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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis, antibacterial evaluation and molecular docking studies of novel pyrazole/1,2,4-oxadiazole conjugate ester derivatives

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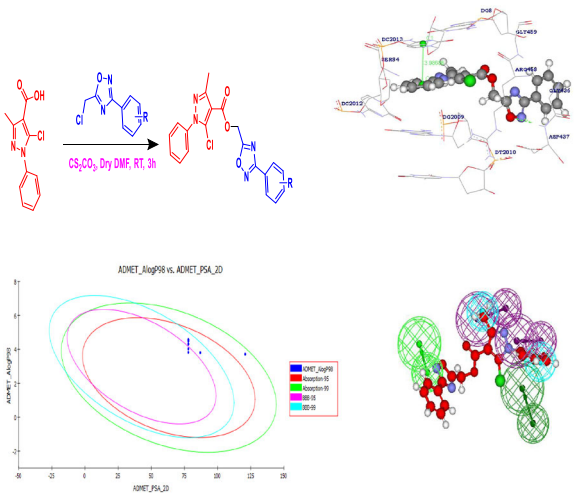
Abstract

The development of new antimicrobial drugs is most needed due to rapid growth in global antimicrobial resistance. Thus, in this context, a series of novel pyrazole/1,2,4-oxadiazole conjugate ester derivatives (**7a–j**) was synthesized. All the derivatives were evaluated for their in vitro antibacterial activity against Gram-positive (*Enterococcus, Bacillus subtilis and Staphylococcus aureus*) and Gram-negative (*Salmonella, Klebsiella and Escherichia coli*) bacteria and their minimum inhibitory concentration (MIC) was determined. Some of the derivatives have shown significant biological activity with a potency comparable to standard drug *Streptomycin*. Moreover, molecular docking studies, pharmacokinetic properties ADMET (absorption, distribution, metabolic, excretion and toxicity), molecular properties and TOPKAT analysis were predicted through in silico method. In vitro and in silico studies revealed that among all the compounds, compound **(7a)** has shown a significant biological activity with a good LibDock score 162.751 kcal/mol. All the synthesized derivatives were confirmed by FTIR, ^{1}H NMR, ^{13}C NMR and mass spectrometry.

Graphical Abstract



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Keywords ADMET · Antibacterial activity · Molecular docking · 1,2,4-oxadiazole · Pyrazole

Introduction

Bacteria and other pathogenic microbes develop resistance to antibiotics treatments through diverse adaptations and mechanisms [1]. Anti-microbial resistance (AMR), acquiring resistance to the existing antibiotics and therapies by pathogenic bacteria and other microbes, is the global health concern [2, 3]. Drug-resistant microbial infections are hard to cure and affect the global economy, especially the low-income and developing countries. Growing AMR among diverse pathogenic bacteria, microbes and the non-availability of potent antimicrobial agents in general and antibacterial agents in particular has drawn the attention of the global science community and the pharma industry [4, 5]. In recent years, significant developments were witnessed in terms of understanding the probable reasons and mechanism of growing AMR, prevention and treatment of drug-resistant infections. Significant progress was made in combating AMR to develop potent molecules/antibiotics mostly through novel heterocyclic compounds [5–11].

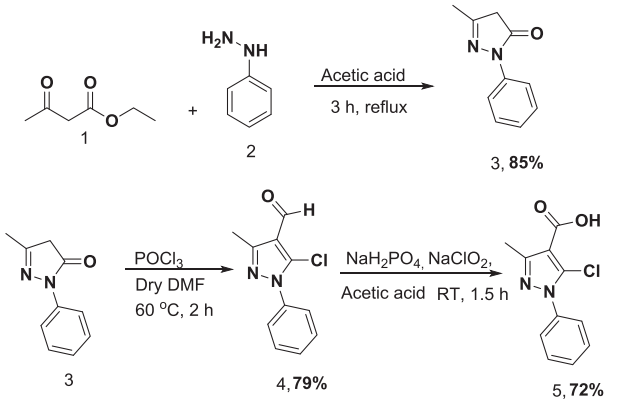
Heterocyclic compounds are a rich source of active functional molecules with diverse biological functions ranging from oxygen carriers (haemoglobin), the storehouse of energy (adenosine triphosphate), genetic materials (DNA), active components of protein synthesis machinery (RNA) neurotransmitters and natural antimicrobial agents (diketopiperazines) [12]. Owing to the various biological activities, heterocyclic compounds with varying functional moieties have been studied for their antibacterial properties. Molecules containing nitrogen-rich five-membered heterocyclic structures, pyrazoles and 1,2,4-oxadiazoles are the indispensable stock of biologically active compounds for a myriad of applications [13–20].

Pyrazoles are five-membered heterocyclic molecules with two nitrogens in the structure and are chemically 1,2-diazoles. Pyrazole-moiety-containing compounds have successfully been developed and studied for their anti-inflammatory, anti-convulsant, anti-cancer, ACE inhibitor, anti-viral and anti-microbial studies [21–26]. Apart from the synthetically made pyrazole-containing biologically active compounds, a handful of natural products showcase the presence of pyrazole nucleus with diverse properties ranging from anti-diabetic to anti-cancer activities [27]. Pyrazole-3 (5)-carboxylic acid, Fluviols A-E, Pyrazofurin and Formycin are a few to list medicinally active natural compounds pyrazole-moiety embedded into the integral structure. Aminophenazone, phenazone, sulfinpyrazone and phenylbutazone are examples of drugs that contain embedded pyrazole moiety in their structure. Similarly, oxadiazoles are five-membered heterocyclic molecules containing oxygen and two nitrogen atoms. Oxadiazole scaffolds are wide range natural products with diverse therapeutic properties. Oxadiazole-containing compounds i.e., 1,2,4-oxadiazole derivatives are well known for their anti-inflammatory, analgesic, agonists fatty acid receptors, anti-tumour and antimicrobial properties [28, 29].

