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Aryl glyoxal: a prime synthetic equivalent for multicomponent reactions in the designing of oxygen heterocycles

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The category of bifunctional building blocks overrides many others because of their fascinating wide applicability in synthetic chemistry. Aryl glyoxal is one of the key molecules used extensively in heterocyclic chemistry to afford nearly all types of five- and six-membered heterocycles, which are the structural constituents of many natural products. The multicomponent reaction is a practical strategy to utilize this wonderful moiety with different types of starting materials to obtain numerous diverse oxygen heterocycles. This review covers the advancement of aryl glyoxal as a prime synthetic equivalent in recent years for the synthesis of oxygen heterocycles.

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Introduction

Organic synthesis has served as an all-time interesting topic for researchers from the very beginning. There have been many changes in synthesis paradigms since the first synthesis of an organic compound by Wöhler.¹ The quest for an easy and efficient methodology brought about the concept of the one-pot multicomponent reaction approach. Multicomponent

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reactions (MCRs) are a type of reaction where at least three different starting materials are made to react in a single reaction vessel.²⁻⁵ The availability of various reacting sites in the reaction mixture increases the chances of probable novelty in the desired product. Therefore, MCRs have expedited organic synthesis to a significant level of novel compound formation. The pronounced benefits of multicomponent reactions, like efficient atom economy, minimization of extra time consumption, and reduced environmental waste over traditional methods have revolutionized the work of synthetic chemists to produce a chemical library of novel moieties.⁶ MCRs are the



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RSC Advances Review

only way to meet the intermittent demands of advanced technology-driven research, such as in medicines, drugs, agrochemicals, polymers and cosmetic industries. Many important building blocks and manifolds are the results of rationally designed multicomponent named reactions. Owing to their significance, reagent- and substrate-based multicomponent reactions have recently been reported in high numbers.^{7,8}

Heterocycles occupy a key functional position in many living processes and therefore they provide an in-line sustained research area to be worked upon. Among the heterocycles, hydrocarbons with oxygen as their constituent element in the ring exhibit a special place in the category owing to their several benefits to life. In addition to their occurrence in natural products and living systems, including the human body, scaffolds belonging to each class are known to show distinctive biological and pharmacological properties. Pyran derivatives are screened for antianaphylatic, diuretic, spasmolytic, anticoagulant and anticancer properties, etc. 9-11 Alkaloids possessing pyranoquinoline as the structural unit feature anti-microbial characteristics.12 Also, a number of them act as photoactive enhancers in the treatment of neurodegenerative diseases. 13,14 Another oxygen heterocycle, namely the furan skeleton, is available in kallolides,15 in fragrances, and dye-like commercial products. The furan derivative furoquinolinone blocks the potassium channel Kv1.3, which is the



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immunosuppressive therapy in the treatment of auto-immune diseases and transplantation.¹⁶ Likewise, the pyrazoline derivative containing a furan moiety shows anti-malarial activity against Plasmodium falciparum.17 Isoxazoles, as oxygen-nitrogen heterocycles, add to the synthetic utility of oxygen heterocycles as they offer anti-tubercular, 18 anti-inflammatory, 19 and COX-2 inhibitor properties,20 and are thus a constituent of many therapeutic drugs. The newly synthesized chroman derivative was tested and found to show potential anti-convulsant21 activity. One of the benzopyranone derivatives, Enasculin, is a pharmacologically tested neuronal activator KA 672-HCl,²² which works as an antagonist by simultaneously activating several neurotransmitters that are deactivated in dementia. Furthermore, the structural presence of benzo[g]chromene in many useful natural products with reported anticancer activity and the synergistic effect of β-lapachone with taxol against tumour growth, 23-25 etc., are driving the search for newer strategies to synthesize oxygen heterocyclic moieties in economical and environmentally friendly conditions. Therapeutic functions of some O-heterocycles are illustrated in Fig. 1.

Revolutionary advancements in the physiological studies of living beings for the sake of mankind and the environment are due to the organic biomimetic pathways adopted by synthetic chemists to produce optimum results. So, the challenging process of synthesizing heterocyclic moieties can be facilitated by employing bifunctional building blocks in the reaction design, in which the multiple reactive centres lead to product diversity. Aryl glyoxal is one of the aldo-ketone bifunctional building block molecules used by synthetic chemists to produce a diverse library of molecules.26 The presence of a reactive aldehyde group adjacent to the carbonyl group is the peculiar structural feature that makes aryl glyoxal a distinctive building block for the synthesis of heterocyclic and carbocyclic compounds. The electron-withdrawing ketone group makes aryl glyoxal more reactive than benzaldehyde and allows the site to be open to nucleophilic attack followed by cyclisation in various ways. Furthermore, the non-enolizability of the ketone group under acidic or basic conditions is responsible for its sufficient stability and for making aryl glyoxal monohydrate commercially available. Interestingly, besides the numerous applications of all types of oxygen heterocycles as drugs and therapeutic agents, there are some biologically potent molecules with a phenyl glyoxal unit embedded in their structure (as shown in Fig. 2), such as 4-aroyl chromene derived from phenyl glyoxal hydrate and naphthyl glyoxal, which has shown anti-bacterial properties by inhibiting Escherichia coli growth with a minimum inhibitory concentration (MIC) of 32 μg cm⁻³.27 A furan-substituted guaiazulene moiety synthesized through a simple route by utilizing phenyl glyoxal exhibited significant in vitro antioxidant activity against lipid peroxidation with a minimum IC_{50} value of 3.9 µg mL⁻¹.²⁸ Guaiazulene, a derivative of azulene, acts therapeutically against skin and asthma-like diseases due to allergy or inflammation reactions.29 Coumarin targets the αglucosidase enzyme, which is responsible for the hydrolysis of starch and higher carbohydrates into simple sugars.30 Dihydrochromeno[4,3-b]pyrrol-3-yl obtained by using phenyl glyoxal as one of the starting materials exhibits α-glucosidase

Review **RSC Advances**

Fig. 1 Some biologically active O-heterocycles.

inhibitory activity,31 thus aiding the drug-development process for hyperglycemia and Type 2 diabetes mellitus (T2DM). This in vitro evaluation was further extended by in silico docking studies with reference to the standard drug acarbose.³² Also, attempts are being made to synthesize the C-4 aroyl group-substituted pyrano[3,2-c]chromene and benzo[g]chromene by employing phenyl glyoxal due to their divergent properties.33 A new HIV integrase inhibitor, namely a pyrano[2,3-d:6,5-d']dipyrimidine (V-165)-like framework of pyrano[2,3-d:6,5-d']dipyrimidines, constructed through phenyl glyoxal showed increased chances for extensive use in drug precursor development.34 Phenyl glyoxal was further used in the synthesis of a furo(2,3-b)furan moiety35 mimicking drug candidates like Brecanavir (GW640385), an HIV inhibitor, 36 and Darunavir (TMC-114), 37,38 another HIV-1 protease inhibitor. A coumarin-glyoxal hybrid, namely the tartrate salt of a Mannich base bearing coumarin derivatives³⁹, was found to be an efficient contraceptive as it shows activity as both a spermicide and a microbicide. The compound was tested for spermicidal activity against nonoxynol (N-9),40 a contraceptive. The two compounds of the series showed activity better than N-9. For anti-microbial activity, again the two compounds showed activity better than the Metronidazole⁴¹ chosen as the standard for the study. For this reason, from many years in the past up to recent years, aryl glyoxal has been extensively used as a key building block in multicomponent single-pot reactions.42

In this review article, we intend to highlight the extensive use of the bifunctional building block known as aryl glyoxal monohydrate as the starting material in the construction of novel, and mimics of, naturally found heterocyclic moieties. Here, is a brief account of the reactivity pattern of aryl glyoxal with different substrates leading to the synthesis of various derivatives and fused oxygen heterocycles.

Use of aryl glyoxal in designing Oheterocycles using multicomponent reactions

Aryl glyoxal is unique in having two adjacent carbonyl groups, but it mostly exists in the hydrated form. It forms different types of five-membered and six-membered heterocyclic rings depending on the type of other substrates, attacking nucleophiles, and cyclisation pattern in the reaction. The application of aryl glyoxal in the synthesis of five- and six-membered Oheterocycles is discussed in the following sections.

2.1. Synthesis of five-membered furan derivatives

Li et al. efficiently utilized aryl glyoxal 1 in the gold-catalysed three-component reaction with amine 2 and a terminal alkyne 3 to obtain substituted furans 4 through cyclisation in a nitrogen atmosphere with methanol as a solvent. This

Anti-coagulant

Fig. 2 Biologically active O-heterocycles obtained from phenyl glyoxal

reaction provides an effective protocol for the preparation of synthetic and pharmacological derivatives of furan (Scheme 1).⁴³ The plausible mechanism of the protocol starts with the coupling of aryl glyoxal 1, amine 2 and alkyne 3 in a Mannich-Grignard pattern to give a propargyl intermediate aa, which is followed by the attack of an oxygen lone pair on the electrophilic triple bond, forming a cation ab, leading to the final product

indolizines 4 through deprotonation and demetallation of **ac** (Scheme 2).

