Appl Microbiol Biotechnol (2017) 101:253–286
DOI 10.1007/s00253-016-7872-2

APPLIED GENETICS AND MOLECULAR BIOTECHNOLOGY

Identification and characterization of antibacterial compound(s) of cockroaches (*Periplaneta americana*)

Salwa Mansur Ali[1] · Ruqaiyyah Siddiqui[1] · Seng-Kai Ong[1] · Muhammad Raza Shah[2] · Ayaz Anwar[2] · Peter J. Heard[1] · Naveed Ahmed Khan[1]

Received: 14 July 2016 / Revised: 21 August 2016 / Accepted: 16 September 2016 / Published online: 14 October 2016

Abstract Infectious diseases remain a significant threat to human health, contributing to more than 17 million deaths, annually. With the worsening trends of drug resistance, there is a need for newer and more powerful antimicrobial agents. We hypothesized that animals living in polluted environments are potential sources of antimicrobials. Under polluted milieus, organisms such as cockroaches encounter different types of microbes, including superbugs. Such creatures survive the onslaught of superbugs and are able to ward off disease by producing antimicrobial substances. Here, we characterized antibacterial properties in extracts of various body organs of cockroaches (*Periplaneta americana*) and showed potent antibacterial activity in crude brain extract against methicillin-resistant *Staphylococcus aureus* and neuropathogenic *Escherichia coli* K1. The size-exclusion spin columns revealed that the active compound(s) are less than 10 kDa in molecular mass. Using cytotoxicity assays, it was observed that pre-treatment of bacteria with lysates inhibited bacteria-mediated host cell cytotoxicity. Using spectra obtained with LC-MS on Agilent 1290 infinity liquid chromatograph, coupled with an Agilent 6460 triple quadruple mass spectrometer, tissues lysates were analysed. Among hundreds of compounds, only a few homologous compounds were identified that contained the isoquinoline group, chromene derivatives, thiazine groups, imidazoles, pyrrole-containing analogs, sulfonamides, furanones, and flavanones and known to possess broad-spectrum antimicrobial properties and anti-inflammatory, anti-tumour, and analgesic properties. Further identification, characterization, and functional studies using individual compounds can act as a breakthrough in developing novel therapeutics against various pathogens including superbugs.

Keywords Cockroach · Antibacterials · Superbugs

Salwa Mansur Ali and Ruqaiyyah Siddiqui contributed equally to this study.

✉ Naveed Ahmed Khan
naveed5438@gmail.com

[1] Department of Biological Sciences, Faculty of Science and Technology, Sunway University, 47500 Subang Jaya, Selangor, Malaysia

[2] International Center for Chemical and Biological Sciences, H.E.J. Research Institute of Chemistry, University of Karachi, Karachi, Pakistan

Introduction

Antibiotic resistance is one of the world's most pressing public healthcare problems (WHO 2002). In recent decades, almost every variant of human pathogenic bacteria has become resistant and/or less vulnerable to available antibiotic treatment, threatening new infectious diseases or emergence of superstrains that are difficult to eradicate (Alanis 2005; Nordmann et al. 2007). Moreover, the current decline in the identification of new antibacterial molecules presents a clear and present danger (Alanis 2005; Nordmann et al. 2007; Devasahayam et al. 2010). In particular, the prevalence of multiple drug-resistant bacterial strains in hospital and community settings is a significant challenge to human health (Alanis 2005; Nordmann et al. 2007; Devasahayam et al. 2010). Among a plethora of multiple drug-resistant bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA) poses a significant threat to human and animal health (Enright 2003). MRSA is a Gram-positive bacteria, which is resistant to many antibiotics and possesses the ability to produce skin and tissue infections that are often nosocomial in nature (Pantosti and Venditti, 2009). Likewise, neuropathogenic *Escherichia coli*

K1 is a leading cause of neonatal meningitis contributing to significant morbidity and mortality, despite advances in antimicrobial chemotherapy (Lee et al. 2011).

We hypothesize that animals living in unsanitary and unhygienic conditions have developed ways of protecting themselves against pathogenic microorganisms (Lee et al. 2011; Sagheer et al. 2014; Bulet et al. 1999; Wilson et al. 1999; Khan et al. 2008). For example, insects such as cockroaches thrive in unhygienic environments. The fact that cockroaches share environmental niches with humans and animals suggests their routine exposure to infectious agents important to human health. The ability of cockroaches to flourish under such threats and ward off diseases indicates their resistance to pathogenic microbes including superbugs as well as toxicants and hazardous materials. Such organisms could be a good source of antibacterials against human pathogens. Insects represent 70 % of living fauna and are the most diverse among the entire animal kingdom. Insects such as cockroaches have survived millions of years and withstood catastrophic events (for comparison, humans have been on the planet for 10,000 years), suggesting their ability to adapt and resist environmental threat. These findings support our hypothesis, to search for potential antimicrobials in such creatures. To this end, our studies suggested that insects such as locusts and cockroaches possess antimicrobials. We characterized antibacterial properties of organ extract of cockroaches (*P. americana*) and tested their effects on human cells, with a view to determine chemical and structural identities as potential therapeutic agents to treat infections.

Materials and methods

Bacterial cultures

A clinical isolate of methicillin-resistant *Staphylococcus aureus* (MRSA) was used in the present study (Malaysian Type Culture Collection 381123). The MRSA strain used in this study was originally derived from blood cultures, obtained from the Luton & Dunstable Hospital NHS Foundation Trust, Luton, England, UK. The sensitivity patterns of MRSA demonstrated its susceptibility to gentamicin, ciprofloxacin, and vancomycin and resistance to amoxicillin, augmentin, cephalaxin, cephtazidim, penicillin, flucloxacillin, tetracycline, and erythromycin. In addition, a Gram-negative neuropathogenic *E. coli* (a cerebrospinal fluid isolate from a meningitis patient; 018:K1:H7), strain E44, was used as described previously (Malaysian Type Culture Collection 710859). Bacteria were cultured in Luria-Bertani (LB) broth and grown overnight at 37 °C, prior to experiments as previously described (Khan et al. 2008).

Organ lysates of cockroaches

Cockroaches (*P. americana*) were reared on a diet of dried dog food pellets and were housed in glass-fronted metal cages in the dark. The cages were kept in a temperature-regulated insectary at 30 °C. For dissections, all instruments were disinfected in 70 % ethanol prior to and during each dissection. Cockroaches were immobilized by exposure to 4 °C for 15 min. Cockroaches were immobilized by removal of legs and wings and securing to a dissection plate, ventral side up, using a pin on either side of the thorax and one through the distal abdomen. The head and legs were removed, prior to a longitudinal incision made down the midline of the abdomen to expose the fat body tissue, a sample of which was removed aseptically. The thoracic cuticle was opened up with a flap-shaped incision to obtain the haemolymph from the cockroach body cavity using a pipette. The upper hind leg of the cockroach was opened up with a longitudinal incision to expose muscle tissue, a sample of which was aseptically removed. The removed cockroach head was dissected to obtain the intact brain aseptically.

Insect tissue samples were collected in 500 μL of sterile water in batches of samples obtained from 500 cockroaches. The samples were kept on ice during dissection and treated in an identical manner. An estimate was made by eye/weight to ensure that the mass of each tissue was approximately similar. The samples were subjected to four cycles of freeze-thawing in order to cause cellular disruption and lysis. The thawing period was kept as brief as possible and organ extracts were kept cold (4 °C) before re-freezing. The samples were then homogenized aseptically with a tissue grinder, prior to centrifugation at 10,000*g* for 30 min at 4 °C. The supernatant (crude extract) was then collected and filtered using a sterilized 0.2-μm pore size filter, and protein concentration was determined using a Bio-Rad Protein Assay kit. Finally, lysates were stored at −20 °C until needed for antibacterial bioassay testing.

Antibacterial assays

To determine the effects of crude extracts of various organ lysates on bacterial viability, antibacterial assays were performed as described previously (Khan et al. 2008). Briefly, the optical density of bacterial broth cultures was adjusted to 0.22 at 595 nm using a spectrophotometer (equivalent to 10^8 colony-forming units per mL and confirmed by plating on nutrient agar plates). Approximately 10^6 colony-forming units (c.f.u.), suspended in 10 μL, were incubated with different concentrations of various organ lysates of cockroaches at 37 °C for 2 h. Following this, bacteria were serially diluted and enumerated by plating on nutrient agar plates (Khan et al.

2008). For negative controls, bacteria were incubated in PBS alone, and for positive controls, bacteria were incubated with 100 μg per mL of gentamicin. Percentage bactericidal effects were determined as the percentage of bacteria surviving relative to the control: 100 − (cfu recovered / original inoculum × 100).

Human brain microvascular endothelial cell (HBMEC) cultures

The primary HBMEC were cultured in RPMI-1640 containing 10 % heat-inactivated fetal bovine serum, 10 % Nu-serum, 2 mM glutamine, 1 mM Na-pyruvate, 100 U penicillin per mL, 100 μg streptomycin per mL, non-essential amino acids, and vitamins as previously described (Khan and Siddiqui, 2009). For cytotoxicity assays, HBMECs were cultured in 24-well plates by inoculating 5×10^5 cells per well per mL and incubating them at 37 °C with 5 % CO_2, which resulted in the formation of complete monolayers within 48 h.

Cytotoxicity assay

Cytotoxicity assays were performed as previously described (Khan and Siddiqui, 2009). Briefly, assays were performed in 24-well plates containing confluent HBMEC monolayers. The organ lysates alone, bacteria alone, or bacteria treated with lysates were added to confluent HBMEC layers (final volume of 500 μL RPMI-1640). For treatment, bacteria were incubated with gentamicin (100 μg per mL) or lysates (100 μg per mL) for 2 h at 37 °C, followed by incubation with HBMEC monolayers. Plates were incubated at 37 °C in a 5 % CO_2 incubator for 20 h. After this incubation, the supernatants were collected from each well and centrifuged to remove cellular debris and then cytotoxic effects were determined by estimating the amount of lactate dehydrogenase released from HBMEC using a Cytotoxicity Detection kit (Roche Applied Sciences). The percent cytotoxicity was calculated as follows: % cytotoxicity = (sample value − control value) / (total LDH release − control value) × 100. Control values were determined by incubating HBMEC monolayers with RPMI-1640 alone, and total LDH release was obtained by completely lysing the HBMEC using 1 % Triton X-100. To determine the molecular mass of the active molecule(s), crude brain lysates were filtered through 30- and 10-kDa molecular weight cutoff Spin-X UF columns (Corning). Both the elutate and retentate were used in the aforementioned antibacterial assays.

Liquid chromatography mass spectrometry (LC-MS): separation and analysis

All samples were analysed using a LC-MS on Agilent 1290 infinity liquid chromatograph (Agilent Technologies, Wilmington, DE), coupled with an Agilent 6460 triple quadruple mass spectrometer. Separation of compounds was achieved using reverse-phase HPLC, with a Merck C-18 column of particle size 3 μm (5.5 cm length and i.d. of 4.6 mm) at 25 °C, and equilibrated with 90 % solvent A (0.1 % formic acid in Milli-Q water) and 10 % solvent B (0.1 % formic acid in MeOH). A flow rate of 0.6 mL per min with a linear gradient was used as follows: 10 % solvent B for 4 min, 80 % solvent B over the course of 3.2 min, and 10 % solvent B for 2.8 min. The total run time was 14 min, including a 5-min equilibration time.

The compounds were ionized using ESI + jet stream ion mode with the QQQ analyser. The parameters of ion source were set as follows: capillary voltage at 4500 V, sheath gas flow at 8 L per min, fragmentor voltage at 135 V, gas temperature at 350 °C, gas flow at 8 L per min, and nebulizer gas at 40 psi, and the detector used was MCP Microchannel Plate detector, while a blank was used after each sample of composition 50 % MeOH + 50 % Milli-Q water.

Identification of compounds through matching with library

Water-soluble and methanol-extracted lysates of brain, haemolymph, and muscles of cockroaches were subjected to LC-MS analysis as described above, to obtain the chromatograms and the prospective mass spectra of every separated fraction of the mixture of compounds. The MS spectra for the compounds present in water-soluble and methanol-extracted lysates were run against the NIST Mass Spectral Search Program-2009 version 2.0f (National Institutes of Standard and Technology, Gaithersburg, MD) for the identification of homologous compounds through Agilent Mass Hunter software, while keeping in view compensation needed for charges in positive ESI MS as well as electron fragmentations, to ensure searches for the correct parent mass. Reported biological activities of the compounds identified and their novelty were determined with the help of Scifinder software.

Results

Cockroach brain crude lysates exhibit potent bactericidal activity against MRSA and neuropathogenic *E. coli* K1

The crude extracts of cockroach fat body, muscle, and brain were prepared and tested along with aspirated haemolymph in antibacterial bioassays against MRSA. Fat body and muscle lysates showed no bactericidal activity against MRSA and *E. coli* K1 at 100 μg per mL, while haemolymph exhibited 35 % ±5.1 and 20 % ±3.5 bactericidal effects, against MRSA and *E. coli* K1, respectively. In contrast, brain extracts exhibited more than 90 % bactericidal effects against both MRSA and neuropathogenic *E. coli* K1 (Fig. 1).

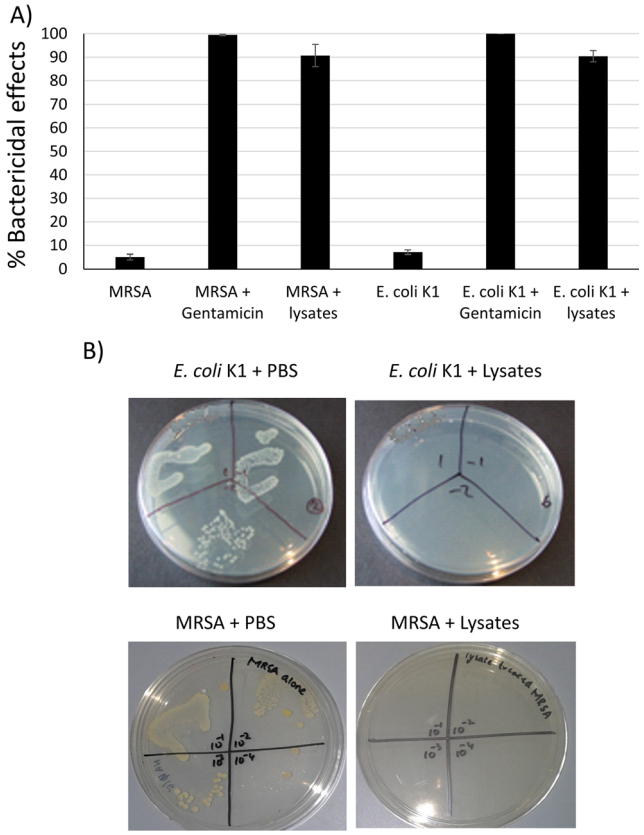


Fig. 1 Crude extract from cockroach brains were prepared and tested (100 μg) for antibacterial activity, as described in 'Materials and methods'. **a** The results revealed that cockroach brain lysates exhibited more than 90 % bactericidal activity against MRSA and neuropathogenic *E. coli* K1. For positive control, gentamicin (100 μg per mL) exhibited more than 99 % killed rate. The data is presented as the mean ± standard mean of three independent experiments performed in duplicate. **b** Representative effects of crude extracts from cockroach brains on MRSA and neuropathogenic *E. coli* K1. Both MRSA and neuropathogenic *E. coli* K1 were treated with lysates for 2 h at 37 °C for then plated on nutrient agar plates. Note that pretreatment of MRSA and neuropathogenic *E. coli* K1 exhibited bactericidal effects

