nº 16.272/2008, inscrita no CNPJ sob nº 01.112.580/0001-71, estabelecida à Rodovia BR-153, Quadra Área, Km 99, CEP: 75132-903, Anápolis/GO, doravante denominada **INSTITUIÇÃO DE ENSINO**, neste ato representada legalmente pelo o seu Magnífico Reitor, professor **Dr. VALTER GOMES CAMPOS**, brasileiro, portador do RG nº 11236414 SSP-SP, inscrito no CPF sob nº 036.225.038-31, residente e domiciliado em Anápolis/GO, e a **CAOA MONTADORA DE VEÍCULOS LTDA**, sociedade empresária limitada, de direito privado, inscrito no CNPJ no 03.471.344/0001-77, sediada na Rua VP 11, s/n, Fazenda Barreiro do Meio, DAIA, CEP 75.133-590, Anápolis, - Goiás, doravante denominada **CONCEDENTE**, neste ato representada legalmente pelo Sócio Administrador **Dr. CARLOS ALBERTO DE OLIVEIRA ANDRADE**, brasileiro, portador do RG nº 125.453 - SSP-PB, inscrito no CPF sob nº 040.341.394-04, residente e domiciliado à Rua Suécia nº 212, Jardim Europa, CEP 01446-000, na Cidade de São Paulo/SP, resolvem celebrar o presente **ACORDO DE COOPERAÇÃO**, regendo-se pelo disposto na Lei Federal nº 8.666/93, Lei Estadual nº 17.928/2012, e demais ordenamentos legais aplicáveis, no que couber, conforme cláusulas e condições seguintes:

CLAUSULA PRIMEIRA – DO OBJETO

1.1. O presente instrumento tem por objeto, estabelecer um regime de cooperação técnico e científica entre a Universidade Estadual de Goiás - UEG e a CAO MONTADORA DE VEÍCULOS LTDA., envolvendo os Campus da UEG que ministrem os cursos relacionados às atividades da CAO MONTADORA DE VEÍCULOS LTDA, com vistas à realização de estudos, pesquisas, desenvolvimento de peças/dispositivos mecânicos, elétricos, eletrônicos, hidráulicos, desenvolvimento de fornecedores, ministração de cursos e programas de capacitação e formação de recursos humanos em nível de graduação e pós-graduação, utilização mútua de equipamentos e publicação de artigos conjuntos e outras atividades relacionadas, mediante a participação de docentes e discentes da UEG e profissionais da CAO MONTADORA DE VEÍCULOS LTDA.

1.2. O presente instrumento será consubstanciado com as necessidades vigentes na CAO MONTADORA DE VEÍCULOS LTDA, estabelecidas consoante o seu planejamento estratégico e missão e na convergência com os preceitos acadêmicos da UEG e seus interesses, a saber:

18/03/2021

SEI/GOVERNADORIA - 000019202772 - Acordo de Cooperação

- a) Adensamento da cadeia de suprimentos regional de autopeças e materiais relacionados à indústria automobilística, mediante o desenvolvimento de fornecedores;
- b) Desenvolvimento conjunto de peças/dispositivos/materiais mecânicos, elétricos, eletrônicos, químicos, hidráulicos e outros relacionados à indústria automobilística;
- c) Pesquisas conjuntas no sentido de adaptar produtos da CAO A MONTADORA DE VEÍCULOS LTDA para as necessidades brasileiras;
- d) Formação de recursos humanos em nível de graduação e pós-graduação;
- e) Pesquisas conjuntas na área de meio ambiente e desenvolvimento sustentável;
- f) Pesquisas conjuntas na área de novas tecnologias de construção;
- g) Pesquisas conjuntas na área de desenvolvimento energético;
- h) Elaboração e publicação de artigos científicos.