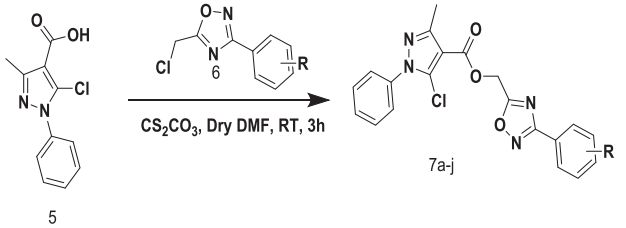
It is evident from the presence in natural products and the recent findings that pyrazole and oxadiazole derivatives are medicinally important moieties with diverse biological activities, especially, antibacterial properties [30–34]. We anticipated that the amalgamation of the two active moieties i.e., pyrazoles and oxadiazoles with appropriate chemistry would result the novel and potent class of antibacterial compounds. However, there are barely any systematic studies reporting development and antibacterial activities of such substituted pyrazole/1,2,4-oxadiazole conjugate ester compounds. Recently, 1,2,4-oxadiazole/2-imidazoline hybrids were successfully developed to treat infectious diseases and certain cancers [35]. In this endeavour, we have prepared a library of rationally designed and selectively substituted pyrazole/1,2,4-oxadiazole conjugate ester derivatives (**7a–j**). The synthesized compounds were screened for superior antibacterial activity against three Gram-positive and three Gram-negative bacteria. Molecular docking studies, ADMET, TOPKAT study and molecular properties were also performed to study the interaction modes of synthesized compounds with the active site of the protein. The results of in vitro and in silico studies showed that substituted pyrazole/1,2,4-oxadiazole conjugate ester derivatives may serve as new antibacterial agents.

Results and discussion

The molecules under study i.e., substituted pyrazole/1,2,4-oxadiazole conjugate ester derivatives (**7a–j**) were synthesized (Schemes 1 and 2) with moderate to good yields (Table 1). Pyrazalone (3-methyl-1-phenyl-1H-pyrazol-5 (4H)-one (**3**)) was obtained by refluxing ethyl acetoacetate with phenyl hydrazine (**2**) in acetic acid. Pyrazole carboxylic acid intermediate (5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic acid (**5**)) was then prepared from (**3**) in successive reactions with $POCl_3$ in dry DMF followed by the oxidation of aldehyde moiety to acid in acetic acid (Scheme 1) [36]. The chloromethyl oxadiazole derivatives (**6**) were synthesized using previously reported method [37–42]. The final compounds under study i.e., pyrazole/



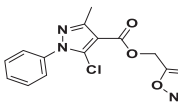
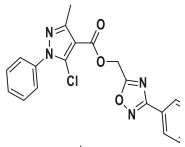
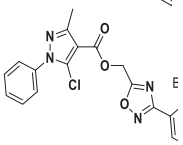
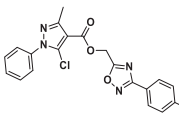
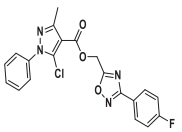
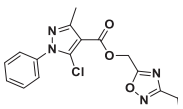
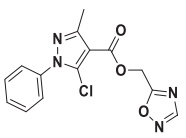
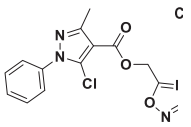
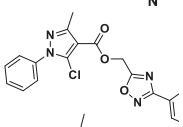
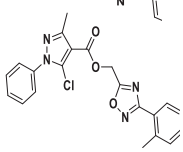
Scheme 1 Synthesis of pyrazole carboxylic acid intermediate **5** (5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic acid)



Scheme 2 Preparation of pyrazole–oxadiazole conjugate ester derivatives (**7a–j**) through esterification of **5** (5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic acid) with chloromethyl oxadiazoles (5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole) derivatives

1,2,4-oxadiazole conjugate ester derivatives (**7a–j**) were obtained by Cs_2CO_3-mediated esterification of (**5**) with corresponding chloromethyl oxadiazoles (**6**) under dry conditions in moderate to good yields (Scheme 2 and Table 1) [43–47]. Thus, obtained target compounds were purified using standard chromatography techniques and characterized by infra-red, NMR and mass spectroscopic data. Pyrazole and oxadiazole conjugation were realized with a biocompatible and biodegradable ester linkage (Scheme 2). The assignment of antibacterial properties was achieved using the zone of inhibition testing and MIC method. The zone of inhibition testing was judiciously chosen owing to the advantages the technique offers for the antibacterial screening of the wide range of candidate molecules. The quick turnaround time, economic experimental setup, applicability to diverse chemical and natural product screening are the advantages of the zone of inhibition technique. All the synthesized pyrazole–oxadiazole conjugate ester derivatives (**7a–j**) were screened for their in vitro antibacterial activity against three Gram-positive bacteria (*Enterococcus, Bacillus subtilis and Staphylococcus aureus*) and three Gram-negative bacteria (*Salmonella, Klebsiella and Escherichia coli*). The anticipated antibacterial properties were evaluated against a standard antibacterial compound by using the zone of inhibition and

Table 1 Synthesis of pyrozole/1,2,4-oxadiazole conjugate ester derivatives (**7a–j**)

Compound number	Structure	Yield (%)[a]
7a		78%
7b		90%
7c		83%
7d		82%
7e		85%
7f		74%
7g		79%
7h		82%
7i		80%
7j		81%

[a]Yield calculated after purification

MIC method. The average zone of inhibition with the standard at 10-µg/ml concentration and minimum inhibitory concentration (MIC) with the standard at 1 mg/ml against each bacterium were studied and measured for all the compounds (**7a–j**) and the obtained results are summarized in Tables 2 and 3.