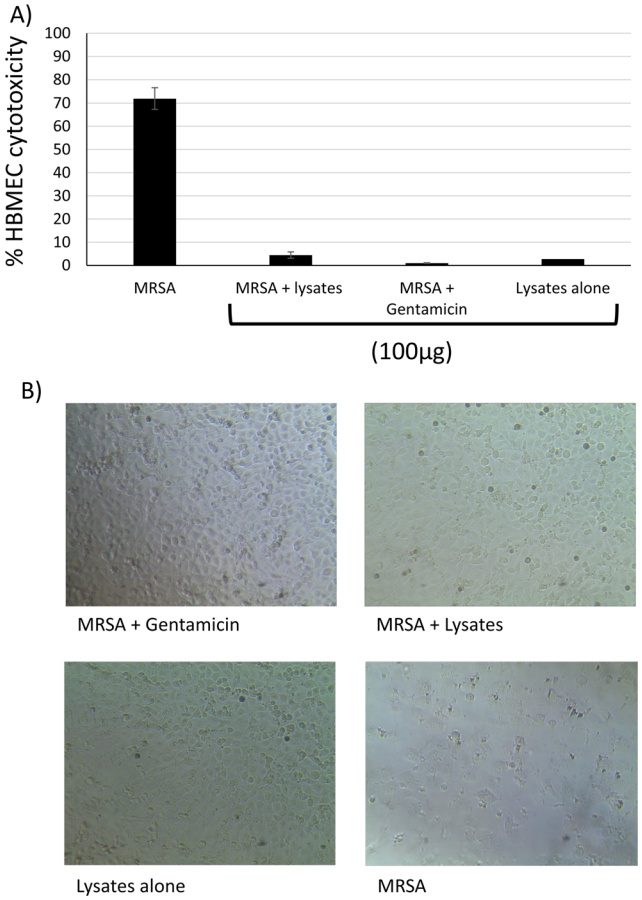


Fig. 2 Cockroach brain lysates inhibited methicillin-resistant *Staphylococcus aureus* (MRSA)-mediated human brain microvascular endothelial cell (HBMEC) cytotoxicity. **a** Cockroach brain lysates were prepared and tested for their protective effects against MRSA-mediated cytotoxicity on HBMEC as described in 'Materials and methods'. Note that MRSA alone exhibited >70 % cell death. In contrast, MRSA pretreated with gentamicin or lysates for 2 h at 37 °C and then incubated with HBMEC monolayers for 20 h exhibited minimal cell death. Likewise, 100 μg of brain lysates alone had minimal cytotoxic effects on HBMEC. The data is presented as the mean ± standard mean of three independent experiments performed in duplicate. **b** Representative effects of MRSA, lysates, gentamicin-treated MRSA, and lysates-treated MRSA on HBMEC monolayers for 20 h. Pretreatment of MRSA with gentamicin did not produce visual disruption of HBMEC monolayers. Similar results were observed with lysates alone and MRSA pretreated with lysates. In contrast, HBMEC monolayers treated with MRSA exhibited complete monolayer disruptions. ×200

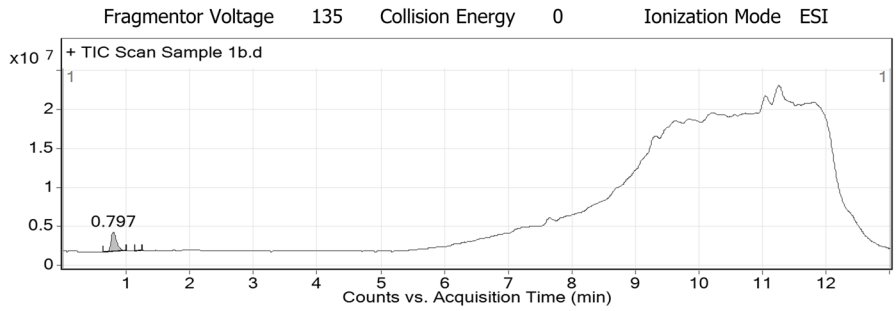
Partial characterization of cockroach brain crude lysates and their effects on human cells

When crude brain lysates were filtered through 30- and 10-kDa molecular weight cutoff Spin-X UF columns, the antibacterial activity was observed in elutate, suggesting that antibacterial compound(s) are less than 10 kDa in molecular mass. To assess potential cytotoxicity to human cells, lysates were added to HBMEC monolayers, and lactate dehydrogenase, a marker for cellular lysis, was measured using a Roche cytotoxicity detection kit. When incubated with MRSA or neuropathogenic *E. coli* K1 alone, more than 70 % HBMEC cytotoxicity was observed (Fig. 2). In contrast, MRSA or neuropathogenic *E. coli* K1 pretreated with gentamicin or lysates followed by incubation with HBMEC produced minimal host cell damage. Notably, lysates alone showed minimal HBMEC cytotoxicity, indicating selective toxicity against bacteria tested.

Identification of compound(s) present in cockroach lysates using liquid chromatography-mass spectrometry

The brain, haemolymph, and muscle lysates of cockroaches were processed for water and methanol extractions and subjected to LC-MS (Agilent Technologies 6460 Triple Quadrupole LC/MS) for qualitative analyses. Figure 3 shows spectra from respective extractions. These compounds were separated based on the *m*/*z* ratio and retention time in the column. The data obtained from the LC-MS for brain lysates

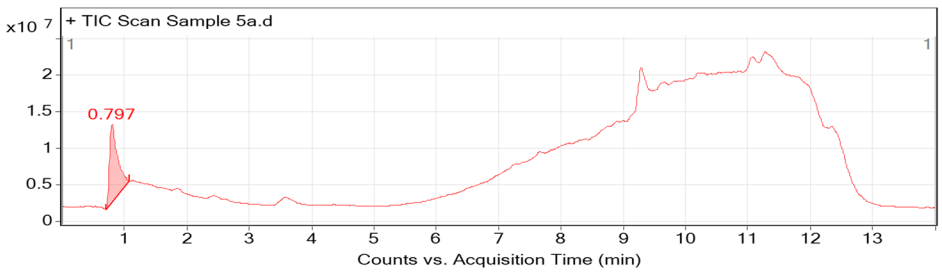
A)



User Chromatogram Peak List

RT	Height	Height %	Area	Area %	Area Sum %	Base Peak m/z	Width
0.797	2E+06	100	15038081	100	98.45	162.1	0.35

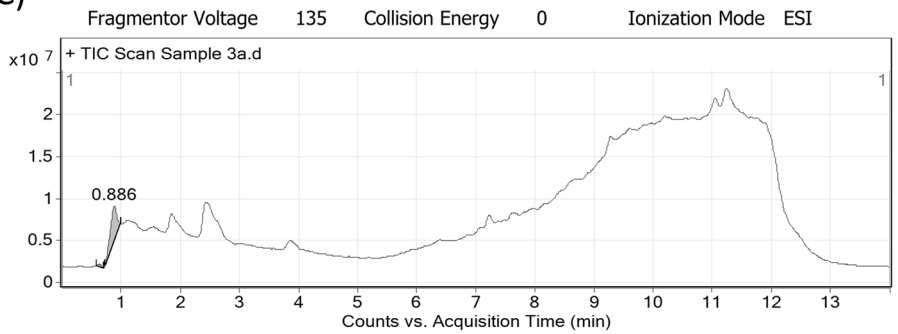
B)



User Chromatogram Peak List

RT	Height	Height %	Area	Area %	Area Sum %	Base Peak m/z	Width
0.797	10706971	100	96213357	100	100%	162	0.373

C)



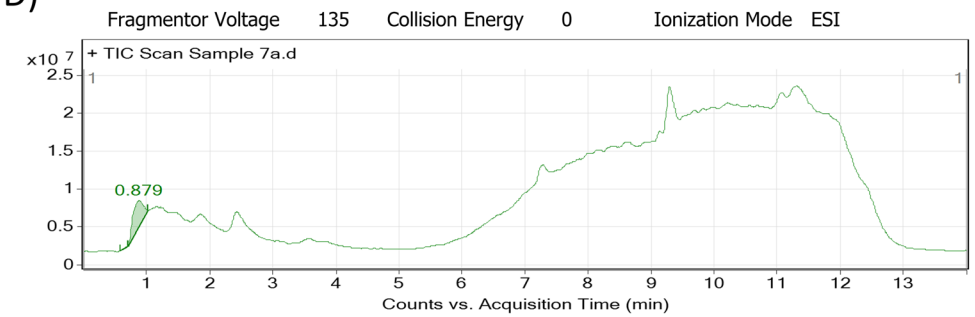
User Chromatogram Peak List

RT	Height	Height %	Area	Area %	Area Sum %	Base Peak m/z	Width
0.886	4E+06	100	33554711	100	95.92	204.1	0.253

Fig. 3 Cockroach brain and haemolymph lysates (water and methanol extractions) were subjected to LC-MS (Agilent Technologies 6460 Triple Quadrupole LC/MS) for qualitative analyses. The compounds were separated based on *m*/*z* ratio and retention time in the column. The data obtained from the LC-MS for brain extract contained over 168 peaks from water-extracted compounds **(a)**, over 193 peaks from methanol-extracted compounds (**b**), and the data obtained from haemolymph extract contained over 182 peaks from water-extracted compounds **(c)** and over 172 peaks from methanol-extracted compounds **(d)**, and the data obtained from muscle extract contained over 180 peaks from water-extracted compounds **(e)** and over 190 peaks from methanol-extracted compounds **(f)**

contained over 168 peaks for water-soluble and over 193 peaks for methanol-extracted brain lysates (Fig. 3). Similarly, the data obtained from LC-MS for haemolymph lysates contained over 182 peaks for water-soluble and over 172 peaks for methanol-extracted haemolymph lysates (Fig. 3). Similarly, the data obtained for muscle extract

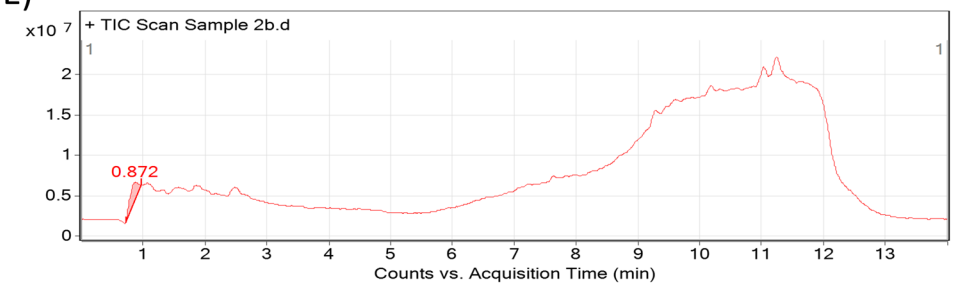
D)



User Chromatogram Peak List

RT	Height	Height %	Area	Area %	Area Sum %	Base Peak m/z	Width
0.879	3E+06	100	42491068	100	98.53	204	0.313

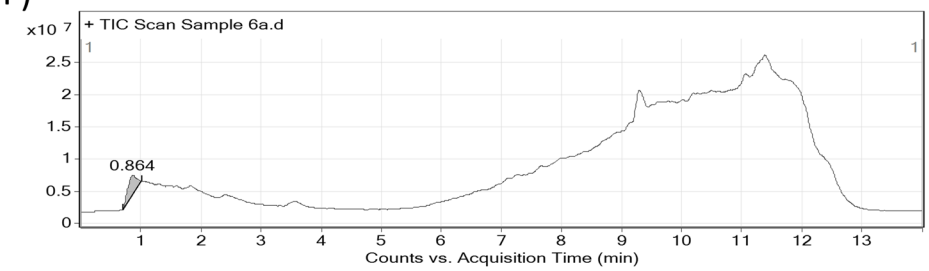
E)



User Chromatogram Peak List

RT	Height	Height %	Area	Area %	Area Sum %	Base Peak m/z	Width
0.872	2E+06	100	23187174	100	100	104.1	0.253

F)



User Chromatogram Peak List

RT	Height	Height %	Area	Area %	Area Sum %	Base Peak m/z	Width
0.864	3E+06	100	32758086	100	100	104.1	0.306

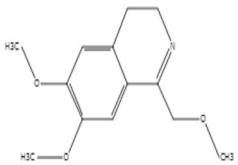
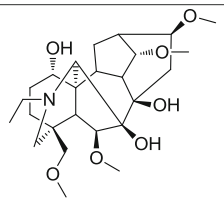
Fig. 3 (continued)

contained over 180 peaks for water-soluble and 190 peaks for methanol-soluble lysates of muscles (Fig. 3).

For brain lysates, among hundreds of compounds, five were identified from water-extracted lysates, and 15 generated from LC-MS were identified from methanol-extracted compounds (Table 1). Similarly, for haemolymph lysates, among hundreds of compounds, 19 were identified from water-extracted lysates and 18 from methanol-extracted compounds (Table 2). For muscle lysates, among hundreds of compounds, 12 were identified from water-soluble lysates, and 18 from methanol-extracted compounds were identified using LC-MS (Table 3).

The compounds were searched through Scifinder software to determine any reported biological activity. Among various homologous compounds from brain lysates, many of them were shown to possess biologically active molecules (Table 1). For example, compounds 1, 2, 3, 6, 10,13, 15, 16, 17, 18, and 19 possess antimicrobial activities against various Gram-positive and Gram-negative bacteria including *Listeria monocytogenes*, *Bacillus subtilis*, *Salmonella typhimurium*,

Table 1 Compounds identified from the cockroach brain lysates

No.	Compound	Formula	Structure	Reported activity
Compounds identified from the water-soluble brain lysates				
1	6,7-Dimethoxy-1-methoxymethyl-3,4-dihydroisoquinoline	$C_{13}H_{17}NO_3$		• Marine derived lamellarin natural products (Tangdenpaisal et al. 2015) • Quorum sensing inhibitors of *Pseudomonas aeruginosa* (Givskov et al. 2014) • Antibacterial activity against *Escherichia coli* O157:H7 and *Listeria monocytogenes* (Seo et al. 2012), *Klebsiella pneumonia* (Mharti et al. 2011) • Antifungal activity against *Candida albicans* (Orhan et al. 2007), *Curvularia lunata* (Brunskole et al.2011) • Antiviral activity against Parainfluenza virus (Orhan et al. 2007) • Anti diabetic activity (Yang et al. 2014) • Used for treating degenerative and ischemic disorders (Mootha et al. 2010) • Anticancer activity against human oral squamous cell carcinoma cells (Hatano et al. 2009), murine mammary cancer cells DA3 cells (Alvarez et al. 2009) , hepatic carcinoma cells Huh7 (Kumar et al. 2015)
2	(3*S*,6*S*,6a*S*,8*S*,10*S*,11a*R*,12*R*,12a*S*,13*S*)-1-Ethyl-8,10,13-trimethoxy-3-(methoxymethyl)tetradecahydro-1*H*-3,6a,12-(epiethane[1,1,2]triyl)-7,9-methanonaphtho[2,3-b]azocine-6,11a,12-triol	$C_{25}H_{41}NO_7$		• Acting as norditerpenoid ligands (Hardick et al. 1996) • Antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus* (Yin et al. 2015), *Salmonella typhimurium*, *Escherichia coli* (Sinam et al. 2012) • Antimicrobial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus mycoides*, *Proteus vulgaris*, *Verticillium alboatrum*, *Colletrichurm lagenarium*, *Alternaria alternate*, *Phytophora infestans* (Yuan and Wang 2012) • Antiviral activity against tobacco mosaic virus (TMV) (Huang et al. 2013) • Used to treat cancer and postoperative pain (Yang et al. 2015) • Antiproliferative activity against lung (A549), prostate (DU145), nasopharyngeal (KB), and vincristine resistant nasopharyngeal (KB-VIN) cancer cell lines (Wada et al. 2015), human breast cancer cell resistant to tamoxifen MCF-7/TAM (Chen and Chen 2012) • Antidiabetic activity (Han et al. 2014) • Antioxidant activity (Yin et al. 2015)

Staphylococcus aureus, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumonia*, *Bacillus mycoides*, *Proteus vulgaris*, *Proteus mirabilis*, *Enterobacter cloacae*, *Enterococcus faecalis*, *Morganella morganii*, and *Providencia stuartii*; fungi including *Candida albicans*, *Curvularia lunata*, *Aspergillus flavus*, *Aspergillus niger*, *Verticillium alboatrum*, *Colletrichurm lagenarium*, *Alternaria alternate*, *Phytophora infestans*, *Dermatophytes* etc.; viruses including Parainfluenza virus, Influenza A virus, Respiratory syncytial virus, Herpes virus, etc. Additionally, compounds homologous to 1, 2, 6, 11, 12, 13, 16, and 17 are shown to possess anti-tumour properties against various types of cancers, including oral squamous cell carcinoma, breast cancer, hepatic carcinoma, nasopharyngeal carcinoma,

Table 1 (continued)