For the synthesis of isoxazolyl amino furo[3,2-*c*]quinolinone scaffolds 7, Modugu and co-workers developed an efficient one-pot, three-component reaction of aryl glyoxal monohydrate, 4-hydroxy-1-methyl-2-quinilinone **6**, and 4-amino-3-methyl-5-styrylisoxazoles **5** under reflux conditions in an aqueous medium with a 5 mol% catalytic amount of *p*-TSA. The scheme

 $R_1 = C_6H_5$, 4-FC₆H₄, 4-MeC₆H₄, 4-pentyl C₆H₄,

 R_2 , R_3 = Sec.amine

 $R_4 = C_6H_5$, $4-FC_6H_4$, $3-CIC_6H_4$, $4-CIC_6H_4$, $4-NO_2C_6H_4$, $4-CF_3C_6H_4$, $4-BrC_6H_4$,

Scheme 1 Gold-catalysed three-component synthesis of furan derivatives 4.

Review **RSC Advances**

OHOHOH
OH
OH
$$R_1$$
 R_2
 R_3
 R_4
 R_4
 R_4
 R_5
 R_4
 R_5
 R_4
 R_5
 R_4
 R_5
 R_5
 R_6
 R_7
 R_8
 R_8

Scheme 2 Mechanism proposed to explain gold-catalysed furan synthesis.

was tested with different Lewis acids and organic acids, but p-TSA in water as the solvent was found to give the best results in terms of the time, yield and environmentally friendly protocol (Scheme 3).44 The reaction mechanism (as shown in Scheme 4) starts from the p-TSA-catalysed condensation of compound 5 and 1 yielding the iminium ion intermediate ba, which serves as an electrophilic site for the nucleophile 6. The nucleophilic addition reaction between ba and 6 produces the bb intermediate, which is in tautomeric isomerisation with bc. The intermediate bd undergoes intramolecular cyclisation initiated by the acid to give the final product 7 through dehydration of be (Scheme 4).

For the synthesis of the furan-2(5H)-one derivative **10** with indole as a structural fragment, Komogortsev and his group

established a facile and one-pot novel methodology, which was completed in two steps starting with the interaction of aryl glyoxal 1, indole 9, and Meldrum's acid 8 in acetonitrile with triethylamine at reflux, followed by an acidic reflux using acetic acid (Scheme 5).45 The formation of the new oxygen heterocycle is considered to go through the aryl glyoxal 1 condensation with Meldrum's acid to generate intermediate ca followed by Michael addition with the indole to give cb and finally cyclisation with the elimination of CO₂ to give 10 (Scheme 6).

Shahbazi-Alavi and co-workers demonstrated an environmentally friendly nano-catalysed synthesis of substituted furans. The target molecule 13 was afforded through the heterogeneous catalysis of aryl glyoxal 1, dimethylacetylenedicarboxylate 11, and primary amine 12 at room temperature

 $Ar = C_6H_5, 4-CH_3C_6H_4, 2-CH_3C_6H_4, 4-OCH_3C_6H_4, 2-OCH_3C_6H_4, 4-CIC_6H_4, 2-CIC_6H_4, 4-BrC_6H_4, 4-NO_2C_6H_4, 4-NO_2C_6H_5, 4-NO_2C_6H_5, 4-NO_2C_6H_5, 4-NO_2C_6H_5, 4-NO_2C_6H_5, 4-NO_2C_6H_5, 4-NO_2C_6H_5, 4-NO_$ $R = C_6H_5, 4-CH_3C_6H_4, 2-CH_3C_6H_4, 4-OCH_3C_6H_4, 4-CIC_6H_4, 2-CIC_6H_4, 4BrC_6H_4, 2-BrC_6H_4, 2-furyl, 2-thienyl, 2-thieny$ 3-pyridyl, CH₃, 4-OCH₃C₆H₄, 4-CIC₆H₄,

Scheme 3 Synthesis of isoxazolyl amino furo[3,2-c]quinolinone scaffolds 7 using P-TSA.

Scheme 4 Mechanistic explanation of the synthesis of isoxazolyl amino furo[3,2-c]quinolinone 7.

Scheme 5 Three-component synthesis of furan-2(5H)-one derivative 10 using Meldrum's acid 8.

using the HPA-ZSM-5 nano-catalyst in dichloromethane (Scheme 7).⁴⁶ The mechanistic pathway of the reaction is initiated by the nucleophilic attack of the amine lone pair 12 on the electrophilic site of dimethyl acetylenedicarboxylate 11 forming an enaminone, namely aminobutenedioate da. This aminobutenedioate acts as a C-nucleophile and attacks the electron-

deficient carbon of phenyl glyoxal **1**, thereby generating the second intermediate iminium-oxoanion **db**, which tautomerizes to the intermediate **dc**. Intermediate **dc** then undergoes γ -lactonization to give 5-oxo-2,5-dihydro-3-furancarboxylate **13** as the final product (Scheme 8). In 2021, the same protocol was also followed by Ebrahimi and co-workers,⁴⁷ this time using

Scheme 6 Mechanism to explain the synthesis of furan-2(5H)-one 10 using indole 9, Meldrum's acid 8, and aryl glyoxal 1 as starting materials.

R₁ = 2-Methoxybenzylamine, 4-Methoxybenzylamine, 4-Methylbezylamine, Benzylamine, 4-Fluorobenzylamine, Propylamine, 3,4-Dichlorobenzylamine.

Scheme 7 Nano-catalysed protocol for the synthesis of substituted furans 13.

$$R_{1}NH_{2} + \begin{pmatrix} CO_{2}Me \\ CO_{2}Me \end{pmatrix} \begin{pmatrix} H \\ N-R_{1} \\ H \end{pmatrix} \begin{pmatrix} O \\ N-R_{1} \\ MeO_{2}C \end{pmatrix} \begin{pmatrix} H \\ N-R_{1} \\ H \end{pmatrix} \begin{pmatrix} O \\ MeO_{2}C \\ N-R_{1} \\ N-R_{1} \\ H \end{pmatrix} \begin{pmatrix} O \\ MeO_{2}C \\ N-R_{1} \\$$

Scheme 8 Mechanistic pathway to explain the nano-catalysed synthesis of furan derivatives 13.

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RSC Advances

Review

nano-CuO. This work gained popularity due to its ease of operation, facile and quick extraction of the product, quick response time, high yield, and low loading and re-utilisation of the catalyst.

Phenyl glyoxal 1 and α-oxoketene dithioacetals 14 with indoles **9** as the precursors were utilized by Liu *et al.* to create six multicomponent reactions, which were used to synthesize a variety of heterocycles, including quinolines, dihydrocoumarins, furans 15, and pyrroles 16. The discovery of these multicomponent reactions was made feasible by the coupling of bifunctional aldo-X reagents and α-oxoketene dithioacetals since these reagents contain a minimum of two reactive sites, therefore diverse substrates can be put together in different ways (Scheme 9).48

Dehghanzadeh and co-workers applied arvl glyoxal 1 for the fabrication of 5-(furan-yl)barbiturate and 5-(furan-3-yl) thiobarbiturate 19 via a one-pot assembly of 1 with acetylacetone 17 and barbituric acid and thiobarbituric acid 18, respectively, in water at 60 °C (Scheme 10).49 The plausible mechanism starts with the Knoevenagel reaction between 1 and 17 to give intermediate ea, which undergoes a 1,4-conjugated addition with barbiturate 18 yielding 1,4-diketone eb, followed by a Paal-Knorr cyclisation ec to finally give 5-(furan-3-yl) barbiturate/thiobarbiturate 19 (Scheme 11).

A further synthesis was done by Khoeiniha and his group using aryl glyoxal 1 as a building block for obtaining novel 4Hindeno[1,2-b]furan-4-ones 23 through its one-pot condensation with 2-aminopyridines 21 and 1,3-indandione 22 in water in the absence of any catalyst. In addition, by employing aryl glyoxal 1, 21 and barbituric acid 18 under the same green conditions, they obtained furo[2,3-d]pyrimidine 24 derivatives in high yield (Scheme 12).50 The reaction is believed to start from the aldol condensation of 1 and 1,3-indanedione 22 generating intermediate fa. Amine 21 is added to this intermediate through

Syntheses of furan 15 and pyrrole 16 derivatives via three-component reactions.

Scheme 10 Three-component synthesis of 5-(furan-yl)barbiturate and 5-(furan-3-yl)thiobarbiturate 19 from acetylacetone 17 and barbituric acid 18.

Review

Scheme 11 Mechanism proposed to explain the formation of 5-(furan-3-yl)barbiturate/thiobarbiturate 19.

Het: Pyridine, 4-NO₂ Pyridine, 2-NO₂ Pyridine, 2-CH₃ Pyridine

Het: Pyridine, 2-Methylpyridine, 3-Methylpyridine, 5-Methylpyridine, 4-CI Pyridine, 4-Br Pyridine

Scheme 12 Three-component synthesis of 4H-indeno[1,2-b]furan-4-ones 23 via aldol condensation.

Scheme 13 Plausible mechanism to represent the synthesis of 4H-indeno[1,2-b]furan-4-ones] 23.

RSC Advances Review

Scheme 14 Synthesis of furo[3,2-c]coumarin 27 via a [4 + 1] cycloaddition reaction.

a Michael addition **fb**, followed by intramolecular cyclisation **fc**, with subsequent dehydration to produce the final product **23**. When 1,3-indandione is replaced with barbituric acid following the same methodology, the furo-pyrimidine derivative **24** is obtained as the product (Scheme 13).