The unsubstituted derivative (**7a**) demonstrated antibacterial activity against both Gram-positive ((*Enterococcus*

Table 2 Antibacterial activity (zone of inhibition) of pyrozole/1,2,4-oxadiazole conjugate ester derivatives (**7a–j**) (µg/ml concentration)

Compound	Zone of inhibition (mm)					
	Gram-positive			Gram-negative		
	Enterococcus	*Bacillus subtilis*	*S. aureus*	*Salmonella*	*Klebsiella*	*E. coli*
7a	32	21	27	-	27	26
7b	32	30	26	-	28	29
7c	-	-	-	-	-	9
7d	33	25	26	-	28	30
7e	30	29	29	-	22	30
7f	-	-	-	-	-	-
7g	33	22	29	-	27	24
7h	35	25	28	-	29	25
7i	-	-	-	-	-	-
7j	-	-	-	-	-	21
Standard (Streptomycin)	37	31	32	-	30	35

- denotes no activity

Table 3 Minimum inhibitory concentration (MIC) data for antibacterial activity of pyrozole/1,2,4-oxadiazole conjugate ester derivatives (**7a–j**) obtained by micro dilution method

Compound	Zone of inhibition in MIC in µg/ml					
	Gram-positive			Gram-negative		
	Enterococcus	*Bacillus subtilis*	*S. aureus*	*Salmonella*	*Klebsiella*	*E. coli*
7a	32	21	27	-	27	26
7b	32	30	26	-	28	29
7c	-	-	-	-	-	13
7d	33	25	26	-	28	30
7e	30	22	29	-	29	30
7f	-	-	-	-	-	-
7g	33	22	29	-	27	24
7h	35	25	28	-	29	25
7i	-	-	-	-	-	-
7j	-	-	-	-	-	-
Standard (Streptomycin)	37	31	32	36	30	35

- denotes no activity

(32 mm), *Bacillus subtilis* (21 mm) and *Staphylococcus aureus* (27 mm)) and Gram-negative (*Klebsiella* (27 mm), and *Escherichia coli* (26 mm)) bacteria as demonstrated by the presence of a zone of inhibition (Table 2). Similar antibacterial activity that was observed with the 4-bromo (**7b**), 4-methoxy (**7d**), 4-fluoro (**7e**), 2-chloro (**7g**) and 3-chloro (**7h**) on the oxadiazole phenyl ring of the pyrazole/1,2,4-oxadiazole conjugates was observed (Table 2). Contrastingly, antibacterial screening of compounds with 2-bromo (**7c**), 3-nitro (**7f**), p-tolyl (**7i**) and o-tolyl (**7j**) substituted phenyl moiety on the oxadiazole indicated that the compounds are not active against Gram-positive and Gram-negative bacteria. Though, o-tolyl (**7j**) substituted phenyl moiety on the oxadiazole demonstrated relatively good activity against Gram-negative E. coli bacteria (Table 2). The graphical representation of antibacterial activity of the synthesized compounds as well as standard drug Streptomycin has shown in Figs. 1 and 2. To further evaluate antibacterial potential, we determined the MIC for the synthesized compounds. The results (Table 3) show that the tested compounds (**7a, 7b, 7d, 7e, 7g, 7h**) possess significant antibacterial activity compared to the standard drug. The graphical representation of antibacterial activity of the synthesized compounds as well as standard drug Streptomycin has shown in Figs. 3 and 4. Apparently, observed antibacterial properties of pyrazole/1,2,4-oxadiazole conjugate molecules are specific to the substitution the oxadiazole moiety. Overall, antibacterial screening of pyrazole/1,2,4-oxadiazole conjugate ester molecules demonstrated the anticipated synergic effect of individual pyrazole and oxadiazole moieties. Further, the observed substitution-specific differential antibacterial

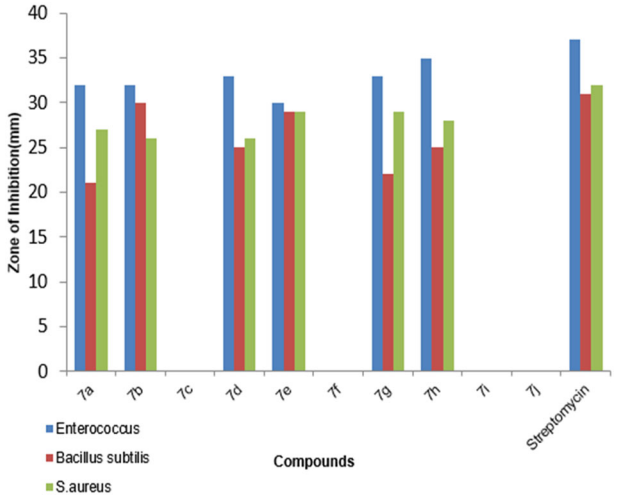


Fig. 1 Zone of inhibition in mm of synthesized pyrazole/1,2,4-oxadiazole conjugate ester derivatives and standard drug (Streptomycin) against Gram-positive bacterial strains

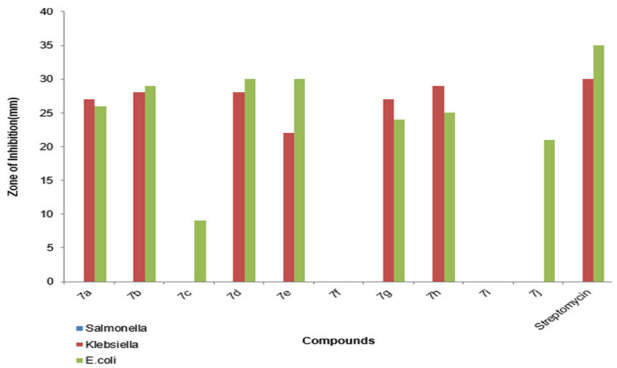


Fig. 2 Zone of inhibition in mm of synthesized pyrazole/1,2,4-oxadiazole conjugate ester derivatives and standard drug (Streptomycin) against Gram-negative bacterial strains