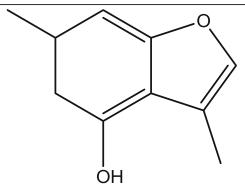
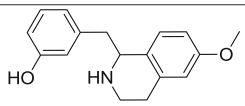
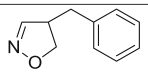
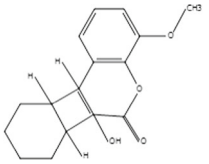
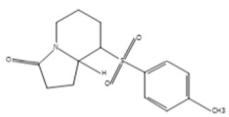
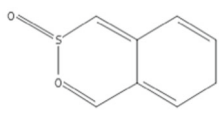
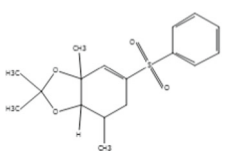
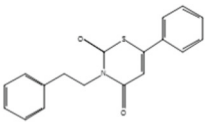
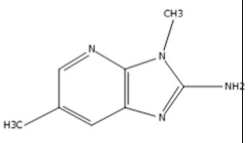
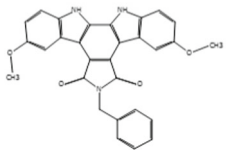
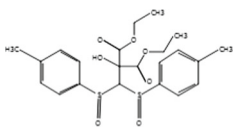
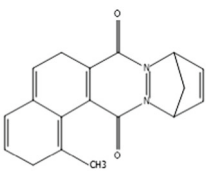
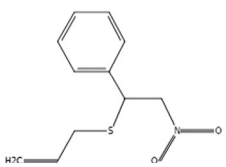
3	3,6-Dimethylbenzofuran-4(5*H*)-ol	$C_{10}H_{10}O_2$		• Herbicidal activity (Zhao et al. 2014) • Inhibition of LPS-induced muscle atrophy (Shiota et al. 2015) • Agonists for enhancing the olfactory effect (Huchel et al. 2015) • Anti platelet aggregation activities (Tang et al. 2015) • Antiviral agent against Herpes virus (Yuan and Xu 2015)
4	3-((6-Methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)phenol	$C_{17}H_{19}NO_2$		• Monoamines in the nervous system of the queensland fruit fly, *Dacus tryoni* (Armati et al. 1976) • Actions of compounds related to dopamine at neuro-secretory synapse (Ginsborg et al. 1976)
5	4-Benzyl-4,5-dihydroisoxazole	$C_{10}H_{11}NO$		• Dihydroisoxazole inhibitors of *Anopheles gambiae* seminal transglutaminase AgTG3 (Le et al. 2014)
Compounds identified from the methanol-extracted brain lysates.				
6	6a-Hydroxy-4-methoxy-6a,6b,7,8,9,10,10a,10b-octahydro-6*H*-benzo[3,4]cyclobuta[1,2-c]chromen-6-one	$C_{16}H_{18}O_4$		• Anti-inflammatory activity (Gao et al. 2015) • Antibacterial activity against multidrug-resistant *Staphyloccus aureus*, *Enterococcus faecalis*, *Escherichia coli*, *Proteus mirabilis*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, *Morganella morganii* and *Providencia stuartii* (Zampini et al. 2013) • Antifungal activity against *Botrytis cinerea* and *Penicillium digitatum* (Exarchou et al. 2015) • Antiviral activity against respiratory syncytial virus (Shin et al. 2013)
				• Antioxidant activity (Breton et al. 2015) • Reduces influenza A virus replication (Perwitasari et al. 2014) • Anticancer activity against human colon cancer HCT116 (Park et al. 2014) , human breast, ovarian, and intestinal tumor cells (Vergara et al. 2014)
7	(8*R*,8a*S*)-8-[(*p*-Toluenesulfonyl)perhydro-3-indolizidinone	$C_{15}H_{19}NO_3S$		• Pesticidal activities (Schnatterer et al. 2009)
8	1,4-Dihydro-2,3-benzoxathin-3-oxide	$C_8H_8O_2S$		No biological activity reported
9	2,2,4,7a-Tetramethyl-6-(phenylsulfonyl)-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxole	$C_{17}H_{22}O_4S$		No biological activity reported

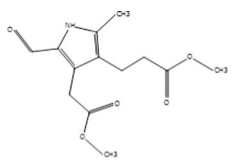
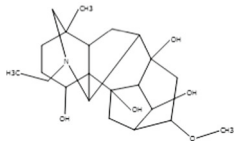
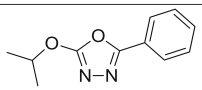
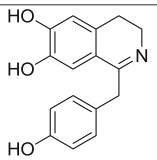
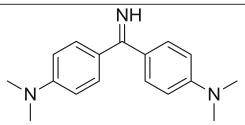
Table 1 (continued)

10	3-(2′-Phenylethyl)-2,3-dihydro-6-phenyl-2,4-dioxo-4*H*-1,3-thiazine	$C_{18}H_{15}NO_2S$		• Antioxidant activity of thiazolidinone derivatives (Amutha et al. 2014) • Antitubercular activity against *Mycobacterium tuberculosis* • Antibacterial activity against *Bacillus subtilis*, *Escherichia coli,* and *Staphylococcus aureus* • Antifungal activity against *Aspergillus niger*, *Aspergillus flavus,* and *Candida albicans* (Samadhiya et al. 2014)
11	2-Amino-3,6-dimethylimidazo[4,5-b]pyridine	$C_8H_{10}N_4$		• Carcinogenic activity (Fang et al. 2008), mutagenic activity (Hatch et al. 2001) • Anticancer activity against HeLa cells (Mackmull et al. 2015) • Increases oxidative stress (Carvalho et al. 2015) • Toxicity against primary dopaminergic neurons (Griggs et al. 2014)
12	3,9-Dimethoxy-12,13-dihydro-5*H*-indolo[2,3-a]pyrrolo[3,4-c]carbazole-6-benzyl	C29H21N3O4		• Anti-inflammatory and analgesic activities,(Alanazi et al. 2015) • Anticancer activities against various cancers including breast, lung, colon etc. by acting as serine/threonine -protein kinase TBK1 inhibitors (Richters et al. 2014)
13	(*S*,*S*)-1,1-Bis(ethoxycarbonyl)-2,2-bis-*p*-tolylsulfinyl-1-ethanol	$C_{22}H_{26}O_7S_2$		• Cytotoxic activity against human promyelocytic leukemia (HL-60) cells (Nagarajan et al. 2015) • Useful for liver regeneration and treatment of liver failure by acting as an inhibitor of mitogen-activated protein kinase kinase 4 (MAP2K4, also termed MKK4) (Zender and Wuestefeld 2012) • Act as inhibitors of bacterial DNA adenine methyltransferases (Mashhoon et al. 2006) • Pesticidal activity (Pisanenko et al. 1986)
14	1-Methyl-[14-(13)*C*]-9,12-methanobenzo[h]pyridazino[1,2-b]phthalazine-7,14-dione	$C_{18}H_{14}N_2O_2$		• Act as glycogen synthase kinase 3 beta inhibitors (Alisi et al. 2013) • Act as cyclin-dependent kinase inhibitors (Raffa et al. 2009) • Act as tyrosine kinase inhibitors (Jansen et al. 2005) • Analgesic activity (Alisi et al. 2010) • Act as 5-HT4 receptor agonists useful in the treatment of digestive tract disorders (Suzuki et al. 2000) • Act as serotoninergic S3 antagonists useful as antiemetics (Kon et al. 1991) • Antiarrhythmic activity (Kane and Levine 1981)
15	Allyl(2nitro-1-phenylethyl)sulfane	$C_{11}H_{13}NO_2S$		• Used to treat metabolic disorders (Pellecchia 2008) • Antibacterial activity against *Helicobacter pylori* (Gokce et al. 2004) • Used for the treatment of seborrhea (Kalopissis and Manoussos 1976) • Antibacterial activity against *Escherichia coli* and antifungal activities against *Candida* species and dermatophytes (Bilich et

prostate cancer, lung cancer, intestinal tumour, etc. while some homologous compounds are shown to exhibit biological activities such as anti-diabetic, anti-inflammatory, anti-platelet aggregation, antioxidant, and analgesic activities (Table 1).

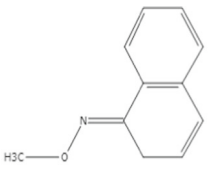
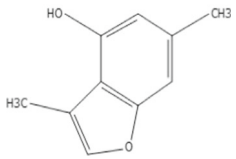
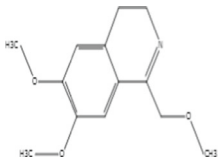
The five compounds identified in water-extracted brain lysates, i.e., Cpd1: 6,7-dimethoxy-1-methoxymethyl-3,4-dihydroisoquinoline, Cpd2: (3*S*,6*S*,6a*S*,8*S*,10*S*,11a*R*,12*R*,12a*S*,13*S*)-1-ethyl-8,10,13-

Table 1 (continued)

				al. 1970)
16	Methyl 5-formyl-4-methoxycarbonylmethyl-2-methylpyrrole-3-propionate	$C_{13}H_{17}NO_5$		• Anti-inflammatory activity (Indumathi et al. 2015) • Act as inhibitors against yeast alpha-glucosidase (Niaz et al. 2015) • Antibacterial activity against ESBL isolates of *Klebsiella pneumonia* (Murthy et al. 2012) , *Escherichia coli*, *Pseudomonas aeruginosa* • Antifungal activity against *Candida albicans* • Anticancer activities against Hep G2 (liver), Hela (cervical), MCF-7 (breast cancer) cells (Idhayadhulla et al. 2013) • Act as non-nucleoside HIV-1 RT inhibitors (Antonucci et al. 1995) • Used for treating liver diseases including necrosis, fatty hepatosis, and viral hepatitis (Giller et al. 1976)
17	KARAKOLIDINE	$C_{22}H_{35}NO_5$		• Antioxidant activity • Antibacterial activity against *Bacillus subtilis* and *Staphyloccus aureus* (Yin et al. 2015) , *Salmonella typhimurium*, *Escherichia coli* (Sinam et al. 2012) *Bacillus mycoides*, *Proteus vulgaris*, • Antifungal activity against *Verticillium alboatrum*, *Colletrichurm lagenarium*, *Alternaria alternate* • Antiparasitic activity against *Phytophora infestans* (Yuan and Wang 2012) • Antiviral activity against tobacco mosaic virus (TMV) (Huang et al. 2013) • Used to treat cancer and postoperative pain (Yang et al. 2015)
				• Antiproliferative activity against lung (A549), prostate (DU145), nasopharyngeal (KB), and vincristine resistant nasopharyngeal (KB-VIN) cancer cell lines (Wada et al.2015), human breast cancer cell resistant to tamoxifen MCF-7/TAM (Chen and Chen 2012) • Antidiabetic activity (Han et al. 2014)
18	2-Isopropoxy-5-phenyl-1,3,4-oxadiazole	$C_{11}H_{12}N_2O_2$		• Anti-inflammatory activity (Akhter et al. 2011) • Antibacterial activity against *Staphyloccus aureus, Escherichia coli, Pseudomonas aeruginosa* • Antifungal activity *Candida krusei,Candida albicans* and *Candida parapsilosis* (Şahin et al. 2002)
19	1-(4-Hydroxybenzyl)-3,4-dihydroisoquinoline-6,7-diol	$C_{16}H_{15}NO_3$		• Antitubercular activity (Guzman et al. 2015)
20	4,4′-(Iminomethylene)bis(*N*,*N*-dimethylaniline)	$C_{17}H_{21}N_3$		• Act as an aniline dye used as a disinfectant and an antiseptic agent. Used to stain *Mycobacterium tuberculosis* (Arrowood and Sterling 1989) • Act as a toxic dye against wood-destroying fungi (Weaver et al. 1985)

trimethoxy-3-(methoxymethyl)tetradecahydro-1*H*-3,6a,12-(epiethane[1,1,2]triyl)-7,9-methanonaphtho[2,3-b]azocine-6,11a,12-triol, Cpd3: 3,6-dimethylbenzofuran-4(5*H*)-ol, Cpd4: 3-((6-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)phenol, and Cpd5: 4-benzyl-4,5-dihydroisoxazole, have reported biological

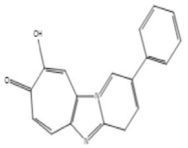
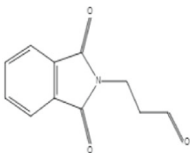
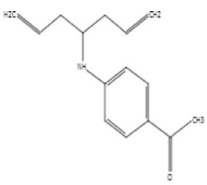
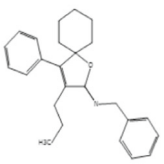
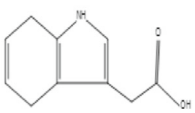
Table 2 Compounds identified from the cockroach haemolymph

No.	Compound	Formula	Structure	Reported activity
Compounds identified from the water-soluble haemolymph				
1	3,4-Dihydro-1(2*H*)-naphthalene *O*-methyloxime	$C_{11}H_{13}NO$		• Antiviral activity against HIV-1 (La et al. 2015), HSV-1 and HSV-2 (Ishikawa et al. 1996) • Fungicidal activity for crop protection (Dubost et al. 2013) • Antibacterial activities against *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, ESBL *Escherichia coli*, *Klebsiella pneumoniae*, • Antifungal activity against *Aspergillus niger*, *Candida albicans* (Gonewar et al. 2012) • Anticancer activity against HeLa and HL60 cancer cells (Wirth et al. 2010), prostate cancer cells (Capitosti et al. 2004)
2	3,6-Dimethylbenzofuran-4-ol	$C_{10}H_{10}O_2$		• Herbicidal activity (Zhao et al. 2014) • Inhibition of LPS-induced muscle atrophy (Shiota et al. 2015) • Agonists for enhancing the olfactory effect (Huchel et al. 2015) • Antiplatelet aggregation activities (Tang et al. 2015) • Antiviral agent against Herpes virus (Yuan and Xu 2015)
3	6,7-Dimethoxy-1-methoxymethyl-3,4-dihydroisoquinoline	$C_{13}H_{17}NO_3$		• Marine-derived lamellarin natural product (Tangdenpaisal et al. 2015) • Quorum sensing inhibitors of *Pseudomonas aeruginosa* (Givskov et al. 2014) • Antibacterial activity against *Escherichia coli* O157:H7 and *Listeria monocytogenes* (Seo et al. 2012) , *Klebsiella pneumonia* (Mharti et al. 2011) • Antifungal activity against *Candida albicans* (Orhan et al. 2007), *Curvularia lunata* (Brunskole et al. 2011) • Antiviral activity against Parainfluenza virus (Orhan et al. 2007) • Antidiabetic activity (Yang et al. 2014) • Used for treating degenerative and ischemic disorders (Mootha et al. 2010) • Anticancer activity against human oral squamous cell carcinoma cells (Hatano et al. 2009), murine mammary cancer DA3 cells (Alvarez et al. 2009) , hepatic carcinoma cells Huh7 (Kumar et al. 2015)

activities mentioned above. Among the 15 compounds identified from brain methanol extracts, 3 of them (Cpd11: 2-amino-3,6-dimethylimidazo[4,5-b]pyridine, Cpd18: 2-isopropoxy-5-phenyl-1,3,4-oxadiazole, and Cpd20: 4,4′-(iminomethylene)bis(*N*,*N*-dimethylaniline) have reported biological activities. However, Cpd8: 1,4-dihydro-2,3-benzoxathin-3-oxide and Cpd9: 2,2,4,7a–tetramethyl-6-(phenylsulfonyl)-3a,4,5,7a–tetrahydrobenzo[d][1,3] dioxole do not have any reported biological activities. The remaining 10 compounds have homologous structures, reported in the literature with various biological activities (Table 1).

