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Functionalized reduced graphene oxide as a useful and efficient base catalyst for the preparation of 4*H*-pyran and pyran-like tacrine compounds and their antibacterial activity

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Abstract. An easy, effective and eco-friendly one-pot process for the preparation of 4*H*-pyran compounds has been established by using a catalytic amount of reduced graphene oxide functionalized with diethylenetriamine (rGO-DETA) in water under mild conditions. The functionalized catalyst was very effective for this one-pot reaction and provided the desired products **1a-t** with good to high yields (87-97%) in short reaction times. Moreover, rGO-DETA composite could be reused for four cycles without obvious decrease of its performance. In the next step, two pyran derivatives **1f** and **1h** were used to synthesize the corresponding pyran-like tacrine derivatives **3f** and **3h** via the reaction of cyclohexanone, aluminum trichloride in reflux of 1,2-dichloroethane as solvent. Antibacterial activity of several of the prepared compounds was assessed against Gram-positive and Gram-negative bacteria by well and disk diffusion techniques. The 4*H*-pyran **1g** and **1s** (2000 µg/mL) were effective against *M. luteus* as Gram-positive bacterium by recording a zone of inhibition of 15 and 16 mm, respectively. 4*H*-pyran **1m** showed a moderate antibacterial behavior against both *M. luteus* and *S. marcescens*. Pyran-like tacrine analogue **3f** (50 mg/mL) displayed antibacterial behavior towards *S. aureus* as Gram-positive and *S. marcescens* as Gram-negative bacteria with zones of inhibition of 13 and 12 mm, respectively. 4*H*-pyran **1j** featured a minimum inhibitory concentration (MIC) value 39.06 µg/mL for *M. Luteus*, which is the closest value to ampicillin.

Keywords: Reduced graphene oxide; Diethylenetriamine; 4*H*-pyrans; Pyran-like tacrine derivative, Antibacterial activity

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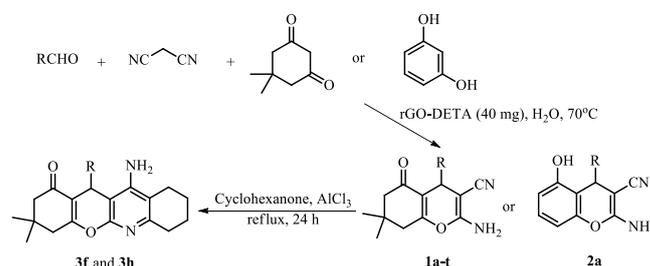
1. INTRODUCTION

Tacrine (1,2,3,4-tetrahydroacridine-9-amine) is an effective prototypic inhibitor of Alzheimer's disease by improving the function of brain neurons [1-2]. Insufficiency of acetylcholine in the brain cell causes Alzheimer's disease (AD). Tacrine, an acetylcholinesterase inhibitor, increases acetylcholine release in the body, and thus it was used for the symptomatic treatment of AD [3]. Synthesis of tacrine analogues was generally performed through the condensation of anthranilonitrile with cyclopentanone or cyclohexanone in the presence of a protic acid, such as *p*-toluenesulfonic acid (PTSA) [4], or a Lewis acid such as ZnCl₂ [5], AlCl₃ [6], BF₃/Et₂O [7], and P₂O₅ [8]. Compared to other catalysts, AlCl₃ was used more often at reflux of dichloromethane or dichloroethane as solvent [9-11]. Various reports have been proposed for the design of novel tacrine analogs by replacing the benzene moiety by a heterocyclic system. The existence of an aromatic or a heteroaromatic ring on tacrine skeleton leads to an increase in the π - π stacking interaction in the structure of the drug, which can be used for the development of new acetylcholinesterase inhibitors [12]. 4*H*-pyran compounds are very interesting, owing to their beneficial biological and pharmacological features, like anti-allergy, antibacterial, antitubercular, antifungal, anticoagulant and antitumor characteristics [13-20]. 4*H*-pyran compounds can also be used as important structural units in the skeleton of many human drugs; for example, to treat Alzheimer, Down syndrome and Parkinson's diseases [21]. Multicomponent reactions (MCRs) have been recognized as an appealing approach for overcoming the toxic reaction conditions and employing green chemistry components. MCR has been successfully applied as an organic synthesis strategy for the preparation of different molecules such as 4*H*-pyran derivatives [22]. Recently, the development of eco-friendly approaches and suitable catalysts in MCRs has attracted much attention [23-24]. For example, Babaei and co-workers have described the synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives using nano-Al₂O₃/BF₃/Fe₃O₄ catalyst in reflux of solvent [23]. In addition, nowadays the utilization of environmentally-friendly solvents along with reusable heterogeneous catalysts represents an appealing approach in green chemistry [25-28]. 2-Amino-3-cyano-4*H*-pyrans are studied as intermediates in the preparation of novel tacrine compounds via the Friedlander reaction of chromene and ketone compounds containing reactive methylene group [10,29-30]. This hetero-annulation reaction was performed for 2-amino benzonitrile synthesis and applied as a good acetylcholinesterase inhibitor to treat Alzheimer disease [2].