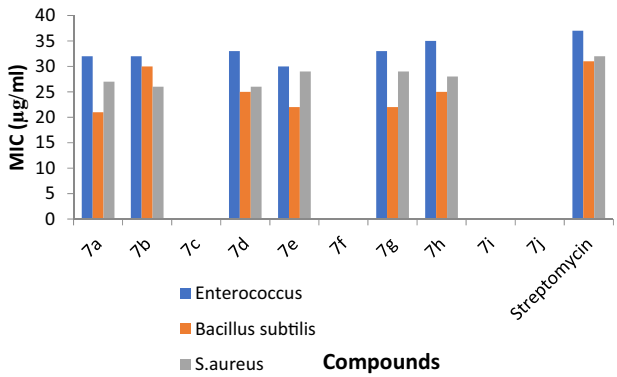


Fig. 3 Graphical representation of MIC values of synthesized pyrazole/1,2,4-oxadiazole conjugate ester derivatives and standard drug (Streptomycin) against Gram-positive bacterial strains

activity strongly supports the need for rational designing of molecules for countering AMR and validates our hypothesis.

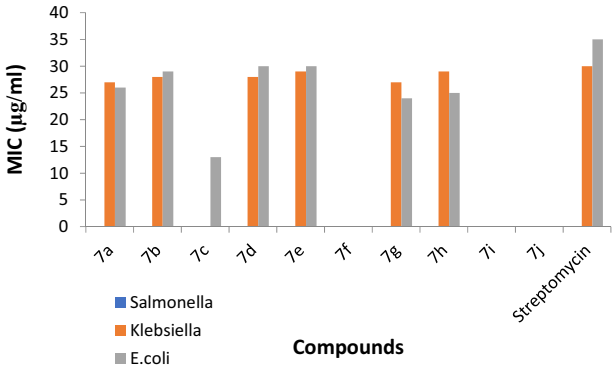


Fig. 4 Graphical representation of MIC values of synthesized pyrazole/1,2,4-oxadiazole conjugate ester derivatives and standard drug (Streptomycin) against Gram-negative bacterial strains

Molecular docking studies

Molecular docking studies were carried out to understand the ligand orientation and the inhibitory ability toward human DNA gyrase by using LibDock module in Accelrys Discovery studio 2.1. The 3D structure of DNA gyrase was retrieved from protein Data Bank (PDBID:5CDP) and it is imported into Accelrys Discovery studio 2.1. Docking was carried out for the synthesized derivatives and later with known inhibitor drug streptomycin. The best ligand conformation was investigated based on high LibDock score, calculated binding energy and higher interaction amino acid residues. The docking information of all synthesized compounds is given in Table 4 and from the docking analysis, the compounds (**7a**) that is active in vitro has shown a good docking score 162.751 kcal/mol as compared to Streptomycin 187.377 kcal/mol. The docking results indicate that the compound (**7a**) fitted good in active site pocket with the good docking score. The best conformation with H-bond interactions for the compounds (**7a**) is shown in Fig. 5. In this study, for the docking validation, co-crystallised ligand etoposide is redocked and evaluated for their effectiveness in binding.

Molecular properties

The drug-likeness of the synthesized compounds was predicted by using Lipinski's rule of 5 which means mol.wt ≤500, logp ≤5, H-bond donors ≤5 and H-bond acceptor ≤10. This rule explains about molecular properties important for pharmacokinetics in the human body. The molecular properties of all compounds are tabulated in Table 5. All the synthesized derivatives obeyed the Lipinski's rule.

ADMET studies

The pharmacokinetic studies were examined by ADMET analysis by using Accelrys Discovery studio 2.1. The

Table 4 Docking conformation of synthesized compounds (**7a–j**)

Name	LibDock score	Calculate BE (kcal/mol)	Interacting amino acids	Interacting atoms	H-bond count	H-distance
7a	162.751	−34.44779	Asp437,Arg458 Gly459,Gly436 Ser84,DC2013 DG2012,DT2010 DG8	B:ASP437:HN - 7a.mol:O18 B:ASP437:HN - 7a.mol:N19	2	2.257000 2.282000
7b	151.012	−31.4895	Asp437,Arg458 Gly459,Gly436 Ser84,DC2013 DG2012,DT2010 DG8	B:ASP437:HN - 7b.mol:N19 7b.mol:H35 - H:DC2012:C2	1	2.151000 2.208000
7c	151.558	−27.69448	Asp437,Arg458 Gly459,Gly436 Ser84,DC2013 DG2012,DT2010 DG8	B:ASP437:HN - 7c.mol:N2 7c.mol:C1 - B:ASP437:HN 7c.mol:H30 - B:ASP437:HN 7c.mol:H30 - B:ASP437:CB	1	2.393000 2.216000 1.725000 2.138000
7d	153.52	−49.22423	Asp437,Arg458 Gly459,Gly436 Ser84,DC2013 DG2012,DT2010 DG8	G:DG2009:H21 - 7d.mol:Cl14 B:ASP437:HN - 7d.mol:O18 7d.mol:H45 - E:DG8:HO3′ 7d.mol:H39 - B:ASP437:HN	1	2.145000 2.251000 1.788000 1.748000
7e	163.475	−55.40352	Asp437,Arg458 Gly459,Gly436 Ser84,DC2013 DG2012,DT2010 DG8	B:ARG458:HH21 - 7e.mol:N19 B:ARG458:HH21 - 7e.mol:O18 G:DG2009:H21 - 7e.mol:O18 7e.mol:H30 - B:ASP437:OD2	3	2.128000 2.494000 2.423000 1.986000
7f	176.174	−35.35721	Asp437,Arg458 Gly459,Gly436 Ser84,DC2013 DG2012,DT2010 DG8	G:DG2009:H21 - 7f.mol:N19 B:ARG458:HH21 - 7f.mol:N19 B:ARG458:HH21 - 7f.mol:O18	3	2.480000 2.499000
7g	162.886	−59.43023	Asp437,Arg458 Gly459,Gly436 Ser84,DC2013 DG2012,DT2010 DG8	B:ARG458:HH21 - 7g.mol:N19 B:ARG458:HH21 - 7g.mol:O18		2.351000 2.291000
7h	165.810	−34.70153	Asp437,Arg458 Gly459,Gly436 Ser84,DC2013 DG2012,DT2010 DG8	B:ASP437:HN - 7h.mol:O18 B:ASP437:HN - 7h.mol:N19 E:DG8:O3′ - 7h.mol:H42 E:DG8:HO3′ - 7h.mol:H42	2	2.048000 2.198000 2.008000 1.714000
7i	159.036	−53.80486	Asp437,Arg458 Gly459,Gly436 Ser84,DC2013 DG2012,DT2010 DG8	G:DG2009:H21 - 7i.mol:O18 G:DG2009:H21 - 7i.mol:N19 B:ARG458:HH21 - 7i.mol:N19 7i.mol:H41 - H:DC2013:O4′	3	2.094000 1.460000 2.334000 1.938000
7j	150.071	−57.92473	Asp437,Arg458 Gly459,Gly436 Ser84,DC2013 DG2012,DT2010 DG8	B:ASP437:HN - 7J.mol:O18 7J.mol:H46 - E:DG8:HO3′ 7J.mol:H46 - E:DG8:O3′	1	2.117000 1.840000 1.873000
Streptomycin	187.377	−102.86163	Asp437,Arg458 Gly459,Gly436 Ser84,DC2013 DG2012,DT2010 DG8	Streptomycin:H42 - E:DG8:O3′ Streptomycin:H47 - E:DG8:N7 Streptomycin:H50 - E:DG8:OP1 Streptomycin:H52 - E:DG8:OP2 Streptomycin:H54 - B:GLU435:O	4	1.959000 2.388000 1.931000 2.444000 2.064000
Etoposide	209.244	−34.15795	DG8, Gly459 Arg458, Ser84 Gly436, DG2009 DT2010, DC2012 Asp437, DC2013	B:ASP437:HN - Etoposide: O13 Etoposide:H44 - E:DG8: O6 H: DC2013:H41 - Etoposide: O8 Etoposide:H45 - B:ASP437:HN Etoposide:H44 - H:DC2013:H41	3	1.995000 2.242000 2.157000 1.642000 1.409000