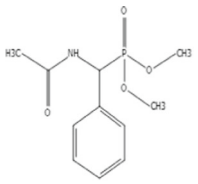
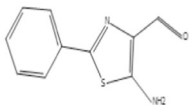
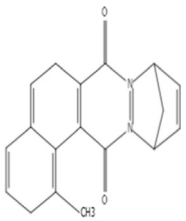
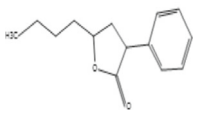
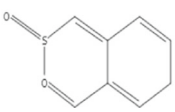
For haemolymph lysates, several homologous compounds were shown to possess biologically active molecules. For example, compounds 1, 2, 3, 4, 6, 10, 12, 14, 15, 16, 19, 20, 23, 24, 26, 28, 29, 30, 31, 32, 33, and 37 were shown to possess antimicrobial activities against a broad range of microorganisms including bacteria such as *Bacillus subtilis*, *Bacillus anthracis*, *Bacillus mycoides*, *Bacillus cereus*, *Enterococcus feacalis*, *Staphylococcus aureus*, *Salmonella typhi*, *Proteus vulgaris*,

Table 2 (continued)

4	2-Phenylpyrido[1′,2′,1,2]imidazo[4,5]tropolone	$C_{18}H_{12}N_2O_2$		• Act as neuroprotective agent by inducing oxidation of protein disulfide isomerase (Kaplan et al. 2015) • Antiparasitic agents that specifically target parasitic worm embryos(Ryder 2010) • Anticancer activity against MCF-7 breast cancer cells (Tapia et al. 2009) • Used for the treatment of Duchenne muscular dystrophy (Wynne et al. 2008) • Antiprotozoal activity against *Plasmodium* and *Theileria* (Rathore et al. 2007) • Used for the prevention and treatment of gastrointestinal diseases by inhibition of acid secretion (Simon et al. 1998) • Nitric oxide synthase (nos) inhibitors (Mjalli et al. 1998) • Fungicidal activity (O'Mahony et al. 1997)
5	3-Phthalimidopropionaldehyde	$C_{11}H_9NO_3$		• Insecticidal activity (Rico and Van 2015) • Anticancer and fluorescence activity (Funk et al. 2015)
6	*N*-(1-Allyl-3-butenyl)-*N*-(*p*-acetylphenyl)amine	$C_{15}H_{19}NO$		• Antiviral activity against HIV-1 (Pery et al. 2015) • Anti- inflammatory activity (Zarzycka et al. 2015) • Used to treat obesity (Richardson and Campbell 2015) • Antidiabetic activity (Tomizawa et al. 2014) • Anticancer activity against prostate (PC3), cervical (HeLa), and breast (MCF7) cells (Istanbullu et al. 2014) • Psychoactive agent (Elliott and Evans 2014)
7	*N*-Benzyl (4-phenyl-3-propyl-1-oxaspiri[4,5]dec-3-enylidene)amine	$C_{25}H_{29}NO$		• No biological activity reported
8	2-(4,7-Dihydro-1*H*-indol-3-yl)acetic acid	$C_{10}H_9NO_2$		• Insect repellent activity (Ray and Boyle 2011) • Antipsychotic activity (Heffernan et al. 2011) • Anti-inflammatory activity (Vance and Kambam 2007) • Used for the treatment of pain (Macias 2001) • Useful for the treatment of renal dysfunction (Macias and Meador 2001) • Useful for the treatment of thrombosis (Girard et al. 1989)

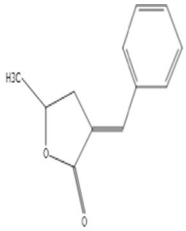
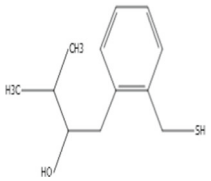
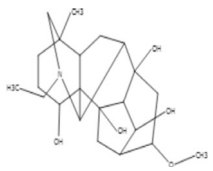
Pseudomonas aeruginosa, *Pseudomonas fluorescens*, *Pasturella multicoda*, *Escherichia coli*, *Klebsiella pneumoniae*, *Listeria monocytogenes*, etc.; fungi such as *Aspergillus niger*, *Fusarium proliferatum*, *Aspergillus parasiticus*, *Trichoderma reesei*, *Candida albicans*, *Curvularia lunata*, *Geotricum candidum*, *Pyricularia oryzae*, *Helminthosporium oryzae*, *Rhizoctonia bataticola*, *Alternata alternate*, *Pythium aphanidermatum*, *Fusarium solani*, and *Sclerotium folfsi*; *Saccharomyces cerevisiae*; parasites such as *Leishmania chagasi*; parasitic worm embryos; *Plasmodium*, *Toxoplasma*, and *Theileria*; phytoparasitic nematodes; viruses such as HIV-1, HSV-1, HSV-2, parainfluenza virus, tobacco mosaic virus,

Table 2 (continued)

9	Dimethyl (acetamido(phenyl) methyl)phosphonate	$C_{11}H_{16}NO_4P$		• Binding potency with Src SH2 protein (Deprez et al. 2002) • Act as inhibitors of cathepsin C (Pawelczap et al. 1998) • Herbicidal activity (Sasaki et al. 1996) • Cytostatic activity against KB cell line (contaminant of Hela cells) (Dus et al. 1984)
10	5-Amino-2-phenylthiazole-4-carbaldehyde	$C_{10}H_8N_2OS$		• Antibacterial activity against *Staphylococcus epidermidis* (Bondock et al. 2013), *Pseudomonas aeruginosa* and *Bacillus anthracis* (Chen et al. 2012), *Staphylococcus aureus* MRSA, *Escherichia coli* (Sadek and Fahelelbom 2011) • Antifungal activity against *Geotricum candidum* (Bondock et al.2013), *Aspergillus niger* (Sadek and Fahelelbom 2011) • Anti-viral activity against *Norovirus* (Rademacher et al. 2011), flavi-virus activity (Mayhoub et al. 2011), retroviruses (Hanauske-Abel et al. 2005) • Used for treatment of cancer and related hyperproliferative disorders (Uesugi et al. 2013) • Anticancer activity against prostate cancer cells (Lack et al. 2011), colon cancer cells (Ontoria et al. 2009) • Used for the treatment of metabolic disorders, e.g., diabetes and obesity (Uesugi et al. 2013)
11	1-Methyl-[14-(13)*C*]-9,12-methanobenzo[h]pyridazino[1,2-b]phthalazine-7,14-dione	$C_{18}H_{14}N_2O_2$		• Act as glycogen synthase kinase 3 beta inhibitors (Alisi et al. 2013) • Act as cyclin-dependent kinase inhibitors (Raffa et al. 2009) • Act as tyrosine kinase inhibitors (Jansen et al. 2005) • Analgesic activity (Alisi et al. 2010) • Useful in the treatment of digestive tract disorders (Suzuki et al. 2000) • Useful as antiemetics (Kon et al. 1991) • Antiarrhythmic activity (Kane and Levine 1981)
12	5-Butyl-3-phenyltetrahydrofuran-2-one	$C_{14}H_{18}O_2$		• Antibacterial activity against *Bacillus cereus*, *Staphylococcus aureus*, *Listeria monocytogenes*, *Salmonella typhimurium* and *Escherichia coli* (Bajpai et al. 2014), *Bacillus subtilus*, *Pseudomonas aeruginosa* (Mehetre 2013) • Antitumor activity against A549 (adenocarcinomic human alveolar basal epithelial cells), CNE (nasopharyngeal epithelial), MCF-7(breast cancer cells), NCI-H460 (human lung cancer cells), HepG2 (hepatocellular carcinoma cells), and KB-3-1 cells (cervix carcinoma cells) (Su et al. 2013)
13	1,4-Dihydro-2,3-benzoxathin-3-oxide	$C_8H_8O_2S$		No biological activity reported

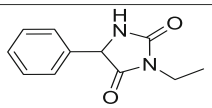
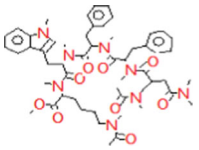
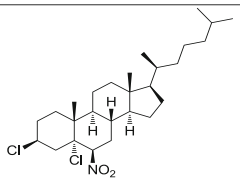
norovirus, and flavivirus, Avian influenza virus (H5N1). Moreover, compounds 1, 3, 4, 5, 6, 9, 10, 12, 14, 15, 16, 19, 23, 24, 25, 27, 28, 29, 31, and 35 were shown to possess anti-tumour activities against ovarian, hepatic, lung, prostate, nasopharyngeal, colon, skin, and vincristine-resistant nasopharyngeal, breast cancer, as well as in the treatment of metabolic disorders, inflammation, diabetes, neurodegenerative diseases, convulsing disease, platelet-related disease conditions.

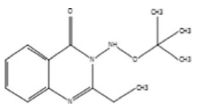
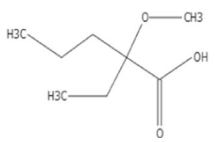
Table 2 (continued)

14	(*E*)-3-Benzylidene-5-methyldihydrofuran-2(3*H*)-one	$C_{12}H_{12}O_2$		• Antibacterial activity against *Bacillus subtilus*, *Staphyloccus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Salmonella typhi* (Mehetre et al. 2013), *Pseudomonas fluorescens* (Miyazawa et al. 2000) • Antifungal activity against *Candida albicans* (Husain et al. 2006) *Saccharomyces cerevisiae* and *Aspergillus niger* (Miyazawa et al. 2000) • Anti-avian influenza virus (H5N1) activity (Flefel et al. 2014) • Nematocidal activity against phytoparasitic nematodes (Gonzalez et al. 1995) • Anticancer activity against A549 : human lung cancer, NIH3T: fibroblast cancer, SK-OV-3 : human ovarian cancer (Bang et al. 2004), neoplastic hepatoma cells (HTC) (Schlewer et al. 1979) • Analgesic and anti-inflammatory properties with reduced gastrointestinal toxicity and lipid peroxidation (Alam et al. 2009)
15	1-[2-(Mercaptomethyl)phenyl]-3-methyl-2-butanol	$C_{12}H_{18}OS$		• Used in perfume compositions (Robvieux and Blanc 2015) • Act as TRPA1 (Transient receptor potential cation channel, member A1) activity inhibitor that can relieve irritation of the skin and mucous membranes (Kinoshita et al. 2015) • Pesticidal and/or acaricidal activity (Kim and Jung et al. 2013) • Antidiabetic activity against type 2 diabetes mellitus (Ley et al. 2011) • Antibacterial activity against *Corynebacterium xerosis*, *Staphylococcus epidermidis* and *Brevibacterium epidermidis* (Schmaus et al. 2006) • Antibacterial activity against Gram-positive bacteria including those responsible for body odor, blemished skin or bad breath (Reckziegel et al. 2005) • Anticancer activities against human ovarian carcinoma cells (HO-8910) and human hepatoma cells (Bel-7402) (Sun et al. 2005)
16	KARAKOLIDINE	$C_{22}H_{35}NO_5$		• Antioxidant activity • Antibacterial activity against *Bacillus subtilis* and *Staphyloccus aureus* (Yin et al. 2015) , *Salmonella typhimurium*, *Escherichia coli* (Sinam et al. 2012) *Bacillus mycoides*, *Proteus vulgaris*, • Antifungal activity against *Verticillium alboatrum*, *Colletrichurm lagenarium*, *Alternaria alternate* • Antiparasitic activity against *Phytophora infestans* (Yuan and Wang 2012) • Antiviral activity against tobacco mosaic virus (TMV) (Huang et al. 2013) • Used to treat cancer and postoperative pain (Yang et al. 2015) • Antiproliferative activity against lung (A549), prostate (DU145), nasopharyngeal (KB), and vincristine resistant nasopharyngeal (KB-VIN) cancer cell lines (Wada et al. 2015) ,human breast cancer cell resistant to tamoxifen MCF-7/TAM (Chen and Chen 2012) • Antidiabetic activity (Han et al. 2014)

Out of 19 compounds identified in haemolymph water lysates, 5 were shown to possess biological activities including Cpd2: 3,6-dimethylbenzofuran-4-ol, Cpd3: 6,7-dimethoxy-1-methoxymethyl-3,4-dihydroisoquinoline, Cpd5: 3-

Table 2 (continued)

17	3-Ethyl-5-phenylimidazolidine-2,4-dione	$C_{11}H_{12}N_2O_2$		• Ethotoin an anticonvulsant drug (Leal and Troupin 1977) • Bioactive hydantoin alkaloids from the Red Sea marine sponge *Hemimycale arabica* (Youssef et al.2015)
18	*N*2-Acetyl-*N*2,*N*4,*N*4-trimethyl-*L*-Asn-*N*-methyl-*L*-Phe-*N*-methyl-*L*-Phe-*N*,1-dimethyl-*L*-Trp-*N*6-acetyl-*N*2,*N*6-dimethyl-*L*-Lys-OMe	$C_{53}H_{72}N_8O_9$		• Act as myotropic peptide, from *Periplaneta americana* (Brown et al. 1975)
19	Cholestane,3,5-dichloro-6-nitro-(3beta,5alpha,6beta)	$C_{27}H_{45}C_{12}NO_2$		• A phyto component in the methanolic extract of *Oldenlandia umbellate* (De et al. 2013) • Improves left ventricular diastolic function (He and Xue 2014) • Involved in the treatment of first-episode schizophrenia (Wang and Jin 2014) • Antibacterial activity against *Bacillus cereus* (Sun et al. 2015) • Therapeutic effect for high uric acid disease and Alzheimer's disease (Yan and Xiao 2015) • Antitumor activity and inhibitory effect on thermal-induced protein denaturation (Rauf et al. 2015) • Lipid-lowering activity in HepG2 hepatocytes (Zhu et al. 2015)

Compounds identified from the methanol-extracted haemolymph				
20	2-Ethyl-3-*tert*-butoxyaminoquinazolin-4(3*H*)-one	$C_{14}H_{19}N_3O_2$		• Antifungal activity against (*Fusarium proliferatum, Aspergillus parasiticus, Aspergillus niger, Trichoderma reesei* (Karakaya, et.a1 2013), *Candida albicans* (Peter and Lucky 2014) • Antifungal activity against (*F. proliferatum*, *A. parasiticus*, *A. niger*, *T. reseii* (Karakaya, et.al 2013), *Candida albicans* (Peter and Lucky 2014) • Antiviral activity against HIV (Sanchez et al. 2013) • Antiparasitic activity against malaria and toxoplasmosis (Riscoe et al. 2011) • Anticonvulsant activity (Chikhale et al. 2012) • Antihyperlipidemic activities (Ganguli et al. 2012)
21	2-Ethyl-2-methoxypentanoic acid	$C_8H_{16}O_3$		• Formed as a part of product in methionine salvage pathway (Dai et al. 2001) • Act as germination inhibitors (Fu et al. 2015) • Used to retain antigenic properties of glutamate dehydrogenase (Bettsworth and Martinez 2015)

phthalimidopropionaldehyde, Cpd17: 3-ethyl-5-phenylimidazolidine-2,4-dione, and Cpd19: cholestane,3,5-dichloro-6-nitro-(3beta, 5alpha, 6beta) (Table 2). For homologous searches, all compounds except Cpd7: *N*-benzyl (4-phenyl-3-propyl-1-oxaspiri[4,5]dec-3-enylidene) amine possess reported biological activities (Table 2). For methanol-extracted haemolymph lysates, 18 compounds were identified and 5 of them were shown to possess biological activities including Cpd21: 2-ethyl-2-methoxypentanoic acid, Cpd23: 7-(isopropoxy)-2,2,5-trimethylchromene, Cpd29: 5-

Table 2 (continued)

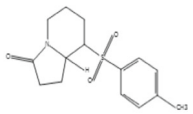
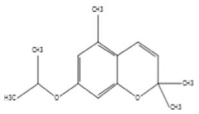
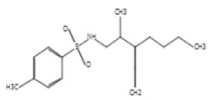
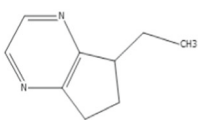
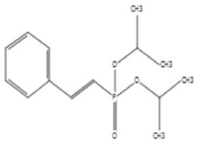
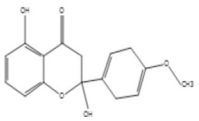
22	(8*R*,8a*S*)-8-[(*p*-Toluenesulfonyl)perhydro-3-indolizidinone	$C_{15}H_{19}NO_3S$		• Pesticidal activities (Schnatterer et al. 2009)
23	7-(Isopropoxy)-2,2,5-trimethylchromene	$C_{15}H_{20}O_2$		• Antiallatal activity against *Caenorhabditis remanei* (nematode) (Fodor et al. 1989) • Leishmanicidal activity (Lima et al. 2015) • Antibacterial activity against *Bacillus subtilis* and *Escherichia coli* (George et al. 2015), *Bacillus megaterium*, (Hussain et al. 2014), *Staphyloccus aureus, Enterococcus faecalis,* and *Micrococcus lysodeikticus* (Mihailovic et al. 2011) • Antialgal activities against *Chlorella fusca* (Hussain et al. 2014) • Antifungal activity against *Penicillium* sp., *Candida albicans*, *Aspergillus glaucus* and *Trichoderma viride,* (Mihailovic et al. 2011), *Microbotryum violaceum* (Hussain et al. 2014) • Anticancer activity against breast, prostate, lung, colon, skin cancer cells (Di Marzo et al. 2008), Dalton's lymphoma ascites cells (George et al. 2015) • Used in the treatment of neurodegenerative diseases, • Anti-inflammatory and antiviral activities (Oberbauer et al. 2013) • Used in therapy for diabetes and atherosclerosis (Korthout 2012)
24	*N*-(2-Methyl-3-butyl-3,4-pentadienyl)-*p*-toluenesulfonamide	$C_{17}H_{25}NO_2S$		• Anticancer activity against prostate cancer cells (Arora and Sawyers 2015) , breast cancer cells (Ren et al. 2015) • Alkaline phosphatase inhibitors (al-Rashida et al. 2015) • Used to treat Alzheimer's disease (Aziz-ur-Rehman et al. 2014) • Antifungal activity against yeast, *Fusarium solani*, *Fusarium moniliforme*, *Penicillium expansum* and *Cladosporium cladosporioides* (Philip Kodi 2014) • Antileishmanial activity (Tiuman et al. 2014) • Antiviral activity against HIV 1 (Bruening et al. 2014) • Antidiabetic activity (Frederico et al. 2013) • Antigenotoxic activity in hypothyroidism (Celikler et al. 2014) • Carbonic anhydrase IX and XII inhibitors (Rosatelli et al. 2014) • Antimycobacterial activity (Villemagne et al. 2014) • Sensitizes Gram-positive bacterial pathogens to beta-lactam antibiotics (Rajagopal et al. 2013) • Antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* (Ajani et al. 2013)
25	5-Ethyl-6,7-dihydro-5*H*-cyclopentapyrazine	$C_9H_{12}N_2$		• Anticancer activity (Gyorfi et al. 2013) • Used to treat platelet-related disease conditions, thrombotic events, thrombosis, cardiovascular diseases, myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism, and respiratory disease conditions such as cystic fibrosis, bronchial asthma, and obstructive airway diseases, also useful as a male contraceptive (Fung et al. 2008)