CLÁUSULA SEGUNDA – DAS DISPOSIÇÕES GERAIS

2.1. - Não constitui fator impeditivo se pesquisas realizadas no âmbito da UEG nas áreas relacionadas e passíveis de se transformarem em produtos inovadores, sejam apresentadas à CAO A MONTADORA DE VEÍCULOS LTDA e que de comum acordo haja a intenção de desenvolvimento e desde que os preceitos relativos aos direitos de propriedade sejam rigorosamente cumpridos, conforme legislação vigente;

2.2 - A Parceria objetiva também a fertilização cruzada na capacitação de recursos humanos, ou seja, através de atividades de pesquisa e pós-graduação vinculadas a UEG, em pesquisas relacionadas às áreas de atuação da CAO A MONTADORA DE VEÍCULOS LTDA;

2.3 - Trata-se de Parceria que se caracteriza pelas múltiplas possibilidades mencionadas no **item 1.2 da Cláusula Primeira**, havendo necessidade de alguma das Partes realizar uma das linhas de pesquisa, a Parte interessada deverá expressar seu desejo e uma vez obtida a anuência da outra Parte, deverá elaborar um Plano de Trabalho Específico, que se constituirá em termo aditivo ao Acordo de Cooperação, no qual serão estabelecidas de comum acordo as prerrogativas de cada Parte, com especial ênfase nos aspectos de propriedade intelectual, encargos financeiros de execução, e nos proventos de possíveis produtos da cooperação.

CLÁUSULA TERCEIRA – DAS RESPONSABILIDADES DOS PARTICÍPES

Além das demais obrigações assumidas neste instrumento, os partícipes se comprometem, especialmente, ainda a:

I - OBRIGAÇÕES ESPECIAIS COMUNS A AMBOS OS PARTICÍPES:

a) Permitir o acesso dos alunos e professores pesquisadores e demais empregados e/ou servidores, bem como de terceiros, seus convidados, nas áreas utilizadas para a condução dos trabalhos objeto deste plano de trabalho, devidamente autorizados;

b) Divulgar os artigos das pesquisas realizadas, se e somente se, não ferirem os direitos de propriedade de ambas as Partes, sob pena de responsabilização por perdas e danos e danos diretos e indiretos;

c) Toda e qualquer informação, seja de que natureza for, decorrente deste Acordo de Cooperação, ou que tenha conexão de qualquer espécie com o seu objeto, deverá ser tratada de forma confidencial e sigilosa pelas Partes. As Partes se obrigam a adotar as medidas necessárias para a manutenção e cumprimento do disposto nesta cláusula, sob pena de indenização por perdas e danos;

d) Havendo desinteresse pela pesquisa, a CAO A MONTADORA DE VEÍCULOS LTDA e a UEG obrigam-se, por si e por seus funcionários e pesquisadores, observado o sigilo, a não divulgar ou utilizar, durante 5 (cinco) anos contados da data da desistência, as informações relativas ao objeto desta Parceria;

e) Assegurar os recursos financeiros que viabilizem a plena realização da Parceria;

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f) Emitir relatórios técnicos e pareceres parciais e conclusivos sobre os resultados obtidos durante os ensaios laboratoriais.

II - OBRIGAÇÕES ESPECÍFICAS DA CAO A MONTADORA DE VEÍCULOS

LTDA:

a) Prover toda a infraestrutura necessária ao adequado desenvolvimento dos trabalhos, mormente ao espaço físico, equipamento, máquinas e implementos, insumos e demais recursos técnicos e administrativos;

b) Facilitar a realização de ensaios laboratoriais nas dependências da CAO A MONTADORA DE VEÍCULOS LTDA;

c) Identificar e quantificar as oportunidades de estágio a serem concebidas aos discentes devidamente matriculados na UEG, conforme as exigências legais e padrões da UEG;

d) Disponibilizar 2 (duas) bolsas de estudos para mestrandos e/ou doutorandos, sendo que as Partes, em comum acordo, poderão alterar esta quantidade.

III – DAS OBRIGAÇÕES DA UEG:

a) Realizar as atividades de estudo, pesquisa e de desenvolvimento dentro dos prazos previamente acordados e dentro dos melhores padrões técnicos e de qualidade, visando o aprimoramento do processo.