In 2009, Mosslemin's group reported the isocyanide-based formation of furo[3,2-c]coumarin 27 through a condensation-cycloaddition of the easily available 4-hydroxy coumarin 25 with the extensively used aryl glyoxal and alkyl isocyanides 26 in a neutral acetonitrile medium. The reaction also gave the same result when 4-hydroxycoumarin was substituted with dimethylcyclohexandione (Scheme 14). The underlying mechanism for the synthesis begins with the generation of the Knoevenagel adduct \mathbf{ga} of 4-hydoxycoumarin $\mathbf{25}$ and $\mathbf{1}$ with a subsequent [4 + 1] cycloaddition reaction between the resulting hetero-diene \mathbf{ga} and isocyanide $\mathbf{26}$ to form iminolactone \mathbf{gb} as an intermediate. Lastly, a [1,3]-H shift in this iminolactone leads to furo[3,2-c] coumarin $\mathbf{27}$ (Scheme 15).

Chang *et al.* developed an effective method for synthesising furo[3,2-*c*]coumarins utilising 1 in multicomponent tandem reactions driven by FeCl₃ or ZnCl₂. As per the reports, this

reaction between 4-hydroxycoumarin 25 and allyltrimethylsilane 28 or toluene 29 produced two C–C bonds and one C–O bond in compounds 30 and 31, respectively. This approach provided the desired furo[3,2-c]coumarin structures in good to outstanding yields. Some notable traits of the method include the ease with which the starting materials may be obtained, the great functional group tolerance, and the outstanding atom economy (Scheme 16).⁵²

The use of aryl glyoxal **1** by Salari and co-workers set an efficient protocol for the synthesis of functionalized *trans*-tetrahydrobenzofuran-4-ones **34** *via* the condensation reaction of aryl glyoxal, *N*-(4-halophenacyl)-pyridinium bromide **33**, and cyclic **1**,3-diketone **32** utilizing DABCO in a catalytic amount with water as the solvent under reflux conditions. Furthermore, optimization of the protocol was accomplished by using different derivatives of aryl glyoxal, showing that *p*-nitroaryl glyoxal and *o*-bromoaryl glyoxal gave the highest yields under the same conditions (Scheme **17**).⁵³

Next, in 2019, the synthetic application of aryl glyoxal was further explored to construct novel moieties of biological importance. Komogortsev *et al.* devised a new convenient

Scheme 15 Mechanism to explain the synthesis of furo[3,2-c]coumarin 27 via a cycloaddition reaction.

Review

28
30
Ar = C₆H₅, 4-MeC₆H₄, 4-OMeC₆H₄, 4-CIC₆H₄,
4-BrC₆H₄, 2-FC₆H₄, thiophene
R₁ = H, Cl, CH₃

29
FeCl₃ (20 mol%)
90 °C

Scheme 16 Tandem reactions leading to diverse furo[3,2-c]coumarin compounds 30 and 31 using allyltrimethylsilane 28 and toluene 29, respectively.

31

 $Ar = C_6H_5$, $4-CIC_6H_4$, $4-BrC_6H_4$, $4-NO_2C_6H_4$,

4-OMeC₆H₄, 3-CIC₆H₄, thiophene, C₆H₃(CH)₄

$$Ar = 4-NO_2C_6H_4$$
, $4-FC_6H_4$, $2-BrC_6H_4$, $4-OHC_6H_4$, $2-Thienyl$ $R'' = H, CH_3$

Scheme 17 Three-component DABCO-catalysed synthetic protocol for the synthesis of trans-tetrahydrobenzofuran-4-ones 34

method to obtain 7-oxo-7*H*-furo[3,2-*b*]pyran-3-ylacetic acid **36** through the reaction of pyranone **35**, Meldrum's acid **8** and aryl glyoxal **1** as the carbonyl compound in one pot. The reaction was accomplished by the catalysis of Et_3N in MeCN under reflux conditions (Scheme **18**).⁵⁴ The distinguishing feature of the protocol is the application of the Kojic acid analogue 3-hydroxypyran-4-one **35**.

Lichitsky *et al.* in 2020 developed a systematic telescoping-synthesis protocol to synthesise substituted furan-2(5*H*)-one derivatives **39** containing a 4*H*-chromen-4-one fragment *via* the multicomponent reaction of 3-(dimethylamino)-1-(2-hydroxyaryl)prop-2-en-1-one **38**, aryl glyoxal **1**, and Meldrum's

acid **8.** The simultaneous production of 4*H*-chromen-4-one and furan-2(5*H*)-one fragments **39** in one synthetic stage is a distinguishing aspect of the suggested methodology. This approach is atom economical, and has other virtues, such as mild reaction conditions and a simple workup approach, which eliminates the need for chromatographic purifications (Scheme 19).⁵⁵

In 2020, Komogortsev *et al.* explored a new one-pot protocol for the synthesis of various substituted 2-aminofuran moieties **41** based on the multicomponent reaction of 3-hydroxy-4*H*-pyran-4-ones **35**, aryl glyoxal **1** and methylene active nitriles **40**. The formation of 2-aminofuran is a distinguishing aspect of

Me O_{R1} R₂ Et₃N 1 1). Et₃N, MeCN, Δ, 2 h 2). HCI, AcOH, Δ,1 h Me Me Me 36

8

 $Ar = 4-OHC_6H_4$, $4-OMeC_6H_4$, $3,4-(OCH_2O)C_6H_3$

Scheme 18 Synthesis of 7-oxo-7H-furo[3,2-b]pyran-3-ylacetic acid 36 through a condensation reaction.

35

 $Ar = C_6H_5$, $4-Me-C_6H_4$, $4-Cl-C_6H_4$, $4-F-C_6H_4$, $4-OMe-C_6H_4$, $3-OMe-C_6H_4$

Scheme 19 3-(Dimethylamino)-1-(2-hydroxyaryl)prop-2-en-1-one 38-derived formation of the substituted furan-2(5H)-one derivative 39.

this protocol. The excellent yield, high atom economy, simple workup procedure and maintenance of mild reaction conditions for the reaction to proceed are all major benefits of this protocol (Scheme 20).⁵⁶ The suggested mechanism (Scheme 21) begins with the generation of a Michael acceptor from the reaction of the C–H active malononitrile 40 with 1. The allomaltol anion (deprotonated by triethylamine) adds to the intermediate, thus forming the adduct ha. This adduct undergoes deprotonation to form an oxoanion hb followed by cyclisation at the nitriles hc, finally leading to furo-pyran as the final product 41.

In 2013, Karami and co-workers regiospecifically synthesized amido-substituted furo[4,5-*c*]coumarins **43** by reacting aryl glyoxal **1**, 4-hydroxycoumarin **25** and benzamide **42** in a single pot through coupling, followed by cyclisation in acetic acid at

reflux (Scheme 22).⁵⁷ The product showed selectivity over isoxazolo-substituted coumarin. The plausible pathway for the reaction is generation of the intermediate in the condensation reaction, followed by its intramolecular cyclisation and then dehydration to give the final product.

Huang and co-workers reported an efficient Lewis-acid-catalysed reaction for synthesizing diverse furo[3,2-c]coumarins 45 by exploiting aryl glyoxal, 4-hydroxycoumarins 25, and methylketone 44 in 1,4-dioxane at 130 °C using 20 mol% Zn(OTf)₂. The substrate scope of the protocol showed that both electron-rich and electron-neutral aryl glyoxal favoured an annulation reaction, while that with an electron-withdrawing group, such as the NO₂-bearing aryl ring of aryl glyoxal, did not yield any product (Scheme 23).⁵⁸ The proposed reaction design (Scheme 24) follows the pathway initially from the loss of

$$R_1$$
 OH R_2 OH R_3 Et_3N R_1 OH R_3 R_2 OH R_3 R_2 R_1 OH R_3 R_2 R_2 R_3 R_4 R_4 R_5 R_5

 $R_1 = OH$

 $R_2 = CH_3$, C_6H_5 , $4-CI-C_6H_4$, $3-OCH_3-C_6H_4$, $4-OCH_3-C_6H_4$

 $R_3 = CN, CO_2Et, CO-4-CH_3O-C_6H_4$

Scheme 20 3-Hydroxy-4H-pyran-4-ones-derived synthesis of 2-aminofuran 41.

Scheme 21 Synthesis of 2-aminofuran 41 through a Michael reaction followed by cyclisation.

Ar = Ph, 4-FC $_6$ H $_4$, 4-BrC $_6$ H $_4$, 4-NO $_2$ C $_6$ H $_4$, 4-OMeC $_6$ H $_4$, 3-OMeC $_6$ H $_4$, 1-naphthyl, 2-naphthyl

Scheme 22 Synthesis of benzamide 42-derived amido-substituted furo[4,5-c]coumarin 43.

 $R_1 = H, Me, F, (CH)_4$

 $R_2 = C_6H_5$, $(CH)_4C_6H_3$, $4-Me-C_6H_4$, $4-OMeC_6H_4$, $4-CI-C_6H_4$, $4-F-C_6H_4$, $4-CF_3-C_6H_4$, $4-CNC_6H_4$, $4-NO_2C_6H_4$, $2-MeC_6H_4$, thiophene, cyclopropane

 $R_3 = H$, (Me)₂, Bu, cyclopropane.

Scheme 23 Lewis-acid-catalysed protocol yielding furo[3,2-c]coumarins 45.

a water molecule through the condensation reaction of 1 and 25 to give the intermediate ia, which reacts with the enol form of acetone in a Michael-type addition to produce the second intermediate ib. The electrophilicity of the condensed adduct ia is enhanced by the $Zn(OTf)_2$. Finally, dehydration preceded by an intramolecular cyclisation leads to the formation of furo[3,2-c]coumarin 45.