Table 2 (continued)

26	Diisopropyl 2-phenylethenylphosphonate	$C_{14}H_{21}O_3P$		• Antioxidant activity, • Antibacterial activity against *Bacillus subtilis*, *Pasturella multicoda*, *Escherichia coli*, *Staphylococcus aureus* (Jahangir et al. 2013) • Act as inhibitors of relaxase activity and conjugative DNA transfer (Lujan et al. 2007) • Used for treating tissue ischemia (Tracey et al. 2000) • Growth-regulating and herbicidal activities (Vassilev 1995) • Anticholesteremic activity (Harada et al. 1996) • Anti-inflammatory and anti-arthritic agents (Johnson 1996) • Act as virucides against Herpes simplex virus (Peyman et al. 1991) • Antifungal activity against *Pyricularia oryzae*, *Helminthosporium oryzae*, *Rhizoctonia bataticola*, *Alternata alternata*, *Pythium aphanidermatum*, *Fusarium solani*, and *Sclerotium folfsi* (Roy and Taneja 1989), *Aspergillus niger* and *Alternia fusarium* (Jahangir et al. 2013)
27	2,5-Dihydroxy-4′-methoxy-flavanone	$C_{16}H_{14}O_5$		• Antioxidant activity, enhance lipid metabolism, anticancer activity against hepatic carcinoma (Chung et al. 2013) (Yen et al. 2013) • Act as stimulants to enhance the expression of NKG2D ligands (Kim and Lee 2015)

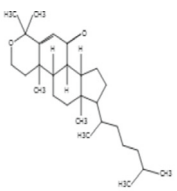
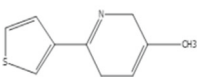
28	4,4-Dimethyl-3-oxacholest-5-en-7-one	$C_{28}H_{46}O_2$		• Improves left ventricular diastolic function (He and Xue 2014) • Involved in the treatment of first-episode schizophrenia (Wang and Jin 2014) • Antibacterial activity against *Bacillus cereus* (Sun et al. 2015) • Therapeutic effect for high uric acid disease and Alzheimer's disease (Yan and Xiao 2015) • Antitumor activity and inhibitory effect on thermal-induced protein denaturation (Rauf et al. 2015) • Lipid-lowering activity in HepG2 hepatocytes.(Zhu et al. 2015)
29	5-Methyl-2-(thiophen-2-yl)pyridine	$C_{10}H_9NS$		• Act as 17-beta hydroxysteroid dehydrogenase-II inhibitors useful for treating cancer, hypercholesterolemia, non-insulin-dependent diabetes mellitus, osteopenia, etc. (Wood et al. 2002) • Antibacterial activity against *Mycobacterium tuberculosis* (Verbitskiy et al. 2015) • Anti-HIV-1 activity (Ganguly and Murugesan 2011) • Act as inhibitors of influenza endonuclease activity (Bauman et al. 2014) • Anticancer activity against MCF-7 (breast cancer), H-460 (lung cancer), and SF-268 (glioblastoma) cells (Kouznetsov et al. 2012) • Antifungal activity against dermatophytes (Gomez et al. 2008), *Sphaerotheca fuliginea* (Tamao et al. 1986) • Antiparasitic activity against *Leishmania chagasi* and *Trypanosoma cruzi* (Kouznetsov et al. 2007) • Used for treating or preventing a disorder of lipid metabolism (pain, diabetes, a vascular condition, demyelination, or

Table 2 (continued)

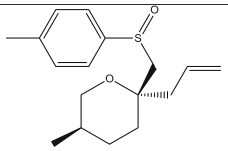
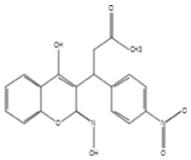
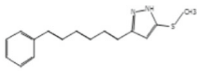
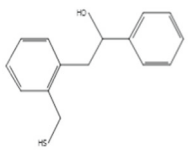
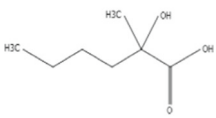
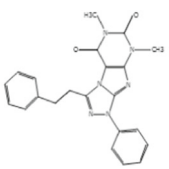
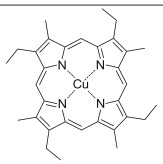
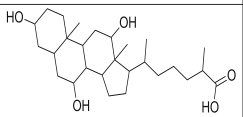
				nonalcoholic fatty liver disease) (Aslanian et al. 2008)
30	(2*S*,5*R*,*R*s)-2-Allyl-5-methyl-2-(*p*-tolylsulfinylmethyl)tetrahydropyran	$C_{17}H_{22}O_2S$		• Antimalarial activity against *Plasmodium falciparum* (Bachi et al. 1998)
31	4-Hydroxy-3-[1′-(*p*-nitrophenyl)-3′-oxobutyl]-2*H*-[1]benzopyran-2-one - oxime	$C_{19}H_{16}N_2O_6$		• Used for treating and/or preventing a cardiovascular event (Nidorf 2015) • Anticoagulant activity (Weitz 2014) • Used for modulating ferroptosis and treatment of excitotoxic disorders (Stockwell et al. 2015) • Used for treating serine protease-related disease (Wei et al. 2015) • Useful for treating hyperproliferative disorders, e.g, cancer (Hamdy et al. 2015) • Used for the treatment and prevention of thromboembolic disease (Antoniou Sotiris 2015) • Antiviral activity against Herpes virus infection (Yuan and Xu 2015) • Used for treatment of pulmonary hypertension (Makowski et al. 2015) • Used for treating neurodegenerative disorders or cognitive deficits (Hung 2015)
32	5-Methylthio-3-(6-phenyl-1,3,5-hexatrienyl)pyrazole	$C_{16}H_{16}N_2S$		• Used for treating and preventing demyelinating diseases including multiple sclerosis, and traumatic injury (Yuzhakov 2011) • Antileishmanial activity (Sunduru et al. 2006)
33	2-[2-(Mercaptomethyl)phenyl]-1-phenylylethanol	$C_{15}H_{16}OS$		• Wound-healing property (Dente E.L. 2014) • Antibacterial activity against *Enterococcus faecium* and *Enterococcus faecalis* (Orabi et al. 2014)
34	2-Hydroxy-2-methylhexanoic acid	$C_7H_{14}O_3$		• Antisecretory activity (Guzzi et al. 1986) • Used in food preservation (Kosakai and Hirose 2015)
35	1,3-Dimethyl-2,4-dioxo-6-(2-phenylethenyl)-8-phenyl-1,2,3,4-tetrahydro[1.2.4...	$C_{22}H_{18}N_6O_2$		• Act as osteoblast activator used for the treatment of osteoporosis (Liou et al. 2015) • Used for the treatment of Parkinson's disease (Kasai 2014) • Act as aldehyde dehydrogenase 1A1 inhibitors used to treat diseases such as cancer, Parkinson's disease, obesity, and cataracts (Morgan and Hurley 2015) • Act as inhibitors of pre-mRNA splicing (Pawellek et al. 2014)

Table 2 (continued)

				• Act as ROS kinase inhibitor (Grueneberg et al. 2014)
36	2,7,12,17-Tetraethyl-3,8,13,18-tetramethyl-21*H*,23*H*-porphine copper	$C_{32}H_{36}N_4C_u$		• Used in photodynamic therapy (Bonnett et al. 2002) • Involved in photosynthesis reactions (Engelsma et al. 1962)
37	2-Methyl-6-(3,7,12-trihydroxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)heptanoic acid	$C_{27}H_{46}O_5$		• Bile acid derivatives (Li et al. 2009) • Broad-spectrum antibacterial activity against Gram-positive and Gram-negative bacteria (Savage and Li 2000)

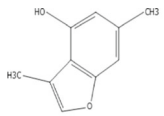
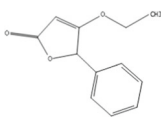
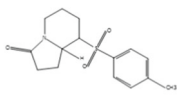
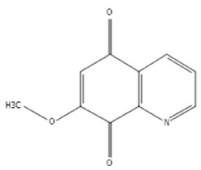
methyl-2-(thiophen-2-yl)pyridine, Cpd34: 2-hydroxy-2-methylhexanoic acid, and Cpd36: 2,7,12,17-tetraethyl-3,8,13,18-tetramethyl-21*H*,23*H*-porphine copper (Table 2). The remaining compounds have homologous structures, reported in the literature with various biological activities (Table 2).

When compared with compounds extracted from muscle lysates with no antibacterial activity, out of a total of 20 compounds identified from cockroach brain lysates, 5 of them were found to be common in muscle lysates and brain lysates, indicating that possibly these were the compounds which are not responsible for the tested biological activities. However, the remaining 15 compounds were absent in the muscle lysates and these included, i.e., Cpd 2: (3*S*,6*S*,6a*S*,8*S*,10*S*,11a*R*,12*R*,12a*S*,13*S*)-1-ethyl-8,10,13-trimethoxy-3-(methoxymethyl)tetradecahydro-1*H*-3,6a,12-(epiethane[1,1,2]triyl)-7,9-methanonaphtho[2,3-b]azocine-6,11a,12-triol, Cpd 3: 3,6-dimethylbenzofuran-4(5*H*)-ol, Cpd 4: 3-((6-methoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)phenol, Cpd 5: 4-benzyl-4,5-dihydroisoxazole, Cpd6: 6a-hydroxy-4-methoxy-6a,6b,7,8,9,10,10a,10b-octahydro-6*H*-benzo[3,4]cyclobuta[1,2-c]chromen-6-one, Cpd 9: 2,2,4,7a-tetramethyl-6-(phenylsulfonyl)-3a,4,5,7a-tetrahydrobenzo[d][1,3]dioxole, Cpd 10: 3-(2′-phenylethyl)-2,3-dihydro-6-phenyl-2,4-dioxo-4*H*-1,3-thiazine, Cpd 11: 2-amino-3,6-dimethylimidazo[4,5-b]pyridine, Cpd 12: 3,9-dimethoxy-12,13-dihydro-5*H*-indolo[2,3-a]pyrrolo[3,4-c]carbazole-6-benzyl, Cpd 13: (*S*,*S*)-1,1-bis(ethoxycarbonyl)-2,2-bis-*p*-tolylsulfinyl-1-ethanol, Cpd 14: 1-methyl-[14-(13)*C*]-9,12-methanobenzo[h]pyridazino[1,2-b]phthalazine-7,14-dione, Cpd 15: allyl(2-nitro-1-phenylethyl)sulfane, Cpd 17: KARAKOLIDINE, Cpd 18: 2-isopropoxy-5-phenyl-1,3,4-oxadiazole, and Cpd 19: 1-(4-hydroxybenzyl)-3,4-dihydroisoquinoline-6,7-diol. However, compounds 1, 7, 8, 16, and 20 are common in muscles and indicated that these might not possess potent biological activities against MRSA and neuropathogenic *E.coli* K1.

Discussion

Infectious diseases remain one of the leading causes of death worldwide (WHO 2002). Antibiotic-resistant bacteria continue to rise at an alarming rate (Nordmann et al. 2007; Devasahayam et al. 2010). Most currently available antibacterial drugs were discovered between 1940 and 1980 using traditional approaches, which have now become saturated. Most of the newer antibacterial drugs have arisen from chemical modification of existing antibiotic structures. Efforts to create new drugs using existing antibiotic scaffolds are challenging because these semi-synthetic derivatives are often not able to penetrate the bacterial cell wall adequately. More innovative, non-traditional strategies are therefore required in order to provide the urgently needed next generation of antimicrobial drugs. Insects represent a plentiful and untapped potential source of new antimicrobial drugs prompting us to investigate the antibacterial activity of their various tissues. The tissues of living multicellular organisms are potentially a rich source of nutrients for microbes, and effective strategies have to be developed by the host organism to prevent microbial digestion. Cockroach lysates prepared from fat body and muscle tissue showed no antibacterial activity against bacteria tested in this study. This is in contrast to previous studies, which showed that insect such as *Drosophila* fat body produce seven distinct antimicrobial peptides, which are then secreted into the haemolymph to participate in a systemic response to septic injuries (Clynen and Schoots 2009; Metz-Boutigue et al. 2003; Amiche et al. 1999; Salzet 2001). However, this response is mounted as a result of microbial challenge. Since cockroaches used in our study were not immune-stimulated, prior to dissection, this could explain why no antibacterial activity was seen in fat and muscle tissues, while limited activity was observed in the haemolymph. Future work will involve immune stimulation of the cockroach, prior to dissection, by injecting heat-killed bacteria into the haemocoel to

Table 3 Compounds identified from the cockroach muscle lysates

No.	Compound	Formula	Structure	Reported activity
Compounds identified from the water-soluble muscle lysates				
1	3,6-Dimethylbenzofuran-4-ol	$C_{10}H_{10}O_2$		• Herbicidal activity (Zhao et al. 2014) • Inhibition of LPS-induced muscle atrophy (Shiota et al. 2015) • Agonists for enhancing the olfactory effect (Huchel et al. 2015) • Antiplatelet aggregation activities (Tang et al. 2015) • Antiviral agent against Herpes virus (Yuan and Xu 2015)
2	4-Ethoxy-5-phenyl-2,5-dihydrofuran-2-one	$C_{12}H_{12}O_3$		• Anti-*Helicobacter pylori*, antioxidant and anti-urease activities thus acting as antigastric ulcer agent (Wang et al. 2015) • Anticancer activity • Antiviral activity against influenza A virus subtype (H3N2) and swine flu (H1N1) viruses • Antibacterial activity against *Mycobacterium tuberculosis* (Sun et al. 2014) • Antiepileptic activity (Liu et al. 2013) • Analgesic activity (Kormann et al. 2012) • Anti-inflammatory and anticancer property (De Simone et al. 2010)
3	(8*R*,8a*S*)-8-[(*p*-Toluenesulfonyl)perhydro-3-indolizidinone	$C_{15}H_{19}NO_3S$		• Pesticidal activities (Schnatterer et al. 2009)
4	7-Methoxy-5,8-quinolinequinone	$C_{10}H_7NO_3$		• Antiviral activity against human immunodeficiency virus and avian myeloblastosis virus (Take et al. 1989), pox virus infections (Huegin Ambros 2012), West Nile virus (Puig-Basagoiti et al. 2009) • Used for treating neurodegenerative diseases (Chen 2013) • Antitrypanosomal activity (Ellendorff et al. 2015) • Antibacterial activity against *Bacillus cereus, Listeria monocytogenes, Salmonella enterica, Shigella sonnei, Staphylococcus epidermidis Staphylococcus intermedius* (Yang and Lee 2015), *Escherichia coli, Staphylococcus aureus* (Naseem and Farrukh 2015) and *Bacillus subtilis* • Antifungal activity against *Candida albicans* (Chansukh et al. 2014), growth inhibitory activity against forest herbs and ectomycorrhiza fungi (Ruckli et al. 2014), dermatophyte fungi • Anticancer activity against cervical cancer (Braud et al. 2008), murine hepatome MH22a cells (Nemeikaite-Ceniene et al. 2015) • Cytotoxic activity against primary mice splenocytes (Miliukiene et al. 2014),

investigate if an inducible antibacterial effect can be detected. In contrast, cockroach brain lysates exhibited high antibacterial activity against bacteria tested in the present study. Furthermore, high antibacterial activity was observed