CLÁUSULA QUARTA – DA PROPRIEDADE INTELECTUAL DOS RESULTADOS

4.1. Todos os direitos de propriedade intelectual, ou seja, os resultados, metodologias e inovações técnicas, produtos ou processos, know-how, invenção, modelo de utilidade, marcas, desenhos industriais (design), topografia de circuito integrado, programa de computador, obra científica, literária e artística, documentação técnica, banco/base de dados, privilegiáveis ou não, que foram obtidas em virtude da tecnologia, serão de propriedade da UEG e CAO A.

4.2. As parceiras acordam, para todos os efeitos legais, que os direitos de propriedade intelectual como marcas, desenhos industriais, direitos autorais e patentes de invenção de produtos/tecnologias existentes anteriormente à celebração deste acordo e utilizadas na obtenção da Tecnologia não encontram-se abrangidas, mantendo-se a titularidade de cada parceiro, no rol descrito no parágrafo acima.

CLÁUSULA QUINTA – DO SIGILO

5.1. As partes se comprometem a manter sigilo com relação às informações obtidas no Página 5 de 12 desenvolvimento dos objetivos do presente Acordo de Cooperação, sendo vedada, sem autorização por escrito, da UEG e da CAO A, sua divulgação a terceiros, dos conhecimentos técnicos específicos adquiridos e outros dados particulares a eles referidos.

5.2 - O descumprimento do pactuado nesta cláusula ensejará a rescisão deste Acordo de Cooperação, e o pagamento, ao parceiro inocente, de perdas e danos efetivamente sofridos.

5.3 - Exclui-se do vedado nesta cláusula a divulgação de conhecimentos técnicos que, embora atinentes ao objeto deste Acordo de Cooperação, sejam utilizados em cursos regulares da UEG.

5.4 - As partes se comprometem a repassar aos seus servidores e empregados envolvidos no objeto deste Acordo de Cooperação, as obrigações de sigilo aqui constantes.

5.5. As parceiras comprometem-se a manter sob estrito sigilo dados e informações intercambiadas em decorrência do presente, não podendo, de qualquer forma, direta ou indiretamente, dar conhecimento a terceiros das informações consideradas e identificadas como confidenciais trocadas entre si ou com terceiros, exceto quando as informações se enquadrarem nos seguintes casos:

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- a) As parceiras anuírem expressamente, por escrito, pela revelação;
- b) tenha caído em domínio público antes de sua divulgação ou mesmo após, desde que não tenha qualquer culpa de uma das partes;
- c) tornar-se de conhecimento público, no futuro, sem que caiba a qualquer das parceiras, a responsabilidade por sua divulgação;
- d) for comprovadamente e de forma legítima do conhecimento da outra parceira em data anterior à assinatura deste Acordo de Cooperação;
- e) forem reveladas por terceira pessoa que não esteja obrigada à confidencialidade de que trata esta cláusula;

5.6. por determinação judicial e/ou governamental para conhecimento das informações, desde que as parceiras, sejam notificadas imediatamente e sendo requerido segredo no seu trato judicial e/ou administrativo.

5.7. Com a finalidade de garantir a preservação de todos os interesses envolvidos na divulgação do resultado da parceira, a UEG e a CAO A dar-se-ão ciência prévia das informações que pretendem divulgar, no prazo de 30 dias antes da divulgação.

5.8. A UEG e a CAO A poderão opor mutuamente objeção formal à publicação de tais informações, por escrito, no prazo de 30 dias a contar da ciência referida no item anterior. Nesta hipótese a divulgação não será realizada.

5.9. O silêncio da parceira científica corresponderá no consentimento tácito à divulgação, desde que esta não implique em violação da propriedade intelectual.

5.10. Serão consideradas informações confidenciais para fins deste Acordo de Cooperação, todas e quaisquer informações ou dados classificados ou classificáveis como sigilosos e assim identificados, acerca das propriedades intelectuais ou pelos partícipes, em qualquer forma ou meio físico que se apresentem, obtidos dos projetos, inclusive durante as negociações ou pesquisas antecedentes à assinatura do presente Acordo de Cooperação.