After this, Lichitsky *et al.* used the Meldrum's acid 8 with hydroxycoumarin derivative 46 to access the novel furylacetic acid moiety 47. The pronounced advantage of the biologically important furo-coumarin derivative synthesis is that the formation was possible through a single-pot approach using easily available starting materials with no harsh reaction conditions (Scheme 25).⁵⁹

Scheme 24 Mechanism showing furo[3,2-c]coumarin 45 synthesis through a condensation reaction followed by intramolecular cyclisation.

Scheme 25 Formation of the hydroxycoumarin 46-derived furylacetic acid moiety 47.

45

In 2022, Jana *et al.* developed a straightforward, facile and efficient approach for the synthesis of novel thioether-linked coumarin-fused furans **49** *via* the Sc(OTf)₃-catalysed one-pot combination of aryl glyoxal **1**, 4-hydroxycoumarin **25** and different aromatic thiols **48**. This approach can yield either a three-component thioether-linked coumarin-fused furan **49** or a two-component furo-coumarin product **50**, depending on the thiols. The key attributes of this approach are its broad substrate range, good to exceptional yields, and products with multiple pharmaceutically significant motifs (Scheme 26).⁶⁰

In 2020, Palanivel explored the combination of 1 and benzimidazole acetonitrile 51 with malononitrile 40 at room temperature in a trifilic acid/acetonitrile system to afford tricyclic aza-cyclopenta(*cd*)diindene 54. The above combination was also executed with benzoyl acetonitrile 53 at room temperature in ethanol/water to access the furo[2,3-*b*]furan derivative 55 in the presence of the organic base DABCO. Furthermore, he obtained the pyrrolo-pyridine carboxamide 57 and furo-pyrrolo imidazole carboxamide 56 when the aryl glyoxal 1 was made to react with two equivalents of benzimidazole acetonitrile 52 in

a pseudo-three-component reaction employing DABCO and NaO^tBu as additives, respectively, in ethanol/water at room temperature (Scheme 27).⁶¹

2.2. Synthesis of benzofuran derivatives

ib

In 2019, El-Harairy *et al.* used aryl glyoxal for synthesizing functionalized benzofuran **59** through an ionic liquid catalysis. The desired product **59** was obtained by the assembly of aryl glyoxal hydrate **1**, sesamol **58**, and indole **9** in an imidazolium-based Brønsted acid ionic liquid/butyl acetate green system. The above catalyst was recovered and used for further reactions (Scheme 28).⁶²

In 2020, Lichitskii and co-workers effectively used aryl glyoxal for the preparation of terarylenes **60**, a starting material for the synthesis of naphtho[1,2-*b*]benzofuran-7(8*H*)-ones **61** *via* a green photochemical rearrangement reaction of 4*H*-chromen-4-one derivatives. Aryl glyoxal **1** underwent a three-component tandem reaction with 3-(dimethylamino)-1-(2-hydroxyaryl) prop-2-en-1-one **38** and cyclic **1**,3-diketone **32** in the presence

Review RSC Advances

Scheme 26 Synthesis of the thioether-linked coumarin-fused furan 49 and the furo-coumarin product 50 through reaction with aromatic thiols 48.

Scheme 27 Synthesis of polyheterocyclic hybrid scaffolds.

of an inert solvent and base at room temperature, followed by the subsequent addition of a hydrochloric acid and acetic acid mixture. The model reaction was optimized by using different solvents and varying the system temperature. Terarylenes were best obtained in good yield at room temperature with acetonitrile and triethylamine as the solvent/base system. The

RSC Advances Review

Synthesis of benzofuran 59 using sesamol 58 and indole 9 in a Brønsted acid system

$$R_{2}$$
 OH R_{1} R_{1} R_{1} R_{1} R_{2} R_{2} R_{2} R_{3} R_{4} R_{1} R_{2} R_{2} R_{3} R_{4} R_{2} R_{2} R_{3} R_{4} R_{4} R_{2} R_{3} R_{4} R_{4} R_{4} R_{5} R

Scheme 29 Synthesis of naphtho[1,2-b]benzofuran-7(8H)-ones 61 via photochemical rearrangement reactions of the 4H-chromen-4-one derivative (terarylene) 60.

limitation of the novel multicomponent methodology to cyclic diketones was also confirmed by the unsuccessful test reaction of 2,4-pentanedione (Scheme 29).63 The plausible mechanism for this reaction includes the expected base-catalysed condensation reaction of 1,3-diketone 32 with 1, followed by the subsequent addition of enaminone 38 to the generated Michael acceptor ja, forming the adduct jb. Intramolecular cyclisation through nucleophilic attack of the hydroxyl group to the iminium ion generates an intermediate jc, which finally undergoes acid-catalysed dehydration to form the desired terarylene 60 with a new furan moiety in the structure. This terarylene 60 was exposed to UV light of 365 nm for 30 hours and yielded the desired benzofuran derivative (Scheme 30).

Recently, Rajesh P. et al. successfully demonstrated a threecomponent calcium-catalysed approach for obtaining naphthofuran (3-aminofurans) 68 in good yield via annulation of the in situ intermediate C,N-diacyliminium ion generated as a result of a three-component reaction between a variety of aryl glyoxal 1 and lactams 62 with 2-naphthols 65 under solvent-free conditions at 100 °C (Scheme 31).64 The proposed mechanism

includes formation of the Ca²⁺-catalysed imine ka in the initial step followed by ligand metathesis between Ca2+ and the hydroxyl group of β-naphthol to form a C-C bond kc, and then an intermediate kd with a new C-O bond. Finally, kd undergoes aromatisation yielding the naphthofuran 68 (Scheme 32). The reaction was also tested against different solvents and Lewis acid catalysts, but none of them gave a yield of more than 50%. The ligand metathesis between Ca(OTf)₂ and Bu₄NPF₆ increases the acidity of the catalyst, making it more efficient and able to provide excellent yields. Interestingly, they also repeated the same protocol by changing the nucleophile source to mequinol (substituted phenol) 63 to access the corresponding benzofuran 66 and later glyoxal with the 9H-fluoren-3-ol derivative 64 and lactam-furnished fluorenofuran 67 in a good yield of 84%. Furthermore, the annulation reaction of glyoxal and lactam with 4-hydroxycoumarin as a nucleophile did not prove efficient under solvent-free conditions. The products were studied for their photophysical properties and a broad substrate scope was established for all of these protocols.

Review **RSC Advances**

Mechanistic pathway representing the synthesis of naphtho[1,2-b]benzofuran-7(8H)-ones 61 via an acid-catalysed dehydration Scheme 30 reaction

The utility of aryl glyoxal as a synthetic building block was explored by Lichitsky et al. through the triethylamine-promoted reaction of the 4-methoxy derivative of 1 with Meldrum's acid 8 and 8-hydroxyquinoline 69 in acetonitrile followed by cyclisation in refluxing acetic acid to afford furylacetic acid 70. Advantages of this protocol include a simple work-up route and high atom economy (Scheme 33).65

In 2021, Lichitsky and co-workers described a simple one-pot approach for synthesizing a regiospecific 4H-furo[2,3-h]chromene 72 core using aryl glyoxal. The proposed method was based on a multicomponent reaction of aryl glyoxal, flavones 71, and Meldrum's acid 8. The mild reaction conditions, atom economy, and simple workup procedure are all advantages of this method, which eliminates the need for chromatographic purification (Scheme 34).66

In 2021, Komogortsev and co-workers performed a reaction involving 1, Meldrum's acid 8, and colchiceine 73, which led to a practical one-pot method to synthesize colchicine derivatives 74 with different substitutions. One of the distinctive aspects of the method is the production of the 2-(7-acetamido-1,2,3-trimethoxy-9-oxo-11-phenyl-5,6,7,9-tetrahydrobenzo[9,10]

heptaleno[3,2-b]furan-12-yl)acetic acid. 74 moiety. Some of the key features of this method include the use of easily available precursors, facile execution of the protocol, and the ease with which the target products were separated. Two-dimensional NMR spectroscopy verified the structure of one of the furotropolone products (Scheme 35).67

A multicomponent reaction protocol was developed by Chen et al. for the formation of 2-aryl-3-aminobenzofuran 75 derivatives by reacting aryl glyoxal monohydrates 1, phenols 63, and para-toluenesulfonamide 12, catalysed by 10 mol% of indium trichloride in the presence of dichloromethane as the solvent to obtain an excellent yield (Scheme 36).68

In 2018, Chang et al. reported the formation of the highly functionalized furan derivatives 76 and 77 via the reaction of aryl glyoxal, phenols 63 and 4-hydroxycoumarin 25 in the presence of MeSO₃H or FeCl₃ as a catalyst. By altering the reaction media, a range of furan derivatives with various substitution patterns were produced. This method's atomeconomical traits and moderate conditions are consistent with the principles of contemporary green chemistry. In a short

 R_1 = Ph, 2-BrC₆H₄, 4-BrC₆H₄, 4-ClC₆H₄, 4-FC₆H₄, 4-OMeC₆H₄, 4-MeC₆H₄, Cyclopronane R_2 = H, Br

Scheme 31 Three-component calcium-catalysed protocol for syntheses of 3-aminofurans 68, fluorenofuran 67 and benzofuran 66.

$$Ca(OTf)_{2} + Bu_{4}NPF_{6} \longrightarrow [Ca(OTf)(PF_{6})] = [Ca]^{2+}$$

$$O \qquad Ca^{2+} \qquad Ca^{2+} \qquad O \qquad R$$

$$O \qquad A, 0.5-1 \text{ h} \qquad O \qquad R$$

$$O \qquad A \qquad Bu_{4}NPF_{6} \longrightarrow Ca^{2+} \qquad Ca^{2+} \qquad O \qquad A$$

$$O \qquad A \qquad Bu_{4}NPF_{6} \longrightarrow Ca^{2+} \qquad Ca^{2+} \qquad O \qquad B$$

$$O \qquad A \qquad Bu_{4}NPF_{6} \longrightarrow Ca^{2+} \qquad Ca^{2+} \qquad O \qquad B$$

$$O \qquad A \qquad Bu_{4}NPF_{6} \longrightarrow Ca^{2+} \qquad Ca^{2+} \qquad O \qquad B$$

$$O \qquad A \qquad Bu_{4}NPF_{6} \longrightarrow Ca^{2+} \qquad Ca^{2+} \qquad O \qquad B$$

$$O \qquad A \qquad Bu_{4}NPF_{6} \longrightarrow Ca^{2+} \qquad Ca^{2+}$$

Scheme 32 Plausible mechanism for the calcium-catalysed synthesis of naphthofuran 68.