Among the heterogeneous catalysts, carbon-based materials such as graphene oxide (GO), and its

functionalized derivatives have been investigated for various organic transformations due to their distinctive chemical and physical characters [31-33]. Surface functionalization of GO by various groups such as SO₃H [34-36], amine [37], and phosphate [38-39] moieties is the most conventional approach to improve the catalytic performance. For example, sulfonated reduced graphene oxide (rGO-SO₃H) was investigated for the preparation of 2-amino-3-cyano-7-hydroxy-4*H*-chromene compounds in water [34-35], and for the direct amidation of carboxylic acids with amines [36]. Immobilized zirconocene chloride on magnetite-rGO showed high catalytic performance in *N*-acetylation of arylamines [40], and rGO@Fe₃O₄@Ni was applied in MCR of dimedone with diverse aromatic aldehydes for the synthesis of xanthenedione derivatives [41]. Amino-grafted graphene oxide showed a super basicity and exhibited significant catalytic activity in typical homogeneous reactions [37]. Phosphate-functionalized graphene oxide was applied for the Biginelli reaction using microwave condition by Achary and co-workers in 2018 [38]. Recently, phosphoric acid-functionalized graphene oxide was used for the preparation of pyrano[2,3-*c*]pyrazole *via* MCR [39].

In continuation of our investigations in heterogeneous catalysis [36,42-46] and the preparation of heterocyclic products [47-51], we describe herein the application of MCR for the preparation of 4*H*-pyran compounds (**1a-t** and **2a**) using an eco-friendly diethylenetriamine-functionalized reduced graphene oxide (rGO-DETA) catalyst as a solid base material in water media under mild conditions (**Scheme 1**). The reaction of 4*H*-pyran compounds with cyclohexanone gave high yields of the corresponding pyran-like tacrine derivatives **3f** and **3h**. The biological activity of the synthesized pyran and pyran-like tacrine derivatives was evaluated against Gram-positive and Gram-negative bacteria.



SCHEME 1 Synthesis of 4*H*-pyran and pyran-like tacrine derivatives catalyzed by rGO-DETA

2. EXPERIMENTAL SECTION

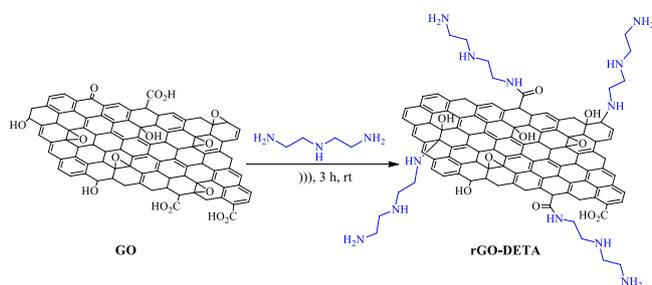
Synthesis of rGO-DETA, general methods for the preparation of 4*H*-pyran and tacrine compounds, antibacterial experiments and evaluation of antibacterial properties by determination of minimum

inhibitory concentration (MIC) are presented in the supplementary section.

3. RESULTS AND DISCUSSION

3.1. Synthesis of rGO-DETA material

GO was obtained using the modified Hummers' method [52] and functionalized with diethylenetriamine (DETA) [43]. DETA (400 mg) was added to an ethanoic solution of GO (40 mg in 40 mL of ethanol) and sonicated (Elmasonic P ultrasonic cleaning unit) for three hours at ambient temperature. The obtained mixture was centrifuged and the formed precipitate was washed with EtOH, MeOH and acetone, and dried at ambient temperature for overnight to yield rGO-DETA. **Scheme 2** depicts the schematic synthesis of the rGO-DETA catalyst.



SCHEME 2 Preparation of rGO-DETA material

3.2. Identification of rGO-DETA material

The rGO-DETA material was characterized using FT-IR, UV-visible spectrophotometry, X-ray diffraction (XRD), thermogravimetric analysis (TGA) and X-ray photoelectron spectroscopy (XPS) measurements to establish its authenticity [43]. The analysis of all data has been fully presented in our previous work [43]. The FT-IR spectrum of rGO-DETA clearly confirms that the GO surface is effectively functionalized by DETA through the formation of amide and amine bonds, respectively by the reaction of -NH_2 groups of DETA with COOH and epoxy groups of GO (**Figure S1**). This is corroborated by the presence of new peaks at 1112 and 1636 cm^{-1} related to C-N and NH-C=O stretching vibrations in the FT-IR spectrum of rGO-DETA, which indicates the formation of amide or amine bonds. A significant decrease is observed in the peaks of 1726, 1200 and 860 cm^{-1} , which indicates the attack of amine groups of DETA to acidic and epoxy groups of GO [53-54]. The UV-vis absorption spectrum of GO dispersion in H_2O shows one major peak at ~ 230 nm and a weak peak at ~ 310 nm due to π - π^* absorption of C=C bonds and n - π^* absorption of C=O bonds, respectively (**Figure S2**). Upon DETA functionalization, a redshift from ~ 230 to ~ 260 nm was observed along with the disappearance of the shoulder at ~ 310 nm, which confirmed the presence of rGO material. The analysis of XRD

pattern of rGO-DETA showed the typical peak at $2\theta = 11.8^\circ$ of GO and a wide peak at about $2\theta = 26^\circ$ due to the presence of rGO through partial elimination of oxygenated functional groups (**Figure S3**). The thermal stability of the catalyst was assessed by thermogravimetric analysis (TGA) under N_2 atmosphere; the weight loss of rGO-DETA composite was comparable to that of GO with a difference of 10% (**Figure S4**). A first weight loss of $\sim 7\%$ at $\sim 105^\circ\text{C}$ was ascribed to the dehydration of adsorbed water molecules. A second weight loss of 21% in the 105-210 $^\circ\text{C}$ temperature range was due to the decomposition of the functional groups like epoxy, hydroxyl, carbonyl, carboxylic acid and amine groups. Finally, a weight loss of 20% (210-900 $^\circ\text{C}$) was detected, due to the combustion of the carbon frame. The XPS analysis of rGO-DETA material approves the presence of N in this material, which was absent in the XPS spectrum of the starting GO (**Figure S5**). The data are presented in the supplementary information. In addition, rGO-DETA was characterized by CHN, zeta potential, SEM imaging and EDS analysis.

Elemental concentrations of GO and rGO-DETA materials were determined using a CHN analyzer with accuracy and precision. The carbon and hydrogen contents of GO were respectively 47.65% and 2.18%. The presence of sulfur (3.08%) originated most likely from residual sulfuric acid used during the GO preparation (**Table 1**, entry 1). Elemental concentrations of rGO-DETA material showed in addition the presence of nitrogen element (7.96%), which is a good indication of the successful grafting of DETA onto rGO surface (**Table 1**, entry 2).

TABLE 1 Elemental analysis and zeta potential values of GO and rGO-DETA materials

Entry	Sample	C (%)	H (%)	S (%)	N (%)	Zeta potential (mV)
1	GO	47.65	2.18	3.08	-	-52.0
2	rGO-DETA	51.58	3.92	2.24	7.96	-45.2

The zeta potential is a physical property revealed by the particles in dispersion. The change of surface charge after the modification of GO by DETA was investigated by zeta potential measurements. The surface potential changed from -52.0 mV for GO to -45.2 mV for GO-DETA, which indicates the partial reduction of GO. In fact, DETA is expected to react with the epoxy and acidic groups of GO; in this way, GO is simultaneously functionalized and partially reduced (**Table 1**, entries 1-2).

SEM image, EDS elemental mapping of C, O, S and N elements, and EDS spectrum of rGO-DETA, are presented in **Figure 1**. The elemental mapping indicated the homogeneous distribution of C, O, S, and N elements on the rGO-DETA surface (**Figure 1(b)-(f)**). The existence of N element infers that

DETA is effectively integrated into the skeleton of rGO after ultrasonic irradiation, which is in perfect agreement with the relevant EDS analysis (presence of N element in 14.81 at%), **Figure 1(g)**.

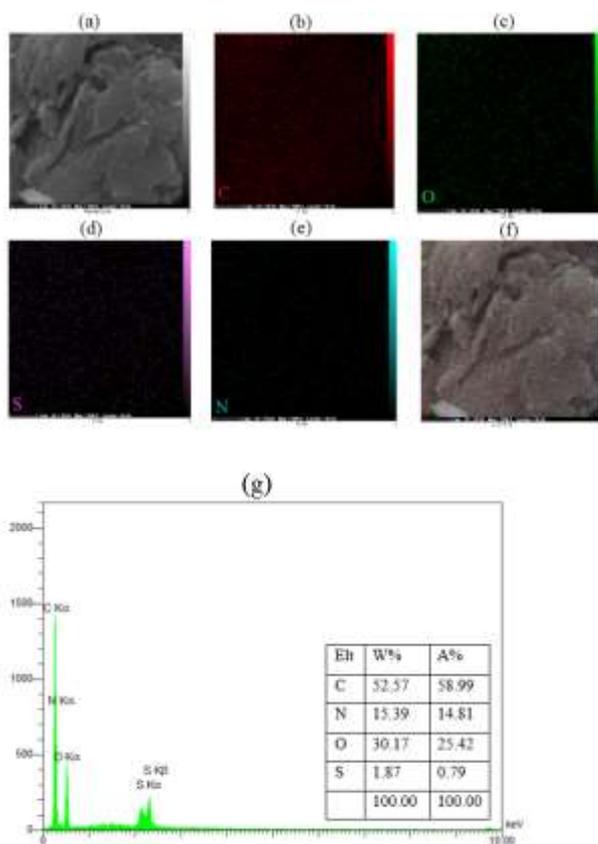


FIGURE 1 (a) SEM image, EDS elemental mapping of (b) C, (c) O, (d) S and (e) N elements, and (g) EDS spectrum of rGO-DETA material

3.3. Catalytic performance of rGO-DETA material

The catalytic performance of rGO-DETA was examined in MCR for the preparation of 4*H*-pyran **1a** from the reaction of benzaldehyde, malononitrile and dimedone in different experiments considered to optimize the reaction conditions (**Table 2**). Since this reaction was reported in water as solvent [35,55-56], water was chosen as a green solvent in this study. This reaction in absence of catalyst was investigated and the results indicated the synthesis of the final compound **1a** only in 18% yield (**Table 2**, entry 1). We then examined the influence of GO and rGO-SO₃H [36] as solid acid catalysts for this reaction (**Table 2**, entries 2-3). The results revealed that the yield of **1a** was higher in presence of rGO-SO₃H catalyst (**Table 2**, entry 3). But, by using this solid catalyst, the yield of product **1a** was not satisfactory. Thus, we assessed rGO-DETA for this reaction as a base catalyst under different conditions (**Table 2**, entries 4-8). An augmentation of the yield of 4*H*-pyran **1a** to 94% was observed using rGO-DETA in H₂O as solvent at 70°C (**Table 2**, entry 8). This result

revealed that rGO-DETA as a base catalyst was effective for this reaction. Moreover, to check the effect of the amine functionalization on the reaction, we have prepared rGO-TETA by the functionalization of GO with triethylenetetramine (TETA). However, the application of rGO-TETA catalyst for the MCR was not satisfactory and **1a** was obtained in 25% yield (**Table 2**, entry 9). The reason of this result is not clear. However, the literature study revealed that by increasing the chain length of the amine ligand, there is a possibility of cross-linking reaction, which could result in a decrease of the efficiency of the rGO-TETA catalyst [57-58]. Decreasing the amount of catalyst to 30 mg led to a drop in the reaction yield to 84% (**Table 2**, entry 10). It should be noted that when this reaction was performed in the presence of DETA as catalyst, the corresponding product was obtained in 42% (**Table 2**, entry 11). This result clearly evidences the importance of rGO-DETA catalyst for the progress of this MCR.

TABLE 2 Different experimental conditions used for the synthesis of **1a**^a

Entry	Solvent	Catalyst	Temperature (°C)	Time (min)	Yield (%) ^b
1	H ₂ O	-	70	30	18
2	H ₂ O	GO	70	30	22
3	H ₂ O	rGO-SO ₃ H	70	30	30
4	EtOH	rGO-DETA	80	30	78
5	CH ₃ CN	rGO-DETA	80	30	57
6	H ₂ O	rGO-DETA	r.t	60	trace
7	H ₂ O	rGO-DETA	60	30	85
8	H ₂ O	rGO-DETA	70	30	94
9	H ₂ O	rGO-TETA	70	30	25
10 ^c	H ₂ O	rGO-DETA	70	30	84
11	H ₂ O	DETA	70	30	42

^a Dimedone (1 mmol), malononitrile (1 mmol), benzaldehyde (1 mmol) and catalyst (40 mg) were used. ^b Isolated yield. ^c 30 mg of rGO-DETA was used.

After finding the optimal conditions, we have prepared 4*H*-pyran derivatives **1a-t** and **2a** by using MCR of a variety of aldehydes and malononitrile with dimedone or resorcinol, respectively. The obtained data are presented in **Table 3**. It could be seen that a variety of substituted 4*H*-pyrans were formed in excellent yields after 30 min upon the

condensation of aldehydes with electron-withdrawing or electron-donating groups as Cl, Br, OH, NO₂, OMe, Me, *tert*-butyl, phenyl, and naphthyl group with malononitrile and dimedone (**Table 3**, entries 1-14). The results also inferred that heterocyclic aromatic aldehydes such as thiophene-2-carbaldehyde, 5-methyl thiophene-2-carbaldehyde, furan-2-carbaldehyde, isonicotininaldehyde, nicotininaldehyde and 4-oxochromene-3-carbaldehyde are good substrates for this MCR and the corresponding products **1o-t** were obtained in 95, 91, 88, 93, 91 and 89% yield, respectively (**Table 3**, entries 15-20). When the condition was extended to MCR of resorcinol with malononitrile and aldehyde such as 4-pyridine carboxaldehyde, the corresponding 4*H*-pyran derivative (**2a**) was readily obtained in 95% yield (**Table 3**, entry 21).

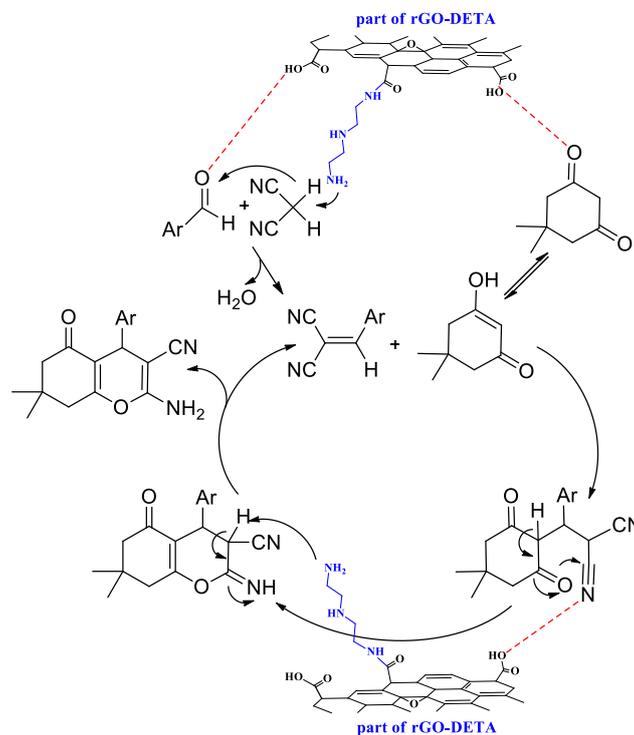
TABLE 3 Preparation of 4*H*-pyrane derivatives using rGO-DETA catalyst

Entry	Aldehyde	Product	Yield ^a (%)	M. P. (°C) Found Reported
1	PhCHO	1a	94	231 229-231 [50]
2	4-OHC ₆ H ₅ CHO	1b	88	214 214-215 [50]
3	3-OHC ₆ H ₅ CHO	1c	90	224 224-226 [59]
4	4-ClC ₆ H ₅ CHO	1d	96	209 208-210 [50]
5	4-BrC ₆ H ₅ CHO	1e	93	201 201-203 [50]
6	4-NO ₂ C ₆ H ₅ CHO	1f	97	152 151-152 [50]
7	3-NO ₂ C ₆ H ₅ CHO	1g	96	213 211-213 [59]
8	4-OMeC ₆ H ₅ CHO	1h	90	197 197-199 [50]
9	3-OMeC ₆ H ₅ CHO	1i	93	197 197-199 [59]
10	2-OMeC ₆ H ₅ CHO	1j	87	199 198-199 [60]
11	4-MeC ₆ H ₅ CHO	1k	93	216 214-216 [50]
12 ^b	4- <i>tert</i> -butylC ₆ H ₅ CHO	1l	92	242 241-242 [61]
13	4-PhC ₆ H ₄ CHO	1m	90	247 246-247 [62]
14	1-naphthaldehyde	1n	95	215 214-215 [63]
15	2-C ₄ H ₃ SCHO	1o	95	212 210-212 [50]
16	5-Me-C ₄ H ₃ SCHO	1p	91	217 217-219 [64]
17	2-C ₄ H ₃ OCHO	1q	88	216 216-217 [50]

18 ^b	4-C ₅ H ₄ NCHO	1r	93	216 214-216 [65]
19 ^b	3-C ₅ H ₄ NCHO	1s	91	225 225-226 [50]
20	4-oxochromene-3-carbaldehyde 1t		89	246 249-252 [66]
21 ^b	4-C ₅ H ₄ NCHO	2a	95	215 214-215 [35]

^a Isolated yield. ^b The reaction was performed during 40 min and resorcinol was used as reagent.

A plausible mechanism for this reaction is presented in **Scheme 3**. rGO-DETA surface comprises different groups such as hydroxyl, carboxyl and amine groups, which confer an acidic [47-48,67] and basic [68] characters to the material. Hydroxyl and carboxyl groups of rGO can activate the aldehyde and dimedone through interaction with the oxygen atom to increase the susceptibility of the aldehyde to nucleophilic attack and dimedone to produce the corresponding enolate, respectively. The amine group of rGO-DETA surface can facilitate the generation of arylidenemalononitrile intermediate, which is formed by *in situ* reaction of an activated aldehyde with malononitrile. The following addition of enolate to the arylidenemalononitrile yields the corresponding intermediate. The cyclization of the later, followed by tautomerization gives the corresponding final product.



SCHEME 3 A plausible mechanism for the preparation of 4*H*-pyrane derivatives using rGO-DETA catalyst

To assess the reusability of rGO-DETA catalyst, the catalytic reaction of benzaldehyde, malononitrile and dimedone in water for the preparation of 4*H*-

pyran **1a** was investigated. After each cycle, the catalyst was recuperated by centrifugation and washed with boiling EtOH and then dried under vacuum for the next cycle. 4*H*-pyran **1a** was isolated in 94, 92, 94, 90% after the 1st, 2nd, 3rd and 4th run, respectively (Table 4). Since, no obvious performance failure was observed after 4 cycles, it could be inferred that rGO-DETA catalyst was stable under our experimental conditions.

TABLE 4 Recycling efficiency of rGO-DETA catalyst for the preparation of product **1a** in H₂O

Run	1	2	3	4
Yield %	94	92	94	90

The FT-IR spectra of fresh and reused rGO-DETA catalyst are depicted in Figure S6 in the Supplementary information. Both spectra display similar features, which approves the stability of the catalyst after 4 cycles.

In the next step, we have performed the synthesis of tacrine analogues by condensation of substituted 4*H*-pyran derivatives **1f** and **1h** with cyclohexanone catalyzed by aluminum trichloride as a Lewis acid. Using the standard conditions, the reaction of 4*H*-pyran compounds with cyclohexanone and AlCl₃, as a promoter, in dry 1,2-dichloroethane as solvent afforded the expected tacrine analogues **3f** and **3h**, respectively, under mild conditions and good chemical yields (Table 5).

Table 5 Synthesis of pyran-like tacrine analogues by AlCl₃

Entry	R	Product	Yield ^a (%)	M. P. (°C) Found	M. P. (°C) Reported
1	4-NO ₂ C ₆ H ₅	3f	94	321	323 [6]
2	4-OMeC ₆ H ₅	3h	88	290	291 [6]

3.4. Antibacterial test

Antibacterial investigation of selected (**1g**, **1l**, **1m**, **1o**, **1p** and **1s**) compounds using well diffusion technique was explored for *M. luteus* ATCC 4698 and *S. aureus* ATCC 6538 microorganisms. The obtained results are depicted in Table 6. Using the well diffusion method, antibacterial activities of the synthesized compounds indicated that the pyrans **1g** and **1s** at a concentration of 2000 µg/mL own a good antibacterial behavior for *M. luteus* with a zone of

inhibition of 15 and 16 mm, respectively. The pyran **1g** (2000 µg/mL) exhibited a good antibacterial activity for *M. luteus* and a moderate antibacterial activity towards *S. marcescens* ATCC 14756 as Gram-positive and Gram-negative bacteria, respectively. **1m** displayed a moderate antibacterial activity against both bacterial strains with zones of inhibition of 10 and 7 mm for *M. luteus* and *S. marcescens*, respectively.

TABLE 6 Antibacterial behavior of pyran and tacrine analogue derivatives assessed by well and disk diffusion approaches

Method	Compound (concentration ppm)	Microorganism			
		Gram-positive		Gram-negative	
		<i>M. luteus</i> ATCC 4698	<i>S. aureus</i> ATCC 6538	<i>S. marcescens</i> ATCC 14756	<i>E. coli</i> ATCC 25922
		Diameter of the zone of inhibition (mm)			
Well diffusion	1g (2000)	15	*	7	*
	1l (2000)	No effect	*	No effect	*
	1m (2000)	10	*	7	*
	1o (2000)	No effect	*	No effect	*
	1p (2000)	No effect	*	7	*
	1s (2000)	16	*	No effect	*
Disk diffusion	1f (50000)	*	11	No effect	No effect
	1h (50000)	*	10	No effect	No effect
	3f (50000)	*	13	12	No effect
	Gentamicin (10 µg/disk) [69]	*	20	*	19.6
	Ampicillin Sodium (10 µg/disk) [70]	*	16	*	10

*The antibacterial behavior was not investigated at this concentration for this microorganism.

Antibacterial activity study of the synthesized compounds by disk diffusion technique was examined for *S. marcescens*, *E. coli* ATCC 25922 and *S. aureus* bacteria. The obtained results showed that the pyrans **1f** and **1h** at a concentration of 50000 µg/mL had a moderate antibacterial action on *S. aureus* with zones of inhibition of 11 and 10 mm, respectively. Tacrine analogue **3f** (50000 µg/mL) displayed a moderate antibacterial activity against *S. aureus* with a zone of inhibition of 13 mm. It should be noted that a zone of inhibition of 12 mm was recorded for **3f** against *S. marcescens* microorganism at the same concentration.

The antibacterial activity of **1f** and **1h** (50000 ppm) towards *S. aureus* and some analogues (20000 ppm) reported in the literature [69] are presented in

Table 7. By comparing the obtained results of **Tables 6** and **7**, the antibacterial behavior of the tested compounds such as **1f** and **1h** in this work are similar to published work [69].

TABLE 7 Comparison of the antibacterial activity of 4*H*-pyrans derivatives by the disk diffusion approach

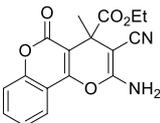
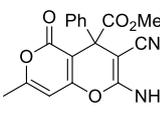
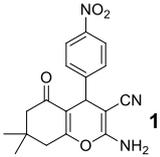
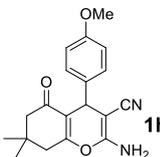
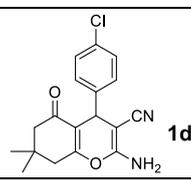
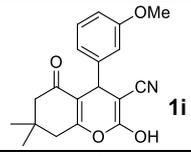
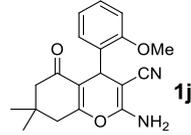
Compound	Concentration (ppm)	Microorganism	
		<i>S. aureus</i> ATCC 6538	<i>E. coli</i> PTCC 1330
Zone of inhibition (mm)			
	20000 [69]	No effect	No effect
	20000 [69]	13	8
	50000	11	No effect
	50000	10	No effect

TABLE 8 Evaluation of antibacterial properties by determination of MIC

Method	Compound	Microorganism	
		Gram-positive <i>M. Luteus</i> TCC 9341	Gram-negative <i>E. coli</i> ATCC 25922
		2500 µg/mL	2500 µg/mL
MIC		78.12 µg/mL	1250 µg/mL
		39.06 µg/mL	625 µg/mL
	Ampicillin	< 9.76 µg/mL	< 9.76 µg/mL

Furthermore, the minimum inhibitory concentration (MIC) value of the prepared products **1d**, **1i**, and **1j** was determined using the microtiter broth dilution technique. The antibacterial behavior of these products was evaluated for *M. Luteus* and *E. coli* bacteria. The MIC values of compounds **1d**, **1i** and **1j** for *M. Luteus* bacteria were 2500, 78.12 and 39.06 µg/mL, respectively, and the MIC value of ampicillin as the standard sample was < 9.76 µg/mL (**Table 8**). The compound **1j** with a MIC value of 39.06 µg/mL for *M. Luteus* bacterium exhibited the closest value to the ampicillin as reference and a MIC value of 625 µg/mL for *E. coli* bacterium [71].

4. CONCLUSION

The catalytic performance of rGO-DETA was explored for the preparation of 4*H*-pyran derivatives. The results revealed that rGO-DETA material as a basic catalyst was active for the preparation of 4*H*-pyran derivatives in high yields (87–97%) under mild reaction conditions. The heterogeneous basic catalyst rGO-DETA was recovered and reused for a minimum of 4 cycles without important diminution in its catalytic performance. Some of the prepared derivatives were examined for their antibacterial behavior towards Gram-positive and Gram-negative bacteria. The 4*H*-pyrans **1g** and **1s** at a concentration of 2000 µg/mL showed a respectable antibacterial behavior towards *M. luteus* with zones of inhibition of 15 and 16 mm, respectively. The 4*H*-pyran **1g** (2000 µg/mL) displayed a good antibacterial activity towards *M. luteus* and a modest antibacterial activity against *S. marcescens*. **1m** showed a moderate antibacterial activity for both bacterial *M. luteus* and *S. marcescens*. Pyran-like tacrine analogue **3f** (50000 µg/mL) featured antibacterial activity for *S. aureus* and *S. marcescens* with a zone of inhibition of 13 and 12 mm, respectively. **1j** compound showed a MIC value of 39.06 µg/mL for *M. Luteus*, which is the closest value to the ampicillin as reference.

SUPPLEMENTARY DATA

Supplementary data is accessible on the publisher's website along with the published article.

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DATA STATEMENT

The data that supports the findings of this study are accessible in the supplementary material of this paper.

AVAILABILITY

REFERENCES

- [1] V. Tumiatti, A. Minarini, M. Bolognesi, A. Milelli, M. Rosini, C. Melchiorre, *Curr. Med. Chem.* **2010**, *17*, 1825.
- [2] M. L. Crismon, *Ann. Pharmacother.* **1994**, *28*, 744.
- [3] G. Fancellu, K. Chand, D. Tomás, E. Orlandini, L. Piemontese, D. F. Silva, S.M. Cardoso, S. Chaves, M. A. Santos, *J. Enzyme Inhib. Med. Chem.* **2020**, *35*, 211.
- [4] M. A. Khalilzadeh, A. Hosseini, M. Tajbakhsh, *J. Heterocycl. Chem.* **2007**, *44*, 535.
- [5] J. Li, L. Zhang, D. Shi, Q. Li, D. Wang, C. Wang, Q. Zhang, L. Zhang, Y. Fan, *Synlett* **2008**, *2008*, 233.
- [6] J. Marco-Contelles, R. León, C. de los Ríos, A. G. García, M. G. López, M. Villarroya, *Bioorg. Med. Chem.* **2006**, *14*, 8176.
- [7] M. T. McKenna, G. R. Proctor, L. C. Young, A. L. Harvey, *J. Med. Chem.* **1997**, *40*, 3516.
- [8] N. S. Girgis, E. B. Pedersen, *Synthesis* **1985**, 547.
- [9] T. J. Eckroat, D. L. Manross, S. C. Cowan, *Int. J. Mol. Sci.* **2020**, *21*, 5965.
- [10] C. Derabli, I. Boualia, A. B. Abdelwahab, R. Boulcina, C. Bensouici, G. Kirsch, A. Debache, *Bioorg. Med. Chem. Lett.* **2018**, *28*, 2481.
- [11] M. Mahdavi, M. Saeedi, L. Gholamnia, S. A. B. Jeddi, R. Sabourian, A. Shafiee, A. Foroumadi, T. Akbarzadeh, *J. Heterocycl. Chem.* **2017**, *54*, 384.
- [12] M. Eghtedari, Y. Sarrafi, H. Nadri, M. Mahdavi, A. Moradi, F. H. Moghadam, S. Emami, L. Firoozpour, A. Asadipour, O. Sabzevari, *Eur. J. Med. Chem.* **2017**, *128*, 237.
- [13] T. Akbarzadeh, A. Rafinejad, J. M. Mollaghasem, M. Safavi, A. Fallah-Tafti, M. Pordeli, S. K. Ardestani, A. Shafiee, A. Foroumadi, *Arch. Pharm.* **2012**, *345*, 386.
- [14] N. R. Kamdar, D. D. Haveliwala, P. T. Mistry, S. K. Patel, *Med. Chem. Res.* **2011**, *20*, 854.
- [15] H. G. Kathrotiya, M. P. Patel, *Med. Chem. Res.* **2012**, *21*, 3406.
- [16] M. M. Khafagy, A. H. A. El-Wahab, F. A. Eid, A. M. El-Agrody, *Il Farmaco* **2002**, *57*, 715.
- [17] Z. Saffari, H. Aryapour, A. Akbarzadeh, A. Foroumadi, N. Jafari, M. F. Zarabi, A. Farhangi, *Tumor Biol.* **2014**, *35*, 5845.
- [18] S. Santhisudha, T. Sreekanth, S. Murali, B. V. Kumar, M. A. Devi, C. S. Reddy, *Cardiovasc. Hematol. Agents Med. Chem.* **2016**, *14*, 167.
- [19] L. Abrunhosa, M. Costa, F. Areias, A. Venâncio, F. Proença, *J. Ind. Microbiol. Biotechnol.* **2007**, *34*, 787.
- [20] A. Mazaheri, M. Bostanian, *Res. Chem. Intermed.* **2020**, *46*, 2327.
- [21] M. I. Fernández-Bachiller, C. Pérez, L. Monjas, J. Rademann, M. I. Rodríguez-Franco, *J. Med. Chem.* **2012**, *55*, 1303.
- [22] R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown, T. A. Keating, *Acc. Chem. Res.* **1996**, *29*, 123.
- [23] E. Babaei, B. B. F. Mirjalili, *Inorg. Nano-Met. Chem.* **2020**, *50*, 16.
- [24] A. V. Chate, A. S. Kulkarni, C. K. Jadhav, A. S. Nipte, G. M. Bondle, *J. Heterocycl. Chem.* **2020**, *57*, 2184.
- [25] S. Saini, N. Kaur, N. Singh, *Green Chem.* **2020**, *22*, 956.
- [26] S. K. Kundu, J. Mondal, A. Bhaumik, *Dalton Trans.* **2013**, *42*, 10515.
- [27] S. Rostamnia, A. Hassankhani, H. G. Hossieni, B. Gholipour, H. Xin, *J. Mol. Catal. A* **2014**, *395*, 463.
- [28] S. Sadjadi, M. M. Heravi, V. Zadsirjan, M. Ebrahimzadeh, *Res. Chem. Intermed.* **2017**, *43*, 5467.
- [29] A. Martínez-Grau, J. Marco, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3165.
- [30] C. de los Ríos, J. Marco-Contelles, *Eur. J. Med. Chem.* **2019**, *166*, 381.
- [31] D. Yang, W. Mo, S. Zhang, B. Li, D. Hu, S. Chen, *S, Dalton Trans.* **2020**, *49*, 1582.
- [32] A. S. Siddiqui, M. A. Ahmad, M. H. Nawaz, A. Hayat, M. Nasir, *Mikrochim. Acta* **2020**, *187*, 47.
- [33] X. Yang, D. Li, J. Zhai, F. Wang, B. Xue, J. Zhu, Y. Li, *Colloids Surf. A* **2020**, *585*, 124138.
- [34] J. Ji, G. Zhang, H. Chen, S. Wang, G. Zhang, F. Zhang, X. Fan, *Chem. Sci.* **2011**, *2*, 484.
- [35] S. Behraves, R. Fareghi-Alamdari, R. Badri, *Polycyclic Arom. Compd.* **2018**, *38*, 51.
- [36] M. Mirza-Aghayan, M. Molae Tavana, R. Boukherroub, *Ultrason. Sonochem.* **2016**, *29*, 371.

- [37] Y. Zhang, C. Chen, G. Wu, N. Guan, L. Li, J. Zhang, *Chem. Commun.* **2014**, 50, 4305.
- [38] L. S. K. Achary, A. Kumar, L. Rout, S. V. S. Kunapuli, R. S. Dhaka, P. Dash, *Chem. Eng. J.* **2018**, 331, 300.
- [39] M. Zakeri, E. Abouzari-lotf, M. Miyake, S. Mehdipour-Ataei, K. Shameli, *Arab. J. Chem.* **2019**, 12, 188.
- [40] M. Bayzidi, B. Zeynizadeh, *RSC Adv.* **2022**, 12, 15020.
- [41] M. Esmati, B. Zeynizadeh, *Appl. Organomet. Chem.* **2022**, 36, e6496.
- [42] M. Mirza-Aghayan, E. Kashef-Azar, R. Boukherroub, *Tetrahedron Lett.* **2012**, 53, 4962.
- [43] M. Mirza-Aghayan, M. Mohammadi, A. Addad, R. Boukherroub, *Appl. Organomet. Chem.* **2020**, 34, e5524.
- [44] M. Mirza-Aghayan, M. Molaee Tavana, R. Boukherroub, *Tetrahedron Lett.* **2014**, 55, 5471.
- [45] M. Mirza-Aghayan, M. Kalantari, R. Boukherroub, *Appl. Organomet. Chem.* **2019**, 33, e4837.
- [46] M. Mirza-Aghayan, M. Mohammadi, Z. Ahmadi, R. Boukherroub, *Catal. Lett.* **2020**, 150, 2959.
- [47] M. Mirza-Aghayan, M. Molaee Tavana, *J. Sulphur Chem.* **2015**, 36, 30.
- [48] M. Mirza-Aghayan, F. Asadi, R. Boukherroub, *Monatsh. Chem.* **2014**, 145, 1919.
- [49] M. Mirza-Aghayan, A. Moradi, M. Bolourtchian, R. Boukherroub, *Synth. Commun.* **2009**, 40, 8.
- [50] M. Mirza-Aghayan, S. Nazmdeh, R. Boukherroub, M. Rahimifard, A. A. Tarlani, M. Abolghasemi-Malakshah, *Synth. Commun.* **2013**, 43, 1499.
- [51] M. Mirza-Aghayan, A. Moradi, M. Bolourtchian, *J. Iran. Chem. Soc.* **2010**, 7, 269.
- [52] X. Zhou, X. Huang, X. Qi, S. Wu, C. Xue, F. Y. C. Boey, Q. Yan, P. Chen, H. Zhang, *J. Phys. Chem. C* **2009**, 113, 10842.
- [53] B. Xue, J. Zhu, N. Liu, Y. Li, *Catal. Commun.* **2015**, 64, 105.
- [54] R. Khatun, S. Biswas, S. Islam, I. H. Biswas, S. Riyajuddin, K. Ghosh, S. M. Islam, *ChemCatChem* **2019**, 11, 1303.
- [55] H. Naeimi, M. Farahnak Zarabi, *Appl. Organomet. Chem.* **2018**, 32, e4225.
- [56] M. Norouzi, D. Elhamifar, S. Abaezadeh, *Appl. Surf. Sci.* **2020**, 2, 100039.
- [57] J. Huo, X. Liu, X. Li, L. Qin, S.-Z. Kang, *Int. J. Hydrogen Energy* **2017**, 42, 15540.
- [58] T. Jin, C. D. Easton, H. Yin, M. de Vries, X. Hao, *Sci. Technol. Adv. Mater.* **2018**, 19, 381.
- [59] A. Maleki, Z. Varzi, F. Hassanzadeh-Afruzi, *Polyhedron* **2019**, 171, 193.
- [60] M. Mashhadinezhad, M. Mamaghani, M. Rassa, F. Shirini, *ChemistrySelect* **2019**, 4, 4920.
- [61] R. Y. Guo, Z. M. An, L. P. Mo, R. Z. Wang, H. X. Liu, S. X. Wang, Z. H. Zhang, *ACS Comb. Sci.* **2013**, 15, 557.
- [62] M. A. Zolfigol, A. Khazaei, A. R. Moosavi-Zare, J. Afsar, V. Khakyzadeh, O. Khaledian, *J. Chin. Chem. Soc.* **2015**, 62, 398.
- [63] S. Gao, C. H. Tsai, C. Tseng, C. F. Yao, *Tetrahedron* **2008**, 64, 9143.
- [64] P. K. Paliwal, S. R. Jetti, S. Jain, *Med. Chem. Res.* **2013**, 22, 2984.
- [65] H. Ahankar, A. Ramazani, K. Slepokura, T. Lis, S. W. Joo, *Turk. J. Chem.* **2018**, 42, 719.
- [66] B. Paplall, S. Nagaraju, P. Veerabhadraiah, K. Sujatha, S. Kanvah, B. V. Kumar, D. Kashinath, *RSC Adv.* **2014**, 4, 54168.
- [67] N. Saravana Ganesan, P. Suresh, *Res. Chem. Intermed.* **2021**, 47, 1197.
- [68] A. Yang, J. Li, C. Zhang, W. Zhang, N. Ma, *Appl. Surf. Sci.* **2015**, 346, 443.
- [69] M. Aghajani, S. Asghari, G. F. Pasha, M. Mohseni, *Res. Chem. Intermed.* **2020**, 46, 1841.
- [70] M. E. Azab, M. M. Youssef, E. A. El-Bordany, *Molecules* **2013**, 18, 832.
- [71] C. V. Subbareddy, S. Sumathi, *New J. Chem.* **2017**, 41, 9388.