CLÁUSULA SEXTA – DA EXPLORAÇÃO DOS RESULTADOS

6.1. A partir da execução dos trabalhos a serem desenvolvidos, caso haja aperfeiçoamentos ou inovações passíveis de privilégios, fica estabelecido que os resultados líquidos financeiros decorrentes do uso ou de possível cessão a terceiros será repartido entre os Partícipes, devendo a porcentagem ser estipulada no Plano de Trabalho específico do projeto a ser desenvolvido.

CLÁUSULA SÉTIMA – DA COORDENAÇÃO

7.1. Para coordenar e supervisionar a execução das atividades propostas no Plano de Trabalho, a UEG e a CAO A designarão, respectivamente, 1 (um) gestor e 1 (um) responsável integrantes do seu quadro de pessoal, os quais atuarão conjuntamente, conforme abaixo indicados:

a) Pela UEG: Nome: **Hamilton Barbosa Napolitano**, Estado Civil: Casado, Profissão: Docente, Endereço de Trabalho: CÂMPUS CENTRAL - ANÁPOLIS CET RODOVIA BR 153 3105, CAIXA POSTAL 459 - Bairro . - ANÁPOLIS - GO - CEP 75132-400. Telefones: (62) 9 8206-7261 / (62) 3099-3625, E-mail: hamilton@ueg.br, CPF: 589.768.501-06;

b) Pela CAO A: Nome: **Aline Magalhães da Silva**, Estado Civil: Casada, Profissão: Gerente de Engenharia, Endereço de Trabalho: Rua 11, s/n, DAIA, CEP 75133610 Telefone: 62 3098-9220 E-mail: aline.silva@caoamontadora.com.br, CPF: 93517912115.

PARÁGRAFO ÚNICO: O gestor do Acordo de Cooperação que, por parte da Administração, fará o acompanhamento e a fiscalização do Acordo de Cooperação e dos recursos repassados, por meio de relatórios, inspeções, visitas e atestado, deverá emitir relatórios no processo SEI n. 202000020010717, a cada 6 meses afim de garantir a satisfatória realização do objeto do instrumento, conforme previsão legal.

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CLÁUSULA OITAVA – DOS RECURSOS FINANCEIROS

8.1. Não está previsto repasse de recursos financeiros. Cada partícipe arcará com o ônus de acordo com as responsabilidades assumidas neste Acordo de Cooperação ao qual o Plano de Trabalho está vinculado.

CLÁUSULA NONA – DA VIGÊNCIA

9.1. O presente instrumento terá a vigência por um período de 60 (sessenta) meses, a contar da data da assinatura do presente Acordo de Cooperação, publicada no Diário Oficial do Estado de Goiás, podendo no entanto, ser modificado mediante termo aditivo, conforme artigo 57, inciso II, da Lei Federal no 8.666/1993, de acordo com a conveniência dos partícipes e a legislação pertinente, exceto no tocante ao seu objeto.

CLÁUSULA DÉCIMA – DAS ALTERAÇÕES

10.1. As adições, supressões ou alterações nas cláusulas deste Acordo de Cooperação, que porventura sejam necessárias, serão formalizadas por meio de Termos Aditivos, conforme previsão legal, os quais passarão a fazer parte integrante do presente Instrumento, vedada a modificação de seu objeto, respeitando-se a ideia proposta na cláusula primeira, deste Acordo de Cooperação.

CLÁUSULA DÉCIMA PRIMEIRA – DA RESCISÃO

11.1. Este Acordo de Cooperação, poderá ser rescindido, sem ônus, encargos, multas e indenizações, por quaisquer das Partes, a qualquer tempo, desde que a Parte que assim o desejar, comunique à outra, sua intenção por escrito, com antecedência de pelo menos 30 (trinta) dias.

11.2. Ademais, o presente instrumento poderá ser rescindido de pleno direito em caso de inadimplemento de qualquer de suas cláusulas, ou ainda, em caso de descumprimento das normas estabelecidas na legislação vigente ou em virtude da superveniência de norma legal ou fato que o torne material ou formalmente inexecutável.

CLÁUSULA DÉCIMA SEGUNDA – DA DENÚNCIA

12.1. A denúncia deste Acordo de Cooperação, poderá ocorrer a qualquer tempo, por iniciativa de qualquer um dos partícipes, mediante notificação escrita, com antecedência mínima de 30 (trinta) dias.