properties like absorption, blood–brain barrier, aqueous solubility, hepatotoxicity, hepatotoxicity probability, cytochrome P450 CYP2D6 and probability enzyme inhibition study are tabulated in Table 6. Figure 6 represents the plot of predicted values of drug absorption for the synthesized derivatives.

In silico toxicity assessment

The drug potential toxicity was predicted by TOPKAT by using Accelrys Discovery studio 2.1. The impact of drug consumption of synthesized compounds have been assessed by using TOPKAT, which determines the

toxicological final points using quantitative structure toxicity relationship. The TOPKAT data of all compounds are tabulated in Table 7.

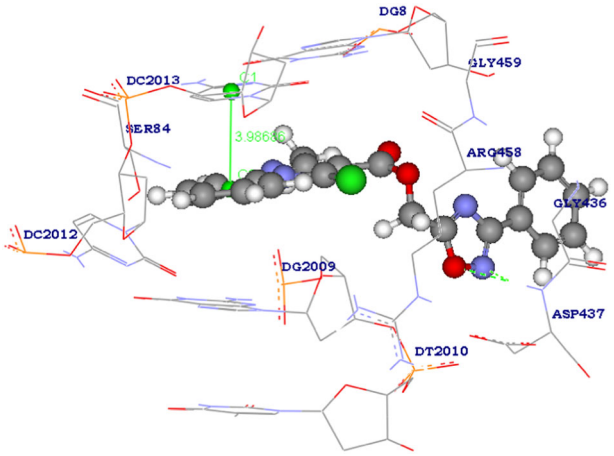


Fig. 5 Hydrogen bonding interactions of **7a** compound with active site residues of (5CDP), green dotted lines indicating hydrogen bonds and pink colour-bumps (colour figure online)

Structure-based pharmacophore modelling

Structure-based pharmacophore modelling is performed for better understanding of the key features that may be responsible for biological function of synthesized derivatives. Figure 7 represents the generated structure-based pharmacophore model with location constrains. Based on the fit value, the compound (**7a**) fitted well on the generated pharmacophore with a fit value 2.877, and Fig. 8 shows the mapping of the high active compound **7a** on the pharmacophore model.

Conclusion

In summary, we have synthesized a novel series of pyrazole/1,2,4-oxadiazole ester derivatives using simple reaction schemes with moderate to good yields. The antibacterial activity of the synthesized compounds was screened against both Gram-positive (*Enterococcus*, *Bacillus subtilis* and *Staphylococcus aureus)* and Gram-negative (*Salmonella*, *Klebsiella* and *Escherichia coli*) bacteria by employing zone of inhibition and MIC technique. The unsubstituted derivative (**7a**), 4-bromo (**7b**), 4-methoxy

Table 5 Molecular properties of synthesized derivatives (**7a–j**)

Name	ALogP	Molecular weight	Num_H_Acceptors	Num_H_Donors	Num_Rotatable bonds
7a	3.82	394.811	5	0	6
7b	4.568	473.707	5	0	6
7c	4.568	473.707	5	0	6
7d	3.804	424.837	6	0	7
7e	4.025	412.802	5	0	6
7f	3.714	439.809	7	0	7
7g	4.484	429.256	5	0	6
7h	4.484	429.256	5	0	6
7i	4.306	408.838	5	0	6
7j	4.306	408.838	5	0	6

Table 6 Absorption, distribution, metabolism, excretion and toxicity (ADMET) of synthesized derivatives (**7a–j**)