HO OH + Ar O Et₃N,MeCN, reflux, 1h AcOH, reflux, 1 h AcOH, reflux, 1 h Ar O 70

Scheme 33 Synthesis of furylacetic acid 70 using Meldrum's acid 8 and 8-hydroxyquinoline 69.

Scheme 34 Regiospecific synthesis of 4H-furo[2,3-h]chromene 72 from flavone 71, Meldrum's acid 8 and aryl glyoxal 1.

 $\begin{array}{l} Ar = 4 - CH_3OC_6H_4, \ 3 - CH_3OC_6H_4, \ C_6H_5, \ 4 - BrC_6H_4, \ 4 - CIC_6H_4, \ 3,4 - (CH_3)_2 \ ,2,6 - (CH_3)_2, \ C_6H_3CH_2O_2, \ C_6H_3(CH_2)_2O_2, \ (C_6H_5)_2, \ 4 - C_6H_{11}C_6H_4 \end{array}$

Scheme 35 Synthesis of 2-(7-acetamido-1,2,3-trimethoxy-9-oxo-11-phenyl-5,6,7,9-tetrahydrobenzo[9,10]heptaleno[3,2-b]furan-12-yl)acetic acid 74 using Meldrum's acid 8 and colchiceine 73.

Scheme 36 Indium-catalysed multicomponent protocol for the synthesis of 2-aryl-3-aminobenzofuran 75.

R₁ = H, Cl, CH₃ R₂ = 4-Cl, H, 4-OMe, 3-Me, 2-Me, 4-NO₂, 4-OH, 4-F, 3-Cl, 2-Cl

R₂ = 4-Cl, 3-CH₃, 3-Cl, 4-OCH₃, 2-CH₃, 4-Br, 4-NO₂, 4-CN R₃ = H, 4-F, 4-Br, 4-t-Bu, 4-CH₃, 3-OCH₃

Scheme 37 Synthesis of 4-hydroxycoumarin 25-derived functionalized furans 76 and 77.

 $Ar = C_6H_5$, $4-BrC_6H_4$, $4-CIC_6H_4$, $3-OMeC_6H_4$, $C_6H_4(CH)_4$ $G = (CH)_4$, 2-OH

TSA: Tungstate sulphuric acid

Scheme 38 Three-component solvent-free TSA-catalysed protocol for the synthesis of 2-aryl-3-benzamido-benzofuran 78.

time, a substantial number of heterocycles of biological importance can be created using this protocol (Scheme 37).⁶⁹

Khodabakhshi and Hashemi demonstrated the application of aryl glyoxal in the construction of 2-aryl-3-benzamido-benzofurans 78 *via* a solvent-free three-component condensation reaction of 1 benzamide 42 and the phenolic substrate 63 with a catalytic amount of tungstate sulfuric acid (TSA) at 120 °C (Scheme 38).⁷⁰ The plausible mechanism for the formation of benzofuran consists of three steps, starting with the generation of the intermediate la through an *in situ* condensation of amide 42 and 1, followed by the regiospecific formation of the oxygencontaining five-membered ring lc *via* the intramolecular cyclisation of lb, and finally dehydration leading to the final product 78 (Scheme 39).

A pentacyclic product named as (7-benzoyl-6,7-dihydro-[1,3] dioxolo[4,5-f]benzofuran-6-yl)(4-chloroaryl)methanone **80** was afforded by Reza Salari *et al. via* a one-pot 1,4-diaza-bicyclo [2.2.2]octane (DABCO)-catalysed condensation of three components, namely 2-(2-(4-chloroaryl)-2-oxoethyl))isoquinolinium bromide **79**, benzo(1,3)dioxol-5-ol **58**, and aryl glyoxal **1** in water at reflux. Furthermore, a library of substrates was constructed by using different halo-, nitro- and hydroxyl-substituted aryl glyoxals (Scheme 40).⁷¹

In 2020, Zhang *et al.* reported a simple and straight-forward protocol for the quick synthesis of the benzofuran derivative **82**, that involved an FeCl₃-mediated intermolecular tandem reaction between anisole **81** and **1** *via* a Friedel–Crafts alkylation and oxidative annulation. This reaction offers a lot of benefits, such as readily available starting materials, high atom economy, and strong functional group tolerance (Scheme 41).⁷² The mechanistic steps for the annulation reaction include the Friedel–Crafts alkylation of **1** with anisole **81** forming the intermediate **ma**, which in turn is oxidised by FeCl₃ to generate the second radical cation intermediate **mb**. FeCl₃ is then reduced a second time to further oxidise **mc** with a subsequent intramolecular cyclisation followed by deprotonation to yield the annulated benzofuran **82** (Scheme 42).

By employing microwave irradiation in the presence of the $\rm H_3PW_{12}O_{40}(BFe_3O_4-ZnO)$ catalyst, Taheri and co-workers in 2021 developed an effective and convenient single-pot reaction of benzo[a]phenazine 85 (synthesized from 2-hydroxynaphthalene-1,4-dione 83 and benzene 1,2-diamine 84) a , aryl glyoxal 1, and indoles 9 to produce benzo[a]furo[2,3-c] phenazine 86 derivatives with excellent yields. The facile and quick extraction of the products, short reaction time, mild reaction conditions, high product yield, solvent-free conditions,

Scheme 39 Mechanistic pathway representing the synthesis of 2-aryl-3-benzamido-benzofuran 78.

 $Ar = 4-NO_2C_6H_4$, $4-FC_6H_4$, $2-BrC_6H_4$, $4-OHC_6H_4$, $2-CIC_6H_4$, $4-CIC_6H_4$

Scheme 40 Synthesis of (7-benzoyl-6,7-dihydro-[1,3]dioxolo[4,5-f]benzofuran-6-yl)(4-chloroaryl)methanone 80 in a one-pot approach using DABCO.

$$\begin{array}{c} \text{OMe} \\ \text{R}_1 & \text{OH} \\ \text{OH} \\ \text{OH} \\ \text{H} & \text{R}_2 \\ \text{I} & \text{R}_2 \\ \text{I} & \text{R}_1 = \text{H}, 4\text{-Me}, 4\text{-OMe}, 4\text{-CI}, 4\text{-NO}_2 \\ \text{4-Br}, 4\text{-F}, C_4 H_4 \\ \text{R}_2 = \text{H}, 2\text{-CI}, 2\text{-F}, 2\text{-Br} \\ \end{array}$$

Scheme 41 Synthesis of benzofuran 82 via an FeCl₃-mediated intermolecular tandem reaction.

OH
$$\frac{O}{OH}$$
 $\frac{O}{FeCl_3}$ $\frac{O}{FeCl_2}$ $\frac{O}{OH}$ $\frac{O}{OH}$

Scheme 42 Plausible mechanism for the synthesis of benzofuran 82 in the presence of FeClz.