CLÁUSULA DÉCIMA TERCEIRA – DOS CASOS OMISSOS

13.1. Aos casos omissos ou excepcionais, não previstos neste acordo, os partícipes deverão ser consultados, por escrito, e resolvidos, conforme disposto na Lei Federal no 8.666/93 e alterações posteriores, e pela Lei Estadual no 17.928/2012, respeitados os princípios da teoria geral dos contratos e disposições de direito privado.

CLÁUSULA DÉCIMA QUARTA – DO USO DA IMAGEM

14.1. Fica terminantemente proibido aos partícipes a utilização do nome e da imagem do outro, sem a prévia autorização de seus representantes legais e obediência a legislação que trata dessa matéria.

CLÁUSULA DÉCIMA QUINTA – DA PUBLICAÇÃO

15.1. O presente instrumento será publicado no Diário Oficial do Estado, na forma de Extrato, às expensas e por iniciativa da UEG.



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CLÁUSULA DÉCIMA SEXTA – DO FORO

16.1. As partes elegem o Foro da Comarca de Anápolis/GO para dirimir quaisquer dúvidas oriundas do presente Acordo de Cooperação, com renúncia de qualquer outro por mais privilegiado que venha a ser, nos termos do artigo 55 §2º da Lei Federal n. 8.666/1993.

E por estarem justos e combinados, as partes assinam o presente instrumento, por meio de seus representantes, em 02 (duas) vias de igual teor e forma, na presença de 02 (duas) testemunhas que também o assinam.

Anápolis/GO, _____ de _____ de 2021.

Pela INSTITUIÇÃO DE ENSINO:

(Assinatura eletrônica)

Prof. Dr. Valter Gomes Campos
Reitor Reitor

ORCPN E TABELIÃO
DO 29º SUBDISTRITO
SANTO AMARO

**Pela CONCEDENTE:**

Dr. Carlos Alberto de Oliveira Andrade
CAOA Montadora de Veículos LTDA

Testemunha: Pela INSTITUIÇÃO DE
ENSINO: (Assinatura eletrônica)

Nome: Edilair Rosália Rezende Bertanzin

CPF nº: 382.748.841-91

Testemunha: Pela CONCEDENTE:

Nome: Giovanna Borges C. de P. mo

CPF nº: 506.536.518-05



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7.4 ANEXO IV

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7.5 ANEXO V

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Author: Vitor S. Duarte, , Raquel F. Naves, et al

Publication: Biofuels

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Arylsulfonamide chalcones as alternatives for fuel additives: antioxidant activity and machine learning protocol studies†



[Vitor S. Duarte](#), ^{*a}, [Igor D. Borges](#), ^{ab}, [Giulio D. C. d'Oliveira](#), ^c, [Eduardo C. M. Faria](#), ^{ab}, [Leonardo R. de Almeida](#), ^a,
[Valter H. Carvalho-Silva](#), ^a, [Caridad Noda-Pérez](#), ^c and [Hamilton B. Napolitano](#), ^{*a}

[Author affiliations](#)

Abstract

Biodiesel is a promising fuel with the potential to reduce some negative aspects of fossil fuels, such as the emission of pollutants and greenhouse gases (GHGs), the scarcity of natural resources and market instability. To amplify its low durability and stability the use of technologies based on molecular compounds that reduce the oxidation rate of biodiesel and preserve its physical–chemical properties is very common and necessary throughout the world. To reduce oxidative stability problems of diesel–biodiesel blends, arylsulfonamide chalcones were evaluated as potential additives for B20 blends. In this study, comprehensive structural, computational, and experimental analyses were undertaken to understand the antioxidant potential of these compounds as possible additives. The supramolecular arrangements were stabilized by weak molecular interactions (C–H⋯O and C–H⋯π), which are related to antioxidant and antibacterial action, and groups can act as electron-donating substituents. The energy range of 593.1–570.2 kJ mol^{−1} in the frontier molecular orbitals indicates high structural stability, due particularly to sulfonamide groups which enable electrophilic attack. Furthermore, the Fukui function aligned with kinetics parameters, obtained using machine learning protocols, provided information to clarify and expand the comprehension of chalcone antioxidant features mediated by free-radical capture. The heat of combustion indicated good energy availability (6530.5–7306.5 kcal