Name	BBB	Absorption	Solubility	Hepatotoxicity	Hepatotoxicity probability	CYP2D6	CYP2D6 probability
7a	2	0	2	1	0.86	0	0.465
7b	1	0	2	1	0.867	0	0.376
7c	1	0	2	1	0.86	0	0.485
7d	2	0	2	1	0.867	0	0.336
7e	2	0	2	1	0.867	0	0.386
7f	4	1	2	1	0.761	0	0.217
7g	2	0	2	1	0.874	0	0.415
7h	2	0	2	1	0.867	0	0.445
7i	2	0	2	1	0.867	0	0.297
7j	2	0	2	1	0.86	0	0.485

(**7d**), 4-fluoro (**7e**), 2-chloro (**7g**) and 3-chloro (**7h**) on the oxadiazole phenyl ring of the pyrazole/1,2,4-oxadiazole conjugates exhibited promising antibacterial activity against various microorganisms. Based on in vitro and in silico studies (docking, molecular properties, ADMET, fit value and structure-based pharmacophore modelling), it was confirmed that (**7a**) has shown a significant biological activity. Therefore, we strongly believe that the promising antibacterial properties exhibited by the rationally designed compounds will inspire the development of novel antibacterial compounds, aiding the combat against global AMR threat.

Experimental

All the reagents and commercial solvents were used without further purification. Melting points were determined by using a Buchi 535 melting point apparatus and were uncorrected. The visualization of compounds was performed with UV light at 254 and 365 nm, I_2 and heating plates dipping in 2% phosphomolybdic acid in 15% aq. H_2SO_4 solution. The reactions were monitored by thin layer chromatography carried on precoated silica gel 60F254 plates (Merck). The IR spectra were recorded on a Perkin-Elmer 683 or a FTIR 1310 spectro-photometers using KBr pellets. ^{13}C NMR spectra using $CDCl_3$ as internal standard were recorded on a Varian Unity 100 MHz. NMR spectra using TMS as an internal standard were recorded on a Varian Unity 500 MHz and BRUKER AMX 300 spectrometers. Mass spectra were performed on a VG Micromass 7070H and a Finnigan Mat 1020B mass spectrometer at 70 eV. NMR, FTIR and mass characterization spectra of all the final compounds are provided in the Supplementary Material.

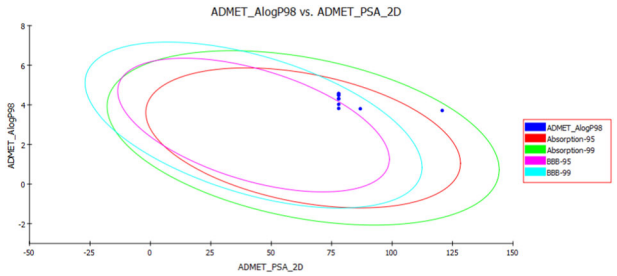


Fig. 6 Plot of polar surface area (PSA) versus LogP for the compounds showing the 95 and 99% confidence limit ellipses corresponding to the blood–brain barrier and intestinal absorption models

Antibacterial studies

Gram-positive (*Enterococcus*, *Bacillus subtilis* and *Staphylococcus aureus*) and Gram-negative (*Salmonella*, *Klebsiella* and *Escherichia coli*) were received from Lavin Laboratories, Hyderabad, India. Nutrient agar medium was used for the bacterial cultures under study and for screening the antibacterial properties of developed compounds. Bacterial stock cultures were prepared and maintained in nutrient agar media. Respective subcultures each bacterium under study were prepared and employed for the antibacterial screening.

Antibacterial activity of each compound prepared against the bacteria under study was evaluated using the zone of inhibition radius measurements. Pyrazole/1,2,4-oxadiazole conjugates were introduced to the agar plates with bacteria and incubated for a period of overnight 12 h and the resulting zone of inhibition is measured. Multiple copies of culture plates per each compound against each bacteria were used to rule out any experimental errors, and the average zone of inhibition values obtained at the end of the incubation period was compared against the standard.

Table 7 Predicted fit values of synthesized derivatives **(7a–j)**

Name	Acceptor 40	Acceptor 94	Donor 161	Donor 97	Fit Value	Hydro-phobe 28	Hydro-phobe 70	Pharm print
7a	1	0	0	0	2.877	1	1	'100011'
7b	1	0	0	0	2.566	1	1	'100011'
7c	1	0	0	0	2.686	1	1	'100011'
7d	1	0	0	0	2.546	1	1	'100011'
7e	1	0	0	0	2.554	1	1	'100011'
7f	0	1	0	0	2.872	1	1	'010011'
7g	0	1	0	0	2.668	1	1	'010011'
7h	1	0	0	0	2.577	1	1	'100011'
7i	1	0	0	0	2.581	1	1	'100011'
7j	1	0	0	0	2.617	1	1	'100011'
Streptomycin	0	1	1	1	3.692	0	1	'011101'
Etoposide	1	0	1	0	3	1	1	'100111'

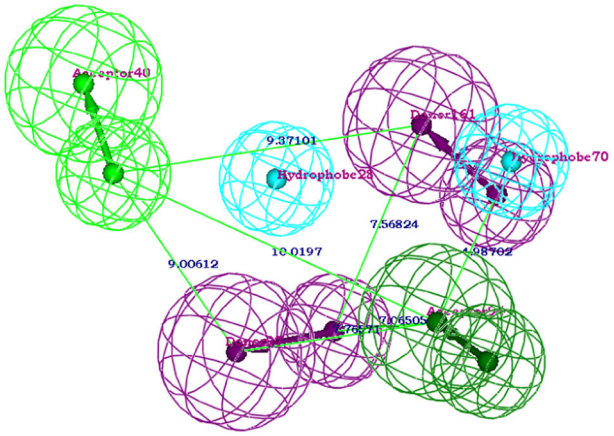


Fig. 7 Generated structure-based pharmacophore model with inter featured distances