 $R = H, CH_{3}, R' = H, NO_{2}$ $Ar = 4-Ph, 4-PhCH_{3}, 4-PhOCH_{3}, 4-PhOEt$

Scheme 43 Synthesis of benzo[a]furo[2,3-c]phenazine 86 via microwave irradiation in the presence of H₃PW₁₂O₄₀@Fe₃O₄-ZnO as a catalyst.

low energy demand and economically affordable chemicals are the major advantages of this reaction protocol (Scheme 43).⁷³

Taheri and colleagues performed the same reaction in 2021 to develop an easy, efficient and straight-forward protocol for the synthesis of benzo[a]furo[2,3-c]phenazine 86 derivatives in excellent yields by the reaction of benzo[a]phenazin-5-ol 85, 1, and 9 utilising the Fe₃O₄@rGO@ZnO-HPA catalyst and keeping other the conditions similar to those in the previous reaction (Scheme 44).⁷⁴

A one-pot multicomponent reaction leading to the synthesis of urea-substituted 2-arylfurans **88** was reported for the first time by Komogortsev's group, and involved the reaction of numerous carbocyclic and heterocyclic enols **25** with cyanamide **87** and aryl glyoxal **1** under reflux conditions in the presence of the solvent acetonitrile, and the base triethylamine (Scheme 45).⁷⁵

For the first time, the synthesis of substituted 2-amino-oxazoles containing the 3-hydroxy-4*H*-pyran-4-one moiety **89** was accomplished by Komogortsev's group in a one-step method *via* the multicomponent condensation of allomaltol derivatives **35** with aryl glyoxal **1** and cyanamide **87**, followed by an acid-catalysed recyclisation into substituted furo[3,2-*b*] pyrans **90**. The formation of the 2-aminooxozole core as opposed to a urea-containing condensed furan is the distinctive feature of this approach (Scheme 46).⁷⁶

2.3. Synthesis of pyran derivatives

A green nanoparticle-catalysed strategy for the production of dihydropyrano[ϵ]chromenes **91** was demonstrated by Khodabakhshi's group using aryl glyoxal **1**, 4-hydroxycoumarin **25**, and malononitrile **40** in a single pot with an ethanol-water

Review RSC Advances

 $R = CH_3$, $R' = NO_2$ $Ar = Ph, 4-PhCH_3, 4-PhOCH_3, 4-PhNO_2, 4-PhBr, 4-PhCl$

Scheme 44 Synthesis of benzo[a]furo[2,3-c]phenazine 86 using Fe_3O_4 @rGO@ZnO-HPA as a catalyst.

Scheme 45 One-pot protocol for the synthesis of urea-substituted 2-arylfurans 88 by employing cyanamide 87 and heterocyclic enols 25.

R = CH_2OH , CH_3 , CH_2OCH_3 , CH_2CI , CH_2 -Piperidine Ar = C_6H_5 , 4- OCH_3 - C_6H_4 , 3- OCH_3 - C_6H_4 , 4-F- C_6H_5 , 3,4-(OCH_3)- C_6H_3

Scheme 46 Synthesis of substituted furo[3,2-b]pyrans 90 derived from allomaltol.

solvent system at reflux. The same reaction was tested against *p*-TSA, Na₂CO₃, FeCl₃, ZnCl₂, and AcOH, and gave no significant yields of the desired products, except for the magnetically recyclable Fe₃O₄ nanoparticles (Scheme 47).⁷⁷

Also in 2014, Khodabakhshi and co-workers explored the use of nanosheets of graphene oxide with the same one-pot three-component combination under reflux conditions in an ethanol/water system with a low loading of GO catalyst. The advantages of the above protocol were marked by the recyclable catalyst with a minimum loading of 0.005 g, a high yield and a simple work-up procedure (Scheme 48).⁷⁸

A synthetic library of multifunctional pyrano[c]chromenes **91** was developed by Khodabakhshi $et\ al.$, this time in the presence of ammonium dihydrogen phosphate at room temperature for the first 30–40 min, and then at reflux in an ethanol/water system (Scheme 49).⁷⁹

In 2014, Khodbakhshi's group successfully executed the same reaction in excellent yield with a high degree of purity in the presence of Mohr's salt (Scheme 50).⁸⁰

Afterwards, they reported a similar three-component reaction protocol where they replaced Mohr's salt with TiO₂ nanoparticles. Their process involved the coupling of **1** with malononitrile **40**,

Ar = C_6H_5 , 4-F- C_6H_4 , 4-CIC₆H₄, 4-BrC₆H₄, 3-NO₂C₆H₄, 4-NO₂C₆H₄, 3-OMeC₆H₄, 4-OMeC₆H₄, 1-Naphthyl, 2-Naphthyl

Scheme 47 Nano-catalysed synthesis of dihydropyrano[c]chromenes 91 by reacting, 4-hydroxycoumarin 25 and malononitrile 40.

$$\label{eq:Ar} \begin{split} \text{Ar} &= \text{C}_6\text{H}_5, \, \text{4-F-C}_6\text{H}_4, \, \text{4-CIC}_6\text{H}_4, \, \text{4-BrC}_6\text{H}_4, \, \text{3-NO}_2\text{-C}_6\text{H}_4, \, \text{4-NO}_2\text{-C}_6\text{H}_4, \\ & \text{3-MeO-C}_6\text{H}_4, \, \text{4-MeO-C}_6\text{H}_4, \, \text{1-Naphthyl}, \, \text{2-Naphthyl} \end{split}$$

Scheme 48 Graphene-oxide-catalysed synthesis of dihydropyrano[c]chromenes 91 by the reaction of 4-hydroxycoumarin and malononitrile.

 $\label{eq:Ar} \begin{array}{l} \text{Ar} = C_6H_5, \ 4\text{-}F\text{-}C_6H_4, \ 4\text{-}CIC_6H_4, \ 4\text{-}BrC_6H_4, \ 3\text{-}NO_2\text{-}C_6H_4, \ 4\text{-}NO_2\text{-}C_6H_4\\ 3\text{-}MeO\text{-}C_6H_4, \ 4\text{-}MeO\text{-}C_6H_4, \ 1\text{-}Naphthyl, \ 2\text{-}Naphthyl \end{array}$

Scheme 49 Pyrano[c]chromenes 91 synthesis in the presence of ammonium dihydrogen phosphate.

and **25** in the presence of a catalytic amount of TiO₂ nanoparticles to give a novel family of pyrano[3,2-*c*]chromenes **91** in excellent yield. Their reaction was both environmentally feasible and economically cost-effective since it utilised a greener solvent, and a reusable and safer catalyst (Scheme 51).⁸¹

Then in 2016, Mishra and Choudhury investigated the possibility of using microwave irradiation as one of the synthetic routes for the reaction of aryl glyoxal monohydrate 1, malononitrile 40, and cyclic 1,3-dicarbonyls 6 to afford several pyrans fused with many functionalities, such as coumarins,

quinolones, naphthoquinones, and pyrones **92**. This approach is a basic and simple way of obtaining functionalized pyrans without the need for a catalyst or column chromatographic purification (Scheme 52).⁸²

In addition, Mishra and Choudhury also explored the scope of this technique to obtain the fused pyrans **91** and **94** by changing 1,3-dicarbonyls to other cyclic functionalities, such as 4-hydroxycoumarin **25** and 4-hydroxy-6-methyl-2*H*-pyran-2-one **93**. The corresponding products were isolated in high yields (Scheme 53).⁸² The reaction pathway is outlined in Scheme 54.

Ar = Ph, 4-CIC_6H_4 , 4-BrC_6H_4 , $3\text{-NO}_2\text{-C}_6H_4$, $4\text{-NO}_2\text{C}_6H_4$, 3-MeOC_6H_4 , 4-MeOC_6H_4 , 1-naphthyl, 2-naphthyl

Scheme 50 Three-component synthesis of pyrano[3,2-c] coumarins 91.

Ar = Ph, 4-F-Ph, 4-Cl-Ph, 4-Br-Ph, 3-NO₂-Ph, 4-NO₂-Ph, 3-MeO-Ph, 1-Naphthyl, 2-Naphthyl

Scheme 51 TiO₂-nanoparticle-catalysed synthesis of pyrano[3,2-c]chromenes 91.

Scheme 52 Microwave-assisted protocol for synthesis of fused pyrone 92.

Scheme 53 Synthesis of fused pyrans 91/94 using a microwave technique in the presence of ethanol.

Scheme 54 Reaction pathway for the formation of fused pyran 91/92.

Scheme 55 SBA-15-catalysed green synthesis of 2-amino-4-aroyl-5-oxo-5,6-dihydro-2*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile 92.

Furthermore, Khalafy's group reported the nano-catalysed synthesis of 2-amino-4-aroyl-5-oxo-5,6-dihydro-2*H*-pyrano[3,2-*c*] quinoline-3-carbonitrile **92** through the same combination of aryl glyoxal **1**, active methylene group **40** and 4-hydroxyquinolin-2(1*H*)-one **6** in a single-pot approach with the SBA-15

nanocatalyst in a green solvent. The simplicity of the workup procedure, the use of an ethanol/water system as the green medium, and the good to extraordinary product yields represent the key benefits of this synthetic technique (Scheme 55).⁸³

 $X = H, 4-CI, 4-F, 4-Br, 4-Me, 4-OMe, 4-OH, 3,4-(OMe)_2$

Scheme 56 Three-component synthesis of 4-aroyl-4*H*-benzo[*g*]chromene 95.

Review **RSC Advances**

Then Khalafy et al. extended the library of oxygen heterocycles in 2018 through 4-aroyl-4H-benzo[g]chromene 95 synthesis using 1, 2-hydroxy-1,4-naphtoquinone(lawsone) 83, and one active methylene species 40 with the effective use of a Zn(L-Pr)₂ metal-amino acid complex. Zn(L-Pr)₂ is a water-soluble catalyst that shows Lewis acid behaviour together with significant reusability. The protocol was also tested with different acid catalysts, namely sulfanilic acid, p-toluenesulfonic acid, the phase-transfer catalyst tetrabutylammonium bromide, and Lcystein obtaining the target molecule 95 in a high yield with 20% L-proline in ethanol/water at 50 °C (Scheme 56).25

Next, in 2018, Nasri et al. successfully employed aryl glyoxal to obtain the biologically important oxygen heterocycle and useful chemical synthon chromene. A chemical library of pyrano[3,2-c]chromene 91 and benzo[g]chromene95 was constructed through a catalyst-free one-pot assembly of aryl glyoxal monohydrate 1, malononitrile as the active methylene group 40, and 4-hydroxycoumarin 25/2-hydroxy-1,4-nephthaquinone 83, respectively, under reflux conditions with ethanol as the solvent. Ethyl cyanoacetate, methyl cyanoacetate and cyanoacetamide favoured the enol product 95a (Scheme 57).33 This assembly is also considered to follow the same mechanistic pathway as explained in the case of other equivalent functionalities, starting from a Knoevenagel condensation to form the Michael acceptor oa, followed by 1-4 addition, thereby generating the open-chain intermediates ob and od, which subsequently undergo intramolecular cyclisation to yield the desired products 91 and 95 (Scheme 58).