Table 3 (continued)

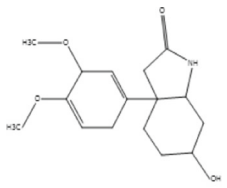
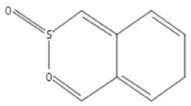
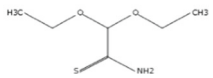
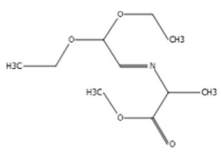
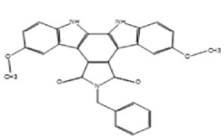
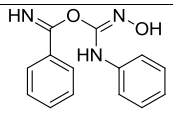
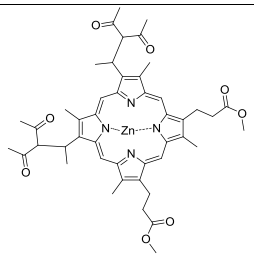
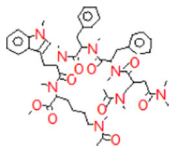
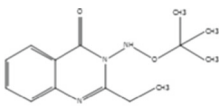
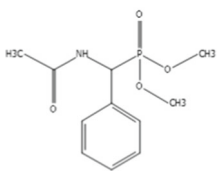
				• Useful in the treatment and control of diabetes, insulin resistance and hyperglycemia (Wilcke et al. 2008)
5	2-Oxo-3a-[3,4-(dimethoxy)phenyl]-6-hydroxy-2,3,3a,4,5,6,7,7a-octahydroindole	$C_{16}H_{21}NO_4$		• Act as phosphodiesterase inhibitors useful to prevent the transmission of malaria parasites from humans to mosquitoes (Ramdani et al. 2015) • Anti-inflammatory activity (Bauquier et al. 2015) • Antiviral activity against influenza viral infections (Altmeyer et al. 2010) • Used for the treatment of cancer (Piazza 2015) • Anticancer activity against hepatocellular carcinoma (Sun et al. 2014), HCT-15 human colon cancer cells (Mareddy et al. 2013)
6	1,4-Dihydro-2,3-benzoxathin-3-oxide	$C_8H_8O_2S$		• No biological activity reported
7	2,2-Diethoxythioacetamide	$C_6H_{13}NO_2S$		• Act as p38MAP kinase and/or TNF-alpha production inhibitor (Ohkawa et al. 2002), integrase inhibiting antiviral activity (Kiyama et al. 2003) • Used to treat disorders of tryptophan-serotonin metabolism (Bur et al. 2015), used for treating obesity (Kasai et al. 2013), possess anti-inflammatory, and anticancer activity and also used to treat disease associated with urinary system (Kawaminami et al. 2012) • Antiproliferative activity (Cheng et al. 2011) • Act as HIV protease inhibitors (Flentge et al. 2011), used for the treatment of atherosclerosis, thrombosis, coronary artery disease, hypertension, and cardiac insufficiency (Strobel et al. 2008) • Antibacterial activity against methicillin-sensitive and methicillin–resistant *Staphyloccus aureus* and antifungal activity against *Aspergillus niger* and *Candida albicans* (Anthony et al. 2007)
8	Methyl *N*-2,2-diethoxyethylidenealaninate	$C_{10}H_{19}NO_4$		• Used in insecticidal compositions (Groves et al. 2012)
9	6 Benzyl-3,9-dimethoxy-12,13-dihydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione	$C_{29}H_{21}N_3O_4$		• Anti-inflammatory and analgesic activities (Alanazi et al. 2015) • TBK1 inhibitors (Richters et al. 2014)

Table 3 (continued)

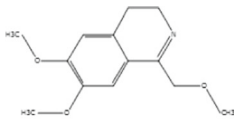
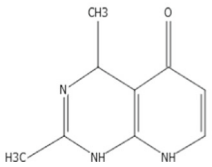
10	Benzimidic (*E*)-*N*′-hydroxy-*N*-phenylcarbamimidic anhydride	$C_{14}H_{13}N_3O_2$		• Used for prophylaxis of vision, eating or cardiovascular disorders, and act as anxiolytic and antiemetic agents (Sit and Kai, 2003)
11	Dimethyl 3,8-di(2,2-diacetyl-1-methylethyl)-2,7,12,18-tetramethyl-21*H*,23*H*-porphine-13,17-dipropionate zinc(II)	$C_{46}H_{52}N_4O_8Zn$		• Photosensitizers of the porphyrin and phthalocyanine series for Photodynamic Therapy (Bonnett 1995)
12	*N*2-Acetyl-*N*2,*N*4,*N*4-trimethyl-*L*-Asn-*N*-methyl-*L*-Phe-*N*-methyl-*L*-Phe-*N*,1-dimethyl-*L*-Trp-*N*6-acetyl-*N*2,*N*6-dimethyl-*L*-Lys-OMe	$C_{53}H_{72}N_8O_9$		• Isolation of proctolin, a myotropic peptide, from *Periplaneta americana* (Brown and Starratt 1975)

Compounds identified from the methanol-extracted muscle lysates				
13.	2-Ethyl-3-*tert*-butoxyaminoquinazolin-4(3*H*)-one	$C_{14}H_{19}N_3O_2$		• Antibacterial activity against Gram-positive bacteria such as *Staphylococcus aureus, Bacillus* species, and *Enterococcus feacalis*; Gram-negative bacteria such as *Escherichia coli, Klebsiella pneumonia* and *Pseudomonas aeruginosa* • Antifungal activity against fungi *Candida albicans* (Peter and Lucky 2014), filamentous fungi (*Fusarium proliferatum*, *Aspergillus parasiticus, Aspergillus niger*, *Trichoderma reesei* (Karakaya et al. 2013) • Antiviral activity against HIV (Sanchez et al. 2013) • Antiparasitic activity against malaria and toxoplasmosis (Riscoe et al. 2011) • Anticonvulsant activity (Chikhale et al. 2012) • Antihyperlipidemic activities (Ganguli et al. 2012)
14.	Dimethyl .alpha.-(*N*-acetylamino)benzylphosphonate	$C_{11}H_{16}NO_4P$		• Binding potency with Src SH2 protein (Deprez et al. 2002), act as inhibitors of cathepsin C (Pawelczap et al. 1998) • Herbicidal activity (Sasaki et al. 1996) • Cytostatic activity against KB cells (Dus et al. 1984)

at micro-level, showing high potency of the active component(s), which is presumably present at even lower amounts. Moreover, antibacterial molecule(s) were less than 10 kDa in molecular mass, and non-toxic to human cells.

Using LC-MS, spectra was acquired from brain, haemolymph and muscles lysates. Out of hundreds of compounds, only few homologous compounds were identified (Tables 1, 2, and 3). The identified compounds possess characteristics in their structure like arrangement of specific functional groups and presence of active components, which make them biologically significant for their potential therapeutic value against various infectious and non-infectious diseases. For example, several compounds in the brain lysates and haemolymph possess the isoquinoline group, chromene derivatives, thiazine groups, imidazoles, and pyrrole-containing analogs, and are biologically active against broad-spectrum microorganisms, such as bacteria, fungi, viruses, and parasites, and known to exhibit anti-tumour and

Table 3 (continued)

15.	6,7-Dimethoxy-1-methoxymethyl-3,4-dihydroisoquinoline	$C_{13}H_{17}NO_3$		• Marine derived lamellarin natural products (Tangdenpaisal et al. 2015) • Quorum sensing inhibitors of *Pseudomonas aeruginosa* (Givskov et al. 2014) • Antibacterial activity against *Escherichia coli* O157:H7 and *Listeria monocytogenes* (Seo et al. 2012), *Klebsiella pneumonia* (Mharti et al. 2011) • Antifungal activity against *Candida albicans* (Orhan et al. 2007), *Curvularia lunata* (Brunskole et al. 2011) • Antiviral activity against Parainfluenza virus (Orhan et al. 2007) • Anti diabetic activity (Yang et al. 2014) • Used for treating degenerative and ischemic disorders (Mootha et al. 2010) • Anticancer activity against human oral squamous cell carcinoma cells (Hatano et al. 2009), murine mammary cancer DA3 cells (Alvarez et al. 2009) , hepatic carcinoma cells Huh7 (Kumar et al. 2015)
16.	2,4-Dimethylpyrido[2,3-d]pyrimidin-5-one	$C_9H_9N_3O$		• Used for treating or preventing cancer e.g. human leukemic lymphoblast carcinoma or a neuropathic disorder, inducing a chemoprotective phase II enzyme, DNA, or protein synthesis, enhancing the immune system, treating inflammation (Danishefsky et al. 2014) • Used to treat IDO-mediated immunosuppression and immunosuppression associated with infectious

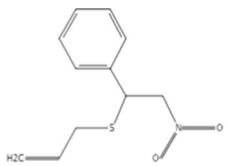
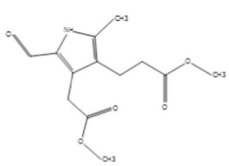
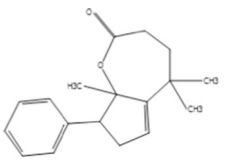
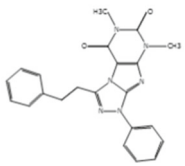
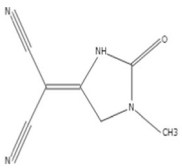
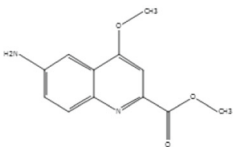
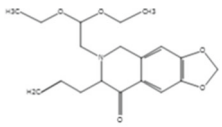
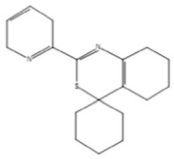
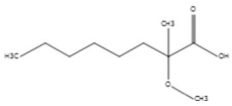
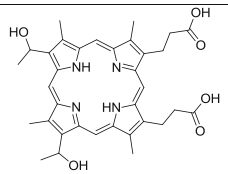
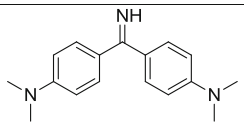
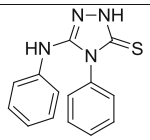
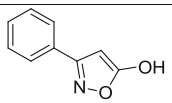
				diseases, including HIV-I., also used for cancer treatment and tumor-specific immunosuppression (Mautino et al. 2009) • Used as anti-infectives (Levy et al. 2005) • Act as angiotensin II antagonists hence used to treat hypertension, diabetic nephropathy, congestive heart failure (Ellingboe et al. 1992) • Antibacterial activity against various Gram-negative bacteria and *Staphylococci* (Desplaces et al. 1986), *Escherichia coli* and *Staphylococci aureus* (Minami, et al. 1971)
17.	2-(Allylthio)-1-nitro-2-phenylethane $$ [1-(allylsulfanyl)-2-nitroethyl]benzene	$C_{11}H_{13}NO_2S$		• Used to treat metabolic disorders (Pellecchia 2008) • Antibacterial activity against *Helicobacter pylori* (Gokce et al. 2004), *Escherichia coli* • Antifungal activities against *Candida* species and dermatophytes (Bilich, et al. 1970) • Used for the treatment of seborrhea (Kalopissis and Manoussos 1976)
18.	Methyl 5-formyl-4-methoxycarbonylmethyl-2-methylpyrrole-3-propionate	$C_{13}H_{17}NO_5$		• Anti-inflammatory activity (Indumathi et al. 2015) • Act as inhibitors against yeast alpha-glucosidase (Niaz et al. 2015) • Antibacterial activity against ESBL isolates of *Klebsiella pneumonia* (Murthy et al. 2012) *Escherichia coli*, *Pseudomonas aeruginosa* • Antifungal activity against *Candida albicans* • Anticancer activities against Hep G2 (liver), Hela

Table 3 (continued)

				(cervical), MCF-7 (breast cancer) cells (Idhayadhulla et al. 2013) • Act as non-nucleoside HIV-1 RT inhibitors (Antonucci et al. 1995) • Used for treating liver diseases including necrosis, fatty hepatosis, and viral hepatitis (Giller et al. 1976)
19.	1-Oxa-2-oxo-5,5,8a-trimethyl-8-phenylbicyclo[3.5.0(5a,8a)]dec-5(4a)-ene	$C_{18}H_{22}O_2$		• Antibacterial activity against *Staphylococcus aureus* (Emran et al. 2015) • Anticyanobacterial activity against *Microcystis aeruginosa* (Wang et al. 2015) • Antifungal activity against phytopathogenic fungi (Ma et al. 2015) • Melanin inhibiting and skin-whitening activity (Okabe 2015)
20.	(*E*)-6,8-Dimethyl-1-phenyl-3-styryl-1H-[1,2,4]triazolo[3,4-f]purine-5,7(6*H*,8*H*)-dione	$C_{22}H_{18}N_6O_2$		• Used for the treatment of osteoporosis (Liou et al. 2015) • Used for the treatment of Parkinson's disease (Kasai 2014) • Used to treat diseases such as cancer, Parkinson's disease, obesity, and cataracts (Morgan and Hurley 2015) • Act as inhibitors of pre-mRNA splicing (Pawellek et al. 2014) • Act as ROS kinase inhibitor (Grueneberg et al. 2014)
21.	(Dicyanomethylene) imidazolidinone	$C_7H_6N_4O$		• Antiproliferative activity against various cell lines including leukemia, melanoma LOX IMVI, non-small cell lung NCI-H522, renal 786-0, CAKI-1, SN12C, UO-31, breast MCF7, MDA-MB-435, T-47D , melanoma SK-MEL-5 cancer cell lines (Cesarini et al. 2009)
22.	Methyl 6-amino-4-methoxy-2-quinolinecarboxylate	$C_{12}H_{12}N_2O_3$		• Antibacterial activity against *Clostridium perfringens* and *Chryseobacterium meningosepticum* (Zheng et al. 2014), *Escherichia coli* (De Troconis et al. 2000) • Antimycobacterial activity (Parmar et al. 2012) • Anti-apoptotic activity against A549 (lung carcinoma) and HeLa (cervical carcinoma) tumor cell lines (Zheng et al. 2014) • Antihyperglycemic activity (Moinet et al. 2005) • Antimalarial activity (Basak et al. 2010) • Used to treat disorders of white blood cells, such as inflammatory and autoimmune diseases, including rheumatism, as well as used as anticoagulant, antivenin, analgesic and for antithrombotic purposes (Correa et al. 2008) • Antiviral activity against against orthopoxvirus (Zemtsova et al. 2011), HIV-1 integrase (Burke et al. 1995)

anti-diabetic properties (Ali and El-Kazak 2010; Iwasa et al. 2001; Khafagy et al. 2002; Vennerstrom et al. 1995; Ozkay et al. 2010; Facchinetti et al. 2012; Bhardwaj et al. 2015). Similarly, sulfonamides and furanones are found to possess active components to treat many tumours, possess broad-spectrum antimicrobial activities, and anti-inflammatory and

Table 3 (continued)

23.	7-Allyl-6-(2,2-diethoxyethyl)-6,7-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-8(5H)-one	$C_{19}H_{25}NO_5$		• No biological activity reported
24.	2-(3,6-Dihydropyridin-2-yl)-5,6,7,8-tetrahydrospiro[benzo[d][1,3]thiazine-4,1'-cyclohexane]	$C_{18}H_{22}N_2S$		• Useful for treating prostate and breast cancer (Bierer et al. 2002) • Useful for treatment of digestive tract and mental disorders (Iwaoka et al. 1998)
25.	2-Methoxy-2-methyloctanoic acid	$C_{10}H_{20}O_3$		• Antibacterial activity against biofilms in combination (Salas et al. 2014)
26.	Hematoporphyrin	$C_{34}H_{38}NO_{46}$		• Studies upon the physiological action of hematoporphyrin. (Smetana 1928) • It is used in photodynamic therapy (Bonnett and Martınez 2001)
27.	4,4′-(Iminomethylene)bis(*N*,*N*-dimethylaniline)	$C_{17}H_{21}N_3$		• Act as an aniline dye used as a disinfectant and an antiseptic agent. Used to stain *Mycobacterium tuberculosis* (Arrowood and Sterling 1989) • Act as a toxic dye against wood-destroying fungi (Weaver et al. 1959)
28.	4-Phenyl-3-(phenylamino)-1*H*-1,2,4-triazole-5(4*H*)-thione	$C_{14}H_{12}N_4S$		• Antibacterial activity against *Escherichia coli, Pseudomonas aeruginosa* and *Bacillus cereus* (Ghattas et al. 2012)
29.	Thiomorpholine	C_4H_9NS		• Degradtion by *Mycobacterium aurum* (Combourieu et al. 2000) • Antibacterial activity against *Staphylococcus aureus, Haemophilus influenzae, Moraxalla catarrhalis* (Singh et al. 2003)
30.	3-Phenylisoxazol-5-ol	$C_9H_7NO_2$		• Antioxidant and antibacterial activities (Musad et al. 2011) • Anticonvulsant activity (Eddington et al. 2002)

analgesic properties (Ozbek et al. 2007; He et al. 2015; Rappai et al. 2009). Other compounds contained flavanones. Flavanones are naturally occurring compounds present in fruits and vegetables and have considerable therapeutic potential in platelet inhibition and antibacterial, anti-tumour, and antioxidant properties (Cushnie and Lamb 2005).