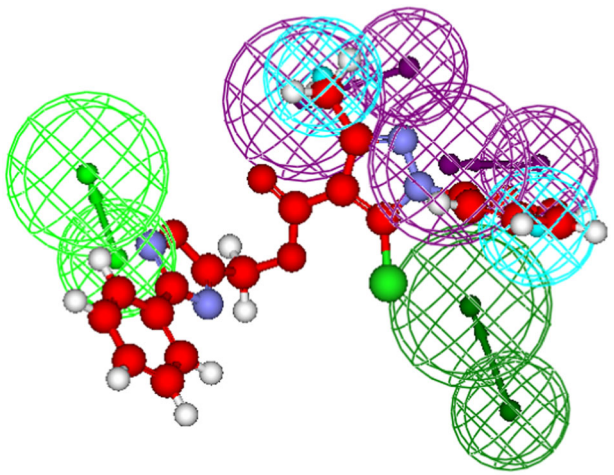


Fig. 8 Structure-based pharmacophore modelling of (**7a**) compound. Green colour represents the hydrogen-bond donor, magenta colour represents the hydrogen-bond acceptor and light blue represents the hydrophobic regions (colour figure online)

For MIC assays, a stock solution was prepared in DMSO for each test compound. The bacterial strains from stock cultures were reactivated by transferring into Mueller Hinton Broth. The tubes are incubated at 37 °C for 18 h. A final bacteria inoculum containing 10^5 colony-forming units was added to MHA medium and poured into petri dishes. Different test compounds at a concentration of 1 mg/ml were added to wells. Antibiotic such as streptomycin at a concentration of 1 mg/ml was used as positive reference to determine the sensitivity of tested microorganisms. The MIC number is a lowest concentration of the compound that inhibits that the bacterial growth was observed.

3-Methyl-1-phenyl-1H-pyrazol-5(4H)-one (3)

Ethyl acetoacetate (10.0 g, 77 mmol) was added to a solution of phenyl hydrazine (8.31 g, 77 mmol) in ethanol (25 mL), then the mixture was refluxed for 3 h, then the ethanol was removed under reduced pressure to give compound (**3**) as a yellow solid (11.34 g, yield 85%, m.p.: 123–124 °C).

5-Chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (4)

Phosphorus oxychloride (144 mmol) was added drop wise into *N*,*N*-dimethylformamide (172.4 mmol) at 0–5 °C. After the mixture was stirred for 30 min, 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**3**) (10.0 g, 57.5 mmol) was added portion wise. Then mixture was heated to 60 °C for another 2 h. The reaction mixture was poured slowly into crushed ice, and the precipitated solid was filtered and dried, to give (**4**) as a light-yellow solid (9.98 g, yield: 79%, m.p.: 135–138 °C).

5-Chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic acid (5)

A solution of $NaClO_2$ (3.15 g, 70 mmol) in 10-ml H_2O was added drop wise into a stirred solution of 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole- 4-carbaldehyde (2.4 g, 36 mmol) in AcOH 10 ml and NaH_2PO_4 (4.2 g, 70 mmol) in 10 ml of H_2O stirred at room temperature for 1.5 h, by monitoring TLC completion the reaction, diluted with water and extracted into ethyl acetate (3 × 10 ml), combined the organic layers dried over Na_2SO_4, concentrated under reduced pressure obtained crude product was purified by column chromatography to give **5** as a white solid (3.1 g, yield: 72%, m.p.: 233–234 °C).

General procedure for the preparation of (3-phenyl-1,2,4-oxadiazol-5-yl) methyl 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxylate derivatives (5a–m)

To a solution of 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic acid (5.7 mmol) and Cs_2CO_3 (7.5 mmol) in dry DMF (5 ml), a substituted 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole (7.50 mmol) was added. Then the mixture was stirred at room temperature for 3 h, the mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by chromatography on a silica gel column using petroleum ether and ethyl acetate as the effluent to give pure product (**7a–j**). All the compounds were synthesized according to this procedure (Scheme 2).

1. (3-phenyl-1,2,4-oxadiazol-5-yl) methyl 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxylate (**7a**): White solid (307 mg, 78%), m.p. 145–147 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.58 (s, 3H, CH_3), 5.60

(s, 2H, CH_2), 7.29 (d, $J = 8.4$ Hz, 1H, Ar-H), 7.46–7.55 (m, 6H, Ar-H), 7.79 (d, $J = 8.4$ Hz, 1H, Ar-H), 7.97–8.01 (m, 1H, Ar-H), 8.10 (t, $J = 1.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.34, 167.61, 161.16, 152.62, 143.10, 139.93, 137.27, 134.96, 132.35, 131.45, 130.20, 129.54, 129.16, 127.95, 127.58, 126.95, 125.56, 125.48, 108.70, 56.23, 14.85; IR (KBr): ν 2828, 2856, 1720, 1659, 1499, 1246, 1095, 760 cm^{-1}; ESI–MS: *m/z* 395 (M + H).