In 2018, Khaligh synthesised 2-amino-4H-benzo[g]chromenes 95 using the same tactic of a condensation-Michael addition reaction by stirring aryl glyoxal 1, malononitrile 40, and 2 hydroxynephthaquinone 83 with the catalyst poly(N-

vinylimidazole) (PVIm) for two hours in refluxing ethanol. The resultant product 95 showed antibacterial activity against Escherichia coli at 32 mg cm⁻³ (Scheme 59).²⁷

Aryl glyoxal monohydrate as the same starting material was explored by Poursattar Marjani et al. in 2018, who reacted it with malononitrile 40 and 1,3-diketones 32 in the presence of the catalyst L-proline in ethanol solvent for the facile construction of 4H-chromenes, namely 2-amino-4-aroyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile 96 (Scheme 60).84

Poursattar Marjani and co-workers revealed the synthetic utility of aryl glyoxal by bringing together substituted aryl glyoxal 1 in a reaction vessel with 4-hydroxyquinolin-2(1H)-one 6 and ethyl cyanoacetate 40 in the presence of the catalyst TPAB in a water/ethanol system at reflux. This assembly yielded a series of ethyl 2-amino-4-benzoyl-5-oxo-5,6-dihydro-4*H*-pyrano[3,2-*c*] quinoline-3- carboxylate compounds 92 (Scheme 61).85

A convenient method for the synthesis of a novel series of 2amino-4-aroyl-4H-benzo[h]chromene-3-carbonitriles 98 was developed by Poursattar Marjani et al. under solvent-free microwave (MW) conditions in high yields by using a multicomponent condensation reaction of aryl glyoxals 1, 1-naphthol 97, and malononitrile 40 in the presence of Mg-Al hydrotalcite (Scheme 62).86 A plausible outline of the scheme starts with the Mg-Al hydrotalcite-accelerated Knoevenagel reaction of 1 with C-H acid 40 to form an intermediate, namely 2-(2-oxo-2arylethylidene)malononitrile pa. In the second step, α -naphthol is added as a C-nucleophile to the pa, forming a new species with the C-C bond **pb**. The intermediate **pc** undergoes intramolecular cyclisation to generate the species pd, which tautomerizes to give the product 98 (Scheme 63).

In 2015, a novel synthetic route was developed by Rimaz et al. to afford a library of biologically active substituted pyrano[2,3-d]

Scheme 57 MCR-based synthesis of the different pyran derivatives 91, 95 and 95a.

Scheme 58 Mechanisms for 91 and 95 formation through Knoevenagel condensation with a subsequent intramolecular cyclisation

95

91

Ar = C_6H_5 , 4-F- C_6H_4 , 4-Cl- C_6H_4 , 4-Br- C_6H_4 , 4-NO₂- C_6H_4 , 4-MeO- C_6H_4 , α -Naphthyl, β -Naphthyl

Scheme 59 Poly(N-vinylimidazole)-catalysed synthesis of 2-amino-4H-benzo[g]chromenes 95

Scheme 60 Formation of 2-amino-4-aroyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile **96**.

pyrimidines **99.** They obtained the desired products through an excess ammonium acetate-catalysed one-pot condensation of aryl glyoxal monohydrate **1** with barbituric acid **18** using the greenest solvent water at room temperature (Scheme 64).⁸⁷

Rimaz and co-workers also reported the synthesis of pyranofused pyrimidine derivatives **99** through the regioselective pseudo-three-component condensation reaction of aryl glyoxal monohydrate **1** and 1-ethyl-2-thioxodihydropyrimidine-4,6(1H,5H)-dione **18** in a catalytic system of DABCO or ZrOCl₂- 8 H₂O in ethanol at 50 °C. The pyrano-fused-pyrimidine scaffold in the synthesized compound was found to possess HIV integrase inhibitor activity (Scheme 65).³⁴

The potassium phthalimide-N-oxyl(PPINO)-organocatalysed one-pot green reaction of aryl glyoxal monohydrate 1 with barbituric acid 18 or thiobarbituric acid and β -naphthol 65 at reflux in water yielding benzo[5,6]chromene 100 and derivatives was single-handedly reported by Etivand $et\ al$. The distinguishing features of the protocol as highlighted were the use of green

Review **RSC Advances**

Scheme 61 Synthesis of ethyl 2-amino-4-benzoyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carboxylate 92 from 4-hydroxyquinoline-2(1H)-one 6

 $Ar = C_6H_5$, $4-BrC_6H_4$, $4CIC_6H_4$, $4-FC_6H_4$, $4-MeC_6H_4$, $3-MeOC_6H_4$, $4-O_2NC_6H_4$

Scheme 62 Microwave-assisted reaction to afford 2-amino-4-aroyl-4H-benzo[h]chromene-3-carbonitriles 98 using Mg-Al hydrotalcite.

Scheme 63 Mechanism for the formation of 2-amino-4-aroyl-4H-benzo[h]chromene-3-carbonitrile 98.

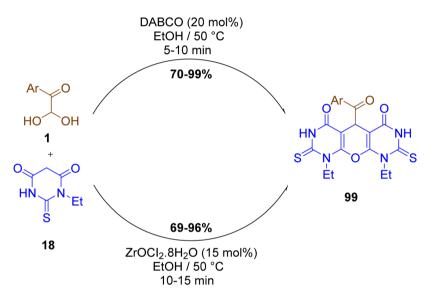
solvents, a short reaction time of only 30 minutes, and the product contained more than one heterocycle centre (Scheme 66).88

In 2020, Taheri and Mohebat proposed a unique greener and environmentally friendly one-pot four-component protocol for

the synthesis of (1-methyl-3-phenyl-3,15-dihydrobenzo[a]pyrazolo[4',3':5,6]pyrano[2,3-c]phenazin-15-yl)methanone scaffolds in a solvent-free medium using nano-Fe₃O₄@TiO₂-SO₃H as the catalyst under microwave monitoring at 75 °C. The major benefits of this green synthetic protocol were the mild

Y = O, S X = 4-H, 4-Br, 4-Cl, 4-F, 4-OCH₃, 3,4-(OCH₂O), 3-Br

Scheme 64 Synthesis of pyrano[2,3-d]pyrimidines 99 via an ammonium acetate-catalysed reaction in the presence of a green solvent.



Ar = Ph, 4-BrC₆H₄, 4-ClC₆H₄, 4-FC₆H₄, 4-MeOC₆H₄, 4-NO₂C₆H₄, 3-MeOC₆H₄, 3-BrC₆H₄, 3, 4-(MeO)₂C₆H₃, 2, 5-(MeO)₂C₆H₃, 3, 4-(OCH₂O)C₆H₃, 4-OH-3MeOC₆H₃

Scheme 65 Three-component reaction to yield pyrano-fused pyrimidine derivatives 99 using a catalytic system of DABCO or ZrOCl₂·8H₂O.

Scheme 66 Organocatalysed reaction of (PPINO) to yield benzo[5,6]chromene 100 using a green solvent.

Review

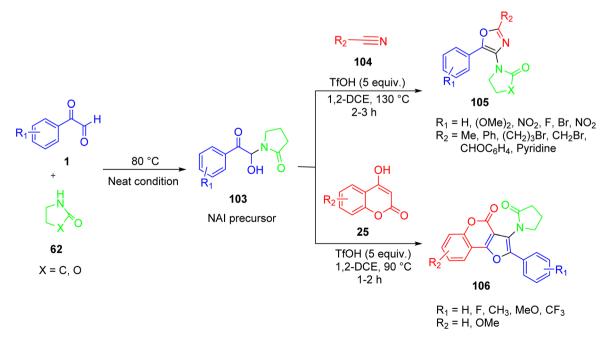
Scheme 67 Nano- Fe_3O_4 @ TiO_2 - SO_3 H catalysed formation of (1-methyl-3-phenyl-3,15-dihydrobenzo[a]pyrazolo[4',3':5,6]pyrano[2,3-c]phenazin-15-yl)methanone 102.

reaction conditions, a high product yield, fast reaction time, solvent-free condition, low energy demand and economic affordability (Scheme 67).⁸⁹

2.4. Miscellaneous reactions

Babu's group reported the simple and efficient synthesis of oxazoles **105** and furocoumarins **106**. The essential step in these transformations comprises the *in situ* formation of *N*-acyliminium ion (NAI) precursors **103** from aryl glyoxal and 2-pyrrolidinone **62** in the absence of a catalyst or solvent, followed by their further transformations aided by trifilic acid in the same vessel. It was demonstrated experimentally that the special exocyclic proto-solvated *N*-acyliminium ion is involved in the

reaction. Additionally, the results of the fluorescence and UV-visible experiments revealed that a limited number of the compounds emit blue light when exposed to light in EtOH in the 404–422 nm wavelength range (Scheme 68). On insight into the mechanism revealed that, at first, formation of the N-acyliminium ion (NAI) precursor **qa** from **1** and 2-pyrrolodinone **62** occurs under acid catalysis. There are two probable cyclisation routes. In route 'a', the attack of acetonitrile on the iminium intermediate **qb** leads to the formation of the nitrilium ion **qc**, which undergoes cyclisation to form the final product **105** through the involvement of an adjacent carbonyl group. While in route 'b', neutralisation of the nitrilium ion by a water molecule generates the bisamide **qd**, which subsequently



Scheme 68 Syntheses of oxazoles 105 and furocoumarins 106 via an in situ N-acyliminium ion (NAI) precursor.