Notably, the majority of compounds in this study remain unidentified and/or whose biological activities have not yet been reported. It is hoped that chemical identities of all compounds and in vitro testing for their antibacterial, anti-tumour, antioxidant, and anti-diabetic properties will determine their value for potential clinical applications. Although a detailed characterization of all compounds is needed, the present study suggests the potential significance of these naturally occurring compounds derived from novel sources, i.e., species living in challenging environments, can be a useful resource. To this end, insects such as cockroaches are potentially an important source of therapeutic molecules, as they share several environmental niches with humans and animals. This is evident from our findings that cockroach brain lysates possess potent antibacterial properties. Compared to vertebrates, the insects' nervous system is far more de-centralized. Behavior such as feeding, movement, and mating is controlled by segmental ganglia running the length of the insects' body, instead of the brain. In some cases, the brain may stimulate or inhibit activity in the segmental ganglia. The neuronal cells of the brain synthesize neurotransmitter and neuropeptide chemical messengers to communicate with each other and with peripheral organs (Clynen and Schoots 2009; Metz-Boutigue et al. 2003; Amiche et al. 1999; Salzet 2001). These chemical messengers represent the highest physiological hierarchy in animals controlling many crucial biological processes. It is therefore essential to the survival of the organism that this system is constantly protected against challenge from pathogens or noxious agents. Constitutive expression of antibacterial factors could provide this protection as a first line of defense before an inducible response has had time to manifest. In addition to metabolites that may possess antibacterial activity and/or inflammatory mediators, large neuropeptide precursor molecules such as proenkephalin and prodermaseptin are known to be processed into smaller peptides, some of which have antibacterial activity (Clynen and Schoots 2009; Metz-Boutigue et al. 2003). The antimicrobial peptides have diverse amino acid sequences and structures, but most are small amphipathic, cationic peptides that exert their antimicrobial effect by disrupting the structural integrity of cell membranes.

In conclusion, these findings suggest that compounds present in cockroach brains are of potential therapeutic value. Further identification, characterization, and functional studies in vitro and in vivo using individual compounds can act as a breakthrough in developing novel therapeutics against various pathogens including superbugs. It is hoped that these molecules could eventually be developed into treatments for bacterial infections that are increasingly resistant to presently available drugs; however, this will require intensive research over the next few years.

Compliance with ethical standards This article does not contain any studies with human participants or animals performed by any of the authors.

Funding This study was funded by the FRGS, Malaysia, as well as the Higher Education Commission, Pakistan.

Conflict of interest The authors declare that they have no conflict of interest.

References

Ajani OO, Familoni OB, Echeme JO, Wu F, Zheng S (2013) Synthesis and antibacterial activity of N,N-diethyl amide bearing benzenesulfonamide derivatives. Am. Chem Sci J 3:34–49

Akhter M, Akhter N, Alam MM, Zaman MS, Saha R, Kumar A (2011) Synthesis and biological evaluation of 2, 5-disubstituted 1, 3, 4-oxadiazole derivatives with both COX and LOX inhibitory activity. J Enzy Inhibit Med Chem 26:767–776

Alam MM, Husain A, Hasan SM, Anwer T (2009) Synthesis and pharmacological evaluation of 2 (3H)-furanones and 2 (3H)-pyrrolones, combining analgesic and anti-inflammatory properties with reduced gastrointestinal toxicity and lipid peroxidation. Eur J Med Chem 44: 2636–2642

Alanazi AM, El-Azab AS, Al-Suwaidan IA, ElTahir KEH, Asiri YA, Abdel-Aziz NI, Alaa AM (2015) Structure-based design of phthalimide derivatives as potential cyclooxygenase-2 (COX-2) inhibitors: anti-inflammatory and analgesic activities. Eur J Med Chem 92: 115–123

Alanis AJ (2005) Resistance to antibiotics: are we in the post-antibiotic era? Arch Med Res 36:697–705

Ali TES, El-Kazak AM (2010) Synthesis and antimicrobial activity of some new 1, 3-thiazoles, 1, 3, 4-thiadiazoles, 1, 2, 4-triazoles and 1, 3-thiazines incorporating acridine and 1, 2, 3, 4-tetrahydroacridine moieties. Eur J Chem 1:6–11

Alisi MA, Cazzolla N, Furlotti G, Guglielmotti A, Polenzani L (2010) U.S. Patent No. 7,662,836. Washington, DC: U.S. Patent and Trademark Office

Alisi MA, Cazzolla N, Garofalo B, Furlotti G, Ombrato R, Mancini F (2013) U.S. Patent Application 14/373, 393

al-Rashida M, SA E, Ali S, Shaukat A, Hamayoun M, Ahmed M, Iqbal J (2015) Diarylsulfonamides and their bioisosteres as dual inhibitors of alkaline phosphatase and carbonic anhydrase: structure activity relationship and molecular modelling studies. Bioorg Med Chem 23:2435–2444

Altmeyer R, Sharma G, Pendharkar VV, Sharma DC (2010) U.S. Patent Application 12/855,046

Alvarez FN, Carlson LM, Lindner I, Lee KP (2009) 6, 7-Dihydroxy-3, 4-dihydroisoquinoline: a novel inhibitor of nuclear factor-κB and *in vitro* invasion in murine mammary cancer cells. Chemother 55: 175–182

Amiche M, Seon AA, Pierre TN, Nicolas P (1999) The dermaseptin precursors: a protein family with a common preproregion and a variable C-terminal antimicrobial domain. FEBS Lett 456:352–356

Amutha C, Saravanan S, Muthusubramanian S (2014) Synthesis and antioxidant characteristic of novel thiazolidinone derivatives. Ind J Chem 53:377–383

Anthony NG, Breen D, Clarke J, Donoghue G, Drummond AJ, Ellis EM, Gemmell CG, Helesbeux JJ, Hunter IS, Khalaf AI, Mackay SP (2007) Antimicrobial lexitropsins containing amide, amidine, and alkene linking groups. J Med Chem 50(24):6116–6125

Antoniou S (2015) Rivaroxaban for the treatment and prevention of thromboembolic disease. J Pharm Pharmacol 67:1119–1132

Antonucci T, Warmus JS, Hodges JC, Nickell DG (1995) Characterization of the antiviral activity of highly substituted pyrroles: a novel class of non-nucleoside HIV-1 reverse transcriptase inhibitor. Anti Chem Chemother 6:98–108

Armati P, Gilmour D (1976) Monoamines in the nervous system of the Queensland fruit fly, *Dacus tryoni*. Aus J Entomol 15:79–84

Arrowood MJ, Sterling CR (1989) Comparison of conventional staining methods and monoclonal antibody-based methods for cryptosporidium oocyst detection. J Clin Microbiol 27:1490–1495

Aslanian RG, Chan TY, Harris JM, McKittrick BA, Neustadt BR, Palani A (2008) Preparation of spirocyclic azetidinone derivatives and therapeutic applications thereof. PCT Int. Appl. WO 2008033465 A1 20080320

Aziz-ur-Rehman Abbasi MA, Rasool S, Ashraf M, Ejaz SA, Hassan R (2014) Synthesis, spectral characterization and enzyme inhibition studies of different chlorinated sulfonamides. Pak J Pharm Sci 27: 1739–1745

Bachi MD, Korshin EE, Ploypradith P, Cumming JN, Xie S, Shapiro TA, Posner GH (1998) Synthesis and in vitro antimalarial activity of sulfone endoperoxides. Bioorg Med Chem Lett 8:903–908

Bajpai VK, Sharma A, Moon B, Baek KH (2014) Chemical composition analysis and antibacterial mode of action of *Taxus cuspidata* leaf essential oil against foodborne pathogens. J Food Safe 34:9–20

Bang SC, Kim Y, Yun MY, Ahn BZ (2004) 5-Arylidene-2 (5H)-furanone derivatives: synthesis and structure-activity relationship for cytotoxicity. Arch Pharm Res 27:485–494

Basak SC, Mills D, Hawkins DM, Bhattacharjee AK (2010) Quantitative structure–activity relationship studies of antimalarial compounds from their calculated mathematical descriptors. Sar Qsar. Environ Res 21(1–2):103–125

Bauman JD, Das K, Patel D, Arnold E (2014) U.S. Patent No. 8,859,290. Washington, DC: U.S. Patent and Trademark Office

Bauquier JR, Tudor E, Bailey SR (2015) Anti-inflammatory effects of four potential anti-endotoxaemic drugs assessed in vitro using equine whole blood assays. J Vet Pharmacol Ther 38(3):290–296

Bettsworth F, Martinez J (2015) Use of carboxylic acids to stabilize aqueous solution of glutamate dehydrogenase. PCT Int. Appl. WO 2015086973 A1 20150618

Bhardwaj V, Gumber D, Abbot V, Dhiman S, Sharma P (2015) Pyrrole: a resourceful small molecule in key medicinal hetero-aromatics. RSC Advance 5:15233–15266

Bierer D, Johnson J, Ladouceur G, Scott W, McClure A, Fu W, Achebe F, Burke M, Bi C, Hart B (2002) 3-Pyridyl or 4-isoquinolinyl thiazoles as c17, 20 lyase inhibitors. U.S. Patent Application 10/490,822

Bilich BE, Vladimirtsev IF, Cherkasov VM, Khripko SS (1970) Search for antimicrobic substances of antibioticlike action among some b-nitrostyrene derivatives. Antibioti (Kiev) 5:31–36

Bondock S, Naser T, Ammar YA (2013) Synthesis of some new 2-(3-pyridyl)-4, 5-disubstituted thiazoles as potent antimicrobial agents. Eur J Med Chem 62:270–279

Bonnett R (1995) Photosensitizers of the porphyrin and phthalocyanine series for photodynamic therapy. Chem Soc Rev 24:19–33

Bonnett R, Martınez G (2001) Photobleaching of sensitisers used in photodynamic therapy. Tetrahedron 57(47):9513–9547

Braud E, Goddard ML, Kolb S, Brun MP, Mondésert O, Quaranta M, Gresh N, Ducommun B, Garbay C (2008) Novel naphthoquinone and quinolinedione inhibitors of CDC25 phosphatase activity with antiproliferative properties. Bioorg Med Chem 16(19):9040–9049

Breton G, Lozachmeur S, Lennon B (2015) Antioxidant composition intended for oxidative stabilization of marine, animal, or plant oils. Fr. Demande FR 3012292 A1 20150501

Brown BE, Starratt AN (1975) Isolation of proctolin, a myotropic peptide, from *Periplaneta americana*. J Insect Physiol 21:1879–1881

Brüning A, Kimmich T, Brem GJ, Buchholtz ML, Mylonas I, Kost B, Gingelmaier A (2014) Analysis of endoplasmic reticulum stress in placentas of HIV-infected women treated with protease inhibitors. Reproduc Toxicol 50:122–128

Brunskole Švegelj M, Turk S, Brus B, LaniŠnik Rižner T, Stojan J, Gobec S (2011) Novel inhibitors of trihydroxynaphthalene reductase with antifungal activity identified by ligand-based and structure-based virtual screening. J Chem Info Mod 51:1716–1724

Bulet P, Hetru C, Dimarcq JL, Hoffmann D (1999) Antimicrobial peptides in insects; structure and function. Develop Compar Immunol 23:329–344

Bur D, Grisostomi C, Nayler O, Remen L, Vercauteren M, Welford R (2015) Preparation of tricyclic piperidine compounds, particularly thiadiazoloimidazopyridines, thiazoloimidazopyridines and derivatives, as inhibitors of tryptophan hydroxylase. PCT Int. Appl. WO 2015075023 A1 20150528

Burke TR, Fesen M, Mazumder A, Yung J, Wang J, Carothers AM, Grunberger D, Driscoll J, Pommier Y, Kohn K (1995) Hydroxylated aromatic inhibitors of HIV-1 integrase. J Med Chem 38(21):4171–4178

Capitosti SM, Hansen TP, Brown ML (2004) Thalidomide analogues demonstrate dual inhibition of both angiogenesis and prostate cancer. Bioorg Med Chem 12:327–336

Carvalho AM, Miranda AM, Santos FA, Loureiro APM, Fisberg RM, Marchioni DM (2015) High intake of heterocyclic amines from meat is associated with oxidative stress. Br J Nutr 113:1301–1307

Celikler S, Tas S, Ziyanok-Ayvalik S, Vatan O, Yildiz G, Ozel M (2014) Protective and antigenotoxic effect of *Ulva rigida* C. Agardh in experimental hypothyroid. Acta Biol Hung 65:13–26

Cesarini S, Spallarossa A, Ranise A, Schenone S, Rosano C, La Colla P, Sanna G, Busonera B, Loddo R (2009) N-Acylated and N, N′-diacylated imidazolidine-2-thione derivatives and N, N′-diacylated tetrahydropyrimidine-2 (1H)-thione analogues: synthesis and antiproliferative activity. Eur J Med Chem 44(3):1106–1118

Chansukh K, Palanuvej C, Ruangrungsi N (2014) Antibacterial activities of selected Thai medicinal plants bearing quinonoids. 425–432

Chen YC (2013) Methods for treating neurodegenerative diseases associated with aggregation of amyloid-beta. U.S. Patent Application No. 14/109,948

Chen HY, Chen XY (2012) Effect of peimine on inhibiting the MCF-7/TAM proliferation of human breast cancer cell and its influence on cell apoptosis. Zhong Xueb 40:12–15

Chen P, Horton LB, Mikulski RL, Deng L, Sundriyal S, Palzkill T, Song Y (2012) 2-Substituted 4, 5-dihydrothiazole-4-carboxylic acids are novel inhibitors of metallo-β-lactamases. Bioorg Med Chem Lett 22:6229–6232

Cheng H, Cong Q, Gangwar S, Zhang Q (2011) Antiproliferative compounds structurally related to tubulysins, conjugates thereof for targeted delivery, methods of preparation, and uses thereof. U.S. Pat. Appl. Publ. US 20110027274 A1 20110203

Chikhale H, Lade K, Joshi P, Kudale S, Nerkar A, Sawant S (2012) In silico design, synthesis & pharmacological screening of some quinazolinones as possible gabaa receptor agonists for anticonvulsant activity. Int J Pharm Pharmac Sci 4:466–469

Chung YS, Siu ML, Lai TH, Yeh SC (2013) U.S. Patent Application 14/144,264

Clynen E, Schoots L (2009) Peptidomic survey of the locust neuroendocrine system. Insect. Biochem. Mol Biol 39:491–507

Combourieu B, Besse P, Sancelme M, Godin JP, Monteil A, Veschambre H, Delort AM (2000) Common degradative pathways of morpholine, thiomorpholine, and piperidine by *Mycobacterium aurum* MO1: evidence from 1H-nuclear magnetic resonance and ionspray mass spectrometry performed directly on the incubation medium. Appl Environ Microbiol 66(8):3187–3193

Correa AG, Baraldi PT, Soares AM (2008) U.S. Patent Application 12/602,347

Cushnie TT, Lamb AJ (2005) Antimicrobial activity of flavonoids. Int J Antimicrob Agents 26:343–356

Dai Y, Pochapsky TC, Abeles RH (2001) Mechanistic studies of two dioxygenases in the methionine salvage pathway of *Klebsiella pneumoniae*. Biochemist 40:6379–6387

Danishefsky SJ, Chou TC, Lei X, Yun H, Ng F, Hartung J, Sames D (2014) Preparation of panaxytriol derivatives useful for reducing toxicity and treating or preventing diseases. U.S. US 8859615 B2 20141014

De S, Dey A, Aneela S (2013) GC-MS analysis of phytocomponents in the methanolic extract of Oldenlandia umbellate. 4:29–32

De Simone R, Andrés RM, Aquino M, Bruno I, Guerrero MD, Terencio MC, Paya M, Riccio R (2010) Toward the discovery of new agents able to inhibit the expression of microsomal prostaglandin E synthase-1 enzyme as promising tools in drug development. Chem Biol Drug Des 76(1):17–24