kg⁻¹), close to those of conventional fuels. In addition, the oxidative stability of the diesel–biodiesel blend (B20) remained at around 27 hours, after 140 days of storage, which is better than for some commercial additives. We hope that this comprehensive study will support the understanding of chalcone-based compounds as alternatives to fuel additives.

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Arylsulfonamide chalcones as alternatives for fuel additives: antioxidant activity and machine learning protocol studies

V. S. Duarte, I. D. Borges, G. D. C. d'Oliveira, E. C. M. Faria, L. R. de Almeida, V. H. Carvalho-Silva, C. Noda-Pérez and H. B. Napolitano, *New J. Chem.*, 2023, Advance Article , DOI: 10.1039/D3NJ00255A

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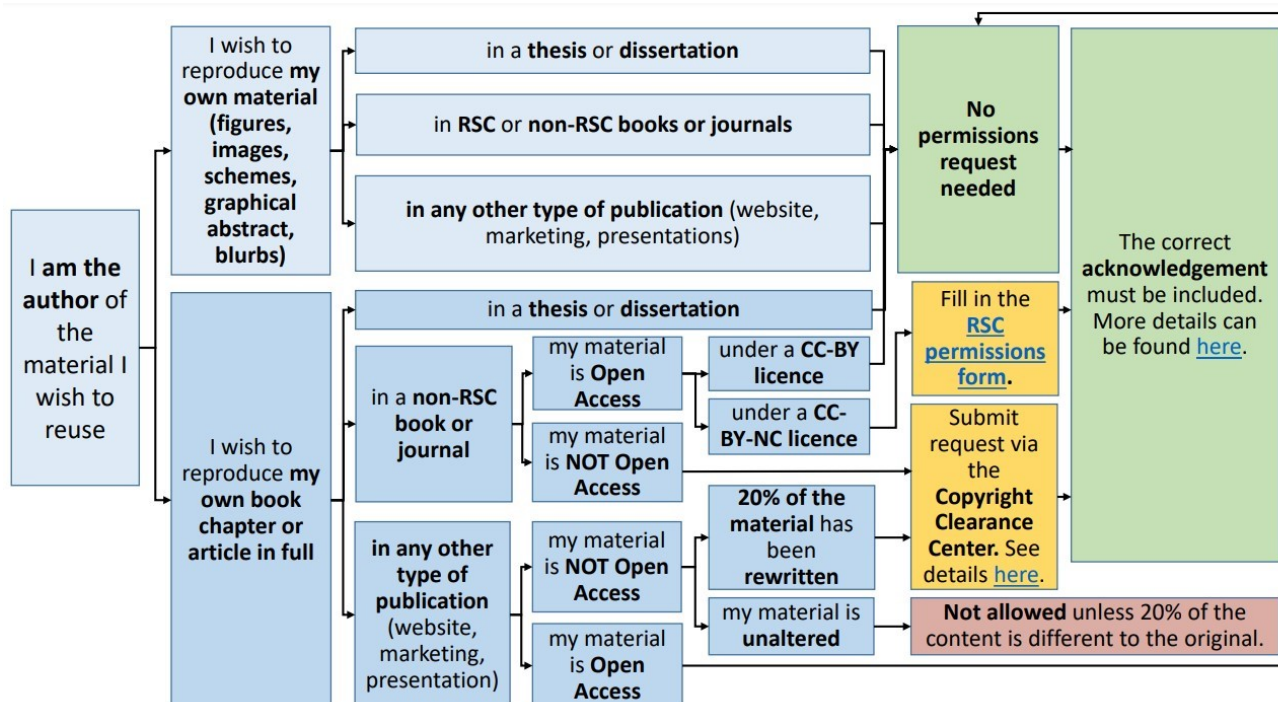
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