Scheme 69 Reaction pathway for the synthesis of substituted oxazoles 105.

undergoes cyclisation, losing a water molecule to yield the desired product **105** (Scheme 69).

In 2008, García-Valverde *et al.* reported the reaction of aryl glyoxal **1** with aniline **12**, cyclohexyl-isocyanide **107**, and trichloroacetic acid **108** in dichloromethane, in the presence of a 3

Å molecular sieve, to afford the oxazolone derivative **109** through the Ugi multicomponent reaction pathway group. The remarkable feature of the strategy is the carbonic acid function of the trichloroacetyl group (Scheme 70).⁹¹

105

Scheme 70 Synthesis of isoxazole 109 through an Ugi multicomponent reaction.

Review

 $R = Ph, 4-CH_3C_6H_4, 4-EtC_6H_4, 4-tBuC_6H_4, (Ph)_2, 4-OMeC_6H_4$ 4-FC₆H₄, 4-CIC₆H₄, 4-IC₆H₄, 3MeSC₆H₄

Scheme 71 Synthesis of oxazole 112 through a domino reaction using toluenesulfonylmethyl isocyanide 111

R₁ = H. Me. CI $R_2 = C_6H_5$, p-MeC₆H₄, p-CIC₆H₄, C₄H₄S

Scheme 72 Furo[3,2-c]coumarin 113 synthesis via in situ-generated phenyl glyoxal.

2.5. In situ domino reactions of aryl glyoxal to afford oxygen heterocycles

A novel method was developed by Pogaku et al. for the production of oxazoles 112 from methyl ketones 110 and Tos-MIC (toluenesulfonylmethyl isocyanide) 111 using a self-sorting domino reaction approach. TosMIC was used as an ammonium

surrogate in contrast to its typical reactivity as a C-N C synthon in the production of oxazoles 112 (Scheme 71).92 The technique is appealing due to its ease of operation, the wide availability of the starting materials, absence of bases and metals, and the production of C-N and C-O bonds with excellent yields.

A facile, straightforward novel, and highly efficient protocol was reported by Kolita et al. in 2016 to obtain functionalized furo[3,2-c]coumarins 113 from 4-hydroxycoumarins 25. The reaction was allowed to proceed by reacting aldehyde/aryl methyl ketone 110 with 25 in the presence of molecular iodine in DMSO at 80 °C. DMSO here works as a solvent as well as an oxidizing agent to recycle the iodine during the reaction process (Scheme 72).93 The plausible mechanism of the reaction is that initially phenylglyoxal 1 is formed from phenyl methyl ketone 110 via sp³-CH activation and oxidation, and is subsequently allowed to react with 4-hydroxycoumarin 25 in the presence of iodine to form the intermediate ra. Species ra loses a water molecule, thereby generating rb. Nucleophilic attack by the second molecule of 4-hydroxycoumarin on the intermediate **rb** yields the final product **113** (Scheme 73).

Cheng's group prepared the highly dense benzofuran 59 by in situ-generating aryl glyoxal from methyl ketone 110, phenol derivatives 58, and indole 9 together in a reaction vessel with molecular iodine in a catalytic amount and DMSO as a solvent. Later, the nucleophile was changed to thiophenol and 1,2,4trimethoxybenzene, etc., in place of indole (Scheme 74).7

In 2012, Xue et al. proposed a novel and highly efficient protocol to synthesize polysubstituted oxazole derivatives 115 from simple and easily available starting materials, that is by reacting methyl ketone 110, benzoin 114, and ammonium

Scheme 73 In situ domino synthesis of furo[3.2-c]coumarin 113 by sp³-CH activation and oxidation.

110 9 58 59

Scheme 74 Synthesis of benzofuran 59 with the indole fragment 9 from methyl ketone 110

 $R = Ph, 4-MeC_6H_4, 4-NO_2C_6H_4, 4-CIC_6H_4, 2-Furyl, 2-Thienyl$

Scheme 75 Domino reaction leading to benzoin 114-derived oxazole 115

acetate *via* the convergent integration of two "self-labour domino sequences". This reaction has wide application in medicinal and life science chemistry (Scheme 75).⁹⁴

In 2018, Zhao and co-workers proposed a novel path for the synthesis of fused heterocycles by employing an iodine-promoted fragment assembly method. They formulated pyrazolone-oxepine-pyrazoles **118** by the reaction of phenylhydrazine **116**, aryl methyl ketones **110**, and acetoacetate ester **117** using molecular iodine at 140 °C in the presence of TfOH, and also explored the application of a five-component reaction. Acetoacetate ester engages in two crucial steps, which are the formation of the 3-methyl-5-pyrazolone skeleton and the formation of the $C(sp^3)$ -O bond (Scheme 76).

In 2011, Yang *et al.* performed a convergent and linear domino reaction for the first time from easily available inexpensive substrates, like methyl ketone **110**, indole **9**, and 1,3-

O Ar₁ + Ar₂-NHNH₂ + O O DMSO, 140 °C
$$\frac{I_2, TfOH}{DMSO, 140 °C}$$
 Ar₂ N N N Ar₂ $\frac{I_10}{N}$ 118 $\frac{I_2 + I_2}{N}$ Ar₂ $\frac{I_2 + I_3}{N}$ Ar₂ $\frac{I_3 + I_4}{N}$ Ar₂ $\frac{I_4 + I_5}{N}$ Ar₂ $\frac{I_4 + I_5}{N}$ Ar₃ $\frac{I_4 + I_5}{N}$ Ar₄ $\frac{I_4 + I_5}{N}$ Ar₅ $\frac{I_4 + I_5}{N}$ Ar₆ $\frac{I_4 + I_5}{N}$ Ar₇ $\frac{I_4 + I_5}{N}$ Ar₇ $\frac{I_4 + I_5}{N}$ Ar₈ $\frac{I_4 + I_5}{N}$ Ar₉ $\frac{I_4 + I_5}{N}$ Ar₉ $\frac{I_4 + I_5}{N}$ Ar₁ $\frac{I_4 + I_5}{N}$ Ar₂ $\frac{I_4 + I_5}{N}$ Ar₄ $\frac{I_4 + I_5}{N}$ Ar₄ $\frac{I_4 + I_5}{N}$ Ar₆ $\frac{I_4 + I_5}{N}$ Ar₇ $\frac{I_4 + I_5}{N}$ Ar₇ $\frac{I_4 + I_5}{N}$ Ar₈ $\frac{I_4 + I_5}{N}$ Ar₉ $\frac{I_4 + I_5}{N}$

Scheme 76 Synthesis of pyrazolone-oxepine-pyrazoles 118 from phenylhydrazine 116, acetoacetate ester 117 and in situ-generated phenyl glyoxal 1.

 R_1 = Ph, Me, 2-Furyl, 3-NO₂C₆H₄, 4-NO₂C₆H₄

R₂ = Ph, OEt, OMe

 $R_3 = H$, Me

Scheme 77 Synthesis of 3-(furan-3-yl or 4-yl) indole derivative 119 from 1,3-diketone 17, indole 9 and methyl ketone 110.

dicarbonyl **17** to afford the 3-(furan-3-yl or 4-yl) indole derivative **119** *via* a direct two-step process without the need for purification of the intermediate. This reaction has a wide range of applications in synthetic and medicinal chemistry due to its operational simplicity (Scheme 77).⁹⁶

3. Conclusions

Review

As a unique molecule with robust applications in organic synthesis, ranging from C–C bond formation reactions to the synthesis of heterocycle libraries, aryl glyoxal is an efficient and easily accessible building block that has been extensively used in the past decade. Exploitation of this commercially available precursor all over the world by chemists has produced many novel functionalized moieties that are both pharmacologically and biologically beneficial to mankind. The different synthetic protocols of aryl glyoxal along with amines and nitrogen heterocycles in multicomponent reaction systems give rise to highly complex synthetic diversity in the products, inspiring researchers to think beyond the current scope towards new horizons.

After the gigantic number of nitrogen heterocycles, oxygen heterocycles are the second category approved for clinical use as medicinal drugs. Their synthesis through different resources has raised the attention of researchers to a significant level, but there is still a huge gap between the synthetic methodologies and application patterns of nitrogen and oxygen scaffolds. The lower reactivity and somewhat complicated biomimicking process compared to nitrogen members are the possible reasons behind their limited number of applications in biosystems. Furthermore, researchers have brought phenyl glyoxal into action using it either as a substitute for mono-functional aldehydes for forming a structural backbone by adding carbon to the target structure, or as an oxygen donor in the product molecule. The optimum use of phenyl glyoxal with new combinations of reagents possessing multiple functionalities is still awaited. The mounting up of oxygen heterocycles' applications is conditional on the proper execution of advanced tools and techniques for their strategic biosynthesis followed by extensive tests and trials.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

There are no conflicts to declare.

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