De Troconis MIC, De Aulacio MP, De TC (2000) Molecular modeling and antibacterial activity-structure relationships of nalidixic acid quinolin anlogs. Bol Soc Chil Quim 45(1):5–13

Dente EL (2014) U.S. Patent Application 14/560,776

Deprez P, Mandine E, Gofflo D, Meunier S, Lesuisse D (2002) Small ligands interacting with the phosphotyrosine binding pocket of the Src SH 2 protein. Bioorg Med Chem Lett 12:1295–1298

Desplaces N, Gutmann L, Carlet J, Guibert J, Acar JF (1986) The new quinolones and their combinations with other agents for therapy of severe infections. J Antimicrob Chemother 17(suppl A):25–39

Devasahayam G, Scheld WM, Hoffman PS (2010) Newer antibacterial drugs for a new century. Expert Opin Investig Drugs 19:215–234

Di Marzo V, De Petrocellis L, Moriello AS (2008) U.S. Patent Application 12/596,500

Dubost C, Vors JP, Coqueron PY (2013) Preparation of 1-methyl-3-dihalomethyl-5-halopyrazole(thio)indanylcarboxamide derivatives as fungicides useful in. PCT Int. Appl. WO 2013167544 A1 20131114

Duś D, Wojdat E, Radzikowski C, Mastalerz P (1984) Cytostatic activity *in vitro* of phosphonic acid derivatives. Arch Immunol Ther Exp 33: 325–329

Eddington ND, Cox DS, Roberts RR, Butcher RJ, Edafiogho IO, Stables JP, Cooke N, Goodwin AM, Smith CA, Scott KR (2002) Synthesis and anticonvulsant activity of enaminones.: 4. Investigations on isoxazole derivatives. Eur J Med Chem 37(8):635–648

Ellendorff T, Brun R, Kaiser M, Sendker J, Schmidt TJ (2015) PLS-prediction and confirmation of hydrojuglone glucoside as the antitrypanosomal constituent of Juglans spp. Molecules 20(6): 10082–10094

Ellingboe JW, Nikaido M, Bagli J (1992) Preparation of pyridopyrimidinones and pyrrolopyrimidinones as angiotensin II antagonists. U.S. US 5149699 A 19920922

Elliott S, Evans J (2014) A 3-year review of new psychoactive substances in casework. Foren Sci Int 243:55–60

Emran TB, Rahman MA, Uddin MMN, Dash R, Hossen MF, Mohiuddin M, Alam MR (2015) Molecular docking and inhibition studies on the interactions of Bacopa monnieri's potent phytochemicals against pathogenic *Staphylococcus aureus*. Daru 23(1):26

Engelsma G, Yamamoto A, Markham E, Calvin M (1962) The effect of light on oxidation and reduction reactions involving phthalocyanine and etioporphyrin I manganese complexes. J Phy Chem 66:2517–2531

Enright MC (2003) The evolution of a resistant pathogen—the case of MRSA. Curr Opin Pharmacol 3:474–479

Exarchou V, Kanetis L, Charalambous Z, Apers S, Pieters L, Gekas V, Goulas V (2015) HPLC-SPE-NMR characterization of major metabolites in *Salvia fruticosa* Mill. Extract with antifungal potential: relevance of carnosic acid, carnosol, and hispidulin. J Agri Food Chem 63:457–463

Facchinetti V, Reis d RR, Gomes RBC, Vasconcelos RAT (2012) Chemistry and biological activities of 1, 3-benzothiazoles. Mini Rev Org Chem 9:44–53

Fang Y, Feng Y, Li M (2008) Optimal QSAR analysis of the carcinogenic activity of aromatic and heteroaromatic amines. QSAR Combin Sci 27:543–554

Flefel EM, Tantawy WA, Abdel-Mageid RE, Amr AEGE, Nadeem R (2014) Synthesis and anti-viral activities of some 3-(naphthalen-1-ylmethylene)-5-phenylfuran-2 (3H)-one candidates. Res Chem Intermed 40:1365–1381

Flentge CA, Chen HJ, Degoey DA, Flosi WJ, Grampovnik DJ, Huang PP (2011) Preparation of sulfonylaminobutanamide derivatives for use as HIV protease inhibitors. U.S. Pat. Appl. Publ. US 20110003827 A1 20110106

Fodor A, Tímár T, Kiss I, Hosztafi S, Varga É, Soos J, Sebök P (1989) Effects of precocene analogs on the nematode *Caenorhabditis remanei* (var. bangaloreiensis): I. Structure/activity relations. Gen Comp Endocrinol 74:18–31

Frederico MJ, Mascarello A, Castro AJ, Mendes CP, Kappel VD, Cazarolli LH (2013) Antidiabetic effects of sulfonamide derivatives based on structural fragment of sulfonylureas. Curr Trend Med Chem 7:11–25

Fu QC, Liu C, Wang Y, Li CH, Hu Q (2015) Germination inhibitors of Sinojackia sarcocarpa L. Q. Luo drupe methanol extract. Beif Yuan 2:6–9

Fung CYE, Fung KP, Mahaut-Smith M (2008) 5-Methyl-6, 7-dihydro-5H-cyclopentapyrazine for use in therapy, especially treating platelet-related diseases such as thrombosis, and as a male contraceptive. GB2439923

Funk P, Motyka K, Dzubak P, Znojek P, Gurska S, Kusz J, Soural M (2015) Preparation of 2-phenyl-3-hydroxyquinoline-4 (1H)-one-5-carboxamides as potential anticancer and fluorescence agents. RSC Adv 5:48861–48867

Ganguli S, Firdous M, Maity TS, Bera RK, Panigrahi M (2012) The study of antihyperlipidemic activities of schiff bases of 4 (3H) quinazolinone derivatives in rats. Int J Pharm Pharmaceut Sci 4: 175–178

Ganguly S, Murugesan S (2011) 3D QSAR-comparative molecular similarity indices analysis of 2-heteroarylquinoline-4-amines as possible anti-HIV-1 agents.

Gao XJ, Wang TC, Zhang ZC, Cao YG, Zhang NS, Guo MY (2015) Brazilin plays an anti-inflammatory role with regulating Toll-like receptor 2 and TLR 2 downstream pathways in *Staphylococcus aureus*-induced mastitis in mice. Int Immunopharmacol 27:130–137

George S, Nair SA, Venkataraman R, Baby S (2015) Chemical composition, antibacterial and anticancer activities of volatile oil of *Melicope denhamii* leaves. Nat Prod Res 29:1959–1962

Ghattas AEBA, Moustafa HM, Hassanein EA, Hussein BR (2012) Synthesis and antibacterial activity of some new 4-anilino-5-phenyl-4H-1, 2, 4-triazole-3-thiol derivatives. Arabian J Chem

Giller SA, Dubur GY, Zilber JA, Bljuger AF, Zarinya LA, Maiore AY (1976) Pharmaceutical composition for treating liver diseases. Brit. GB 1426499 A 19760225

Ginsborg BL, Turnbull KW, House CR (1976) On the actions of compounds related to dopamine at a neurosecretory synapse. Br J Pharmacol 57:133–140

Girard Y, Yoakim-Rancourt C, Hamel P, Gillard JW, Guindon Y, Letts G, Lord A (1989) Tetrahydrocarbazol-1-acetic acids: new class of thromboxane receptor antagonists. Prog Clin Biol Res 301:585

Givskov M, Yang L, Tan YY (2014) Quorum sensing inhibitors and uses thereof as antibacterial agents. PCT Int. Appl. WO 2014142748 A1 20140918

Gökce M, Özcelik B, Akyon Y, Berçin E, Noyanalpan N (2004) Activity of l-[(2-aminophenyl) thio]-l-phenyl-2-nitroalkane derivatives against *Helicobacter pylori*. Turk. J Pharm Sci 1:55–64

Gómez CMM, Kouznetsov VV, Sortino MA, Álvarez SL, Zacchino SA (2008) *In vitro* antifungal activity of polyfunctionalized 2-(hetero) arylquinolines prepared through imino Diels–Alder reactions. Bioorg Med Chem 16:7908–7920

Gonewar NR, Jadhav VB, Killedar AA, Sakure SS, Jadhav KD, Sarawadekar RG (2012) Synthesis, characterization and antimicrobial activities of 1,2 naphthoquinone-1-oxime ligand and its metal chelates of. Int J Chem Sci 10:1493–1505

Gonzalez Perez JA, Estevez Braun A, Gutierrez Ravelo A, Estevez Reyes R (1995) Phenyl compounds for the control of phytoparasitic nematodes. PCT Int. Appl. WO 9515082 A1 19950608

Griggs AM, Agim ZS, Mishra VR, Tambe MA, Director-Myska AE, Turteltaub KW, Cannon JR (2014) 2-amino-1-methyl-6-phenylimidazo [4, 5-b] pyridine (PhIP) is selectively toxic to primary dopaminergic neurons *in vitro*. Toxicol Sci 140:179–189

Groves RL, Chapman S, Lowenstein DM, Huseth AS, Groves CL (2012) Registeted and experimental foliar insecticides to control Colorado potato beetle and potato leafhopper in potato, 2011. Arthropod Management Tests 37(1):E47

Grueneberg DA, Kalid O, Xian J, Rajur SB, Kim HO, Neelagiri VR (2014) Novel methods, compounds, and compositions for inhibition of ROS kinase. PCT Int. Appl. WO 2014141129 A2 20140918

Guzman JD, Pesnot T, Barrera DA, Davies HM, McMahon E, Evangelopoulos D, Angell R (2015) Tetrahydroisoquinolines affect the whole-cell phenotype of *Mycobacterium tuberculosis* by inhibiting the ATP-dependent MurE ligase. J Antimicrob Chem 70:1691–1703

Guzzi U, Ciabatti R, Padova G, Battaglia F, Cellentani M, Depaoli A, Spina G (1986) Structure-activity studies of 16-methoxy-16-methyl prostaglandins. J Med Chem 29:1826–1832

Győrfi J, Geösel A, Kiss M, Nemes K, Csóka M, Korány K (2013) Gas chromatography–mass spectrometry confirmation of the sensory scent features of the most commonly consumed *Agaricus bisporus* and *Agaricus subrufescens* exhibiting anticancerous traits. J Med Food 16:167–175

Hamdy A, Rothbaum W, Izumi R, Lannutti B, Covey T, Ulrich R (2015) Therapeutic combination of a phosphoinositide 3-kinase (PI3K) inhibitor and a Bruton's tyrosine kinase (BTK) inhibitor for treating hyperproliferative disorders such as cancer. PCT Int. Appl. WO 2015083008 A1 20150611

Han J, Tan P, Li Z, Wu Y, Li C, Wang Y, Liu Y (2014) Fuzi attenuates diabetic neuropathy in rats and protects Schwann cells from apoptosis induced by high glucose. PLoS One 9(1):e86539

Hanauske-Abel HM, Palumbo P, Cracchiolo BM, Park MH, Wolff EC, Hanauske AR (2005) Method using ciclopirox and other heterocyclic compounds for preventing survival of retrovirally infected cells and of inhibiting formation of infectious retroviruses. PCT Int. Appl. WO 2005055931 A2 20050623

Harada K, Matsushita A, Kawachi Y, Sasaki H (1996) Preparation of b-ketophosphonate derivatives as anticholesteremic intermediates. Jpn Kok Tok Koho JP 08099982 A 19960416

Hardick DJ, Blagbrough IS, Cooper G, Potter BV, Critchley T, Wonnacott S (1996) Nudicauline and elatine as potent norditerpenoid ligands at rat neuronal α-bungarotoxin binding sites: importance of the 2-(methylsuccinimido) benzoyl moiety for neuronal nicotinic acetylcholine receptor binding. J Med Chem 39:4860–4866

Hatano H, Takekawa F, Hashimoto K, Ishihara M, Kawase M, Qing C, Sakagami H (2009) Tumor-specific cytotoxic activity of 1, 2, 3, 4-tetrahydroisoquinoline derivatives against human oral squamous cell carcinoma cell lines. Anticancer Res 29:3079–3086

Hatch FT, Knize MG, Colvin ME (2001) Extended quantitative structure–activity relationships for 80 aromatic and heterocyclic amines: structural, electronic, and hydropathic factors affecting mutagenic potency. Environ Mol Mutagen 38:268–291

He W, Xue C (2014) Effects of rosuvastatin on left ventricular diastolic function in older patients with hypertension. Xinfei Xueguan Zazhi 33:699–701

He X, Du X, Zang X, Dong L, Gu Z, Cao L, Guan X (2015) Extraction, identification and antimicrobial activity of a new furanone, grifolaone A, from *Grifola frondosa*. Nat Prod Res 30:941–947

Heffernan ML, Fang QK, Foglesong RJ, Hopkins SC, Ogbu CO, Soukri M (2011) Preparation of fused pyrrole derivatives as inhibitors of D-amino acid oxidase. PCT Int. Appl. WO 2011011330 A2 20110127

Huang LJ, Ge YH, Liu KX, Zhang JX, Hao XJ (2013) Chemical constituents from Aconitum recemulosum and their effects against TMV. Nongyao 52:295–297

Huchel U, Materne M, Levert I, Smyrek H, Bunn R, Rittler F (2015) Use of CNGA2 agonists for enhancing the olfactory effect of an odorant. Ger Offen DE 102013226602 A1 20150625

Huegin A (2012) 1,4-Naphthoquinones for treating pox virus infections. PCT Int. Appl. WO 2012052956 A1 20120426

Hung KS (2015) Use of indolyl and indolinyl hydroxamates for treating neurodegenerative disorders or cognitive deficits. PCT Int. Appl. WO 2015077685 A1 20150528

Husain A, Hasan SM, Lal S, Alam MM (2006) Antibacterial and antifungal activities of 2-arylidene-4-(4-methylphenyl) but-3-en-4-olides and their pyrrolone derivatives. Ind J Pharmaceut Sci 68:536

Hussain H, Kock I, Al-Harrasi A, Abbas G, Green IR, Draeger S, Krohn K (2014) Anti microbial and phytochemical investigation of the endophytic fungus *Acremonium* sp. J Herb Med 3:1–4

Idhayadhulla A, Kumar RS, Nasser AJA, Manilal A, Ismail IB, Al-Busadah KA, Ortiz GG (2013) Nurulisa Zulkifle. Int J Biol Chem 7:15–26

Indumathi S, Karthikeyan R, Nasser A, Jamal A, Idhayadhulla A, Surendra Kumar R (2015) Anticonvulsant, analgesic and anti-inflammatory activities of some novel pyrrole and 1, 4-dihydropyridine derivatives. J Chem Pharmaceut Res 7:434–440

Ishikawa T, Watanabe T, Tanigawa H, Saito T, Kotake KI, Ohashi Y, Ishii H (1996) Nitrosation of phenolic substrates under mildly basic conditions: selective preparation of p-quinone monooximes and their antiviral activities. J Org Chem 61:2774–2779

Istanbullu H, Erzurumlu Y, Kirmizibayrak PB, Erciyas E (2014) Evaluation of alkylating and intercalating properties of Mannich bases for cytotoxic activity. Lett Drug Desig Discov 11:1096–1096

Iwaoka K, Imanishi N, Ito H, Miyata K, Ota M (1998) Pharmaceuticals containing 2-phenylthiazoles as 5-HT3 receptor agonists, and preparation of the compounds. Jpn Kokai Tokkyo Koho JP 10017569 A 19980120

Iwasa K, Moriyasu M, Tachibana Y, Kim HS, Wataya Y, Wiegrebe W, Lee KH (2001) Simple isoquinoline and benzylisoquinoline alkaloids as potential antimicrobial, antimalarial, cytotoxic, and anti-HIV agents. Bioorg Med Chem 9:2871–2884

Jahangir M, Ilyas SA, Mazhar F, Abbasi MA, Usman MF, Rehman J, Ajaib M (2013) Antimicrobial and antioxidant potential of *Astragalus psilocentros*. Asia J Chem 25:175

Jansen J, McBride C, Renhowe P, Shafer C (2005) U.S. Patent Application 11/261,995

Johnson RA (1996) U.S. Patent No. 5,500,417. Washington, DC: U.S. Patent and Trademark Office

Kalopissis G, Manoussos G (1976) U.S. Patent No. 3,950,542. Washington, DC: U.S. Patent and Trademark Office

Kane VV, Levine SD (1981) U.S. Patent No. 4,250,180. Washington, DC: U.S. Patent and