2. (3-(4-bromophenyl)-1,2,4-oxadiazol-5-yl) methyl 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxylate (**7b**): Brown solid (426 mg, 90%), m.p. 155–157 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.57 (s, 3H, CH_3), 5.60 (s, 2H, CH_2), 7.45–7.55 (m, 5H, Ar-H), 7.63 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.97 (d, $J = 8.5$ Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.69, 141.45, 140.01, 137.29, 134.74, 134.23,130.22, 129.10, 128.53, 128.27, 126.39, 124.42, 123.31, 119.04, 114.02, 62.40, 14.09; IR (KBr): ν 2929, 2851, 1595, 1490, 1389, 1252, 1173, 1119, 1025, 819, 752 cm^{-1}; ESI–MS: *m/z* 474.90 (M + H).
3. (3-(2-bromophenyl)-1,2,4-oxadiazol-5-yl) methyl 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxylate (**7c**): Brown solid (393 mg, 83%), m.p. 168–170 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.58 (s, 3H, CH_3), 5.59 (s, 2H, CH_2), 7.18 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.45–7.55 (m, 5H, Ar-H), 7.80 (d, $J = 7.91$ Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.34, 157.40, 157.10, 152.80, 145.33, 136.31, 135.41, 134.59, 129.90, 128.88, 128.77, 128.71, 121.75, 120.75, 118.74, 114.79, 114.05, 133.27, 61.98, 14.09; IR (KBr): ν 2982, 2927, 1716, 1497, 1317, 1242, 1154, 773 cm^{-1}; ESI–MS: *m/z* 474.90 (M + H).
4. (3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl) methyl 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxylate (**7d**): Pale yellow solid (347 mg, 82%), m.p. 140–142 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.56 (s, 3H, CH_3), 3.96 (s, 3H, OCH_3), 5.60 (s, 2H, CH_2), 7.40–7.60 (m, 5H, Ar-H), 7.62 (d, $J = 8.2$ Hz, 2H, Ar-H), 8. 36 (d, $J = 8.2$ Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.13, 167.76, 161.17, 152.42, 139.28, 132.35, 129.73, 129.76, 129.65, 129.16, 129.11, 129.02, 125.02, 116.25, 116.21, 116.03, 115.98, 56.78, 46.28, 14.84; IR (KBr): ν 2929, 2859, 1688, 1592, 1442, 1296, 1130,1023, 792, 743 cm^{-1}; ESI–MS: *m/z* 425 (M + H).
5. (3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl) methyl 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxylate (**7e**): Pale red solid (350 mg, 85%), m.p. 152–154 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.58 (s, 3H, CH_3), 5.59 (s, 2H, CH_2), 7.18–7.21 (m, 3H, Ar-H), 7.46–7.54 (m,6H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.44, 158.07, 139.65, 133.99, 133.50, 131.84, 131.62, 131.25, 129.76, 128.69, 128.09, 126.85, 126.17, 118.39, 113.68, 112.35, 58.18, 13.09; IR (KBr): ν 2931, 2860, 1718, 1600, 1548, 1446, 1251, 1168, 1090, 756 cm^{-1}; ESI–MS: *m/z* 413 (M + H).
6. (3-(3-nitrophenyl)-1,2,4-oxadiazol-5-yl) methyl 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxylate (**7f**): Yellow solid (324 mg, 74%), m.p. 170–172 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.49 (s, 3H, CH_3), 5.50 (s, 2H, CH_2), 7.45–7.59 (m, 7H, Ar-H), 8.0 (d, $J = 8.5$ Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.93, 148.76, 147.74, 138.17, 137.50, 137.20, 135.76, 135.40, 134.33, 133.66, 130.55, 129.63, 129.56, 129.43, 129.32, 128.06, 116.48, 125.59, 61.87, 14.10; IR (KBr): ν 2924, 2854, 1707, 1497, 1372, 1240, 1168, 1081, 770 cm^{-1}; ESI–MS: *m/z* 440 (M + H).
7. (3-(2-chlorophenyl)-1,2,4-oxadiazol-5-yl) methyl 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxylate (**7g**): White solid (338 mg, 79%), m.p. 168–170 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.58 (s, 3H, CH_3), 5.60 (s, 2H, CH_2), 7.42–7.57 (m, 7H, Ar-H), 8.08-8.13 (m, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.16, 163.70, 157.35, 157.16, 145.24, 136.27, 133.27, 128.79, 122.69, 122.60, 121.03, 118.68, 116.82, 116.58, 114.83, 114.11, 112.82, 57.03, 13.76; IR (KBr): ν 2930, 2857, 1724, 1605, 1404, 1359, 1256, 1117,1044, 755 cm^{-1}; ESI–MS: *m/z* 429 (M + H).
8. (3-(3-chlorophenyl)-1,2,4-oxadiazol-5-yl) methyl 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxylate (**7h**): White solid (351 mg, 82%), m.p. 167–169 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.57 (s, 3H, CH_3), 5.60 (s, 2H, CH_2), 7.47–7.54 (m, 7H, Ar-H), 8.07-8.14 (m,2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.27, 174.26, 162.70, 158.87, 154.39, 149.66, 136.46, 134.92, 131.25, 130.24, 129.22, 128.75, 121.11, 120.11, 115.32, 114.25, 112.93, 111.44, 56.34, 14.10; IR (KBr): ν 2929, 1724, 1640, 1450, 1278, 1127, 1021 cm^{-1}; ESI–MS: *m/z* 429 (M + H).
9. (3-(*p*-tolyl)-1,2,4-oxadiazol-5-yl) methyl 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxylate (**7i**): Pale red solid (326 mg, 80%), m.p. 155–157 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.42 (s, 3H, CH_3), 2.57 (s, 3H, CH_2), 5.59 (s, 2H, CH_2), 7.29 (d, $J = 7.94$ Hz, 2H, Ar-H); 7.47–7.56 (m, 5H, Ar-H), 7.98 (d, $J = 8.19$ Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.30, 157.40, 157.12, 144.34, 136.27, 133.43, 130.55, 129.39, 128.85, 128.75, 128.53, 128.26, 124.67, 118.71, 114.84, 114.08, 61.90, 50.65, 14.17; IR (KBr): ν 2929, 2860, 1747, 1600, 1519, 1338, 1258, 1173, 1027, 752 cm^{-1}; ESI–MS: *m/z* 409 (M + H).
10. (3-(*o*-tolyl)-1,2,4-oxadiazol-5-yl) methyl 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carboxylate (**7j**): Pale

red solid (330 mg, 81%), m.p. 169–171 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.40 (s, 3H, CH_3), 2.57 (s, 3H, CH_2), 5.60 (s, 2H, CH_2), 7.47–7.57 (m, 3H, Ar-H), 7.92–8.04 (m, 6H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.74, 168.51, 162.44, 161.12, 152.55, 141.74, 137.25, 132.26, 129.52, 129.09, 128.98, 127.34, 125.43, 123.36, 108.74, 56.29, 21.50, 14.80; IR (KBr): ν 2925, 2847, 1680, 1595, 1551, 1483, 1252, 1177, 1033, 745 cm^{-1}; ESI–MS: *m/z* 409 (M + H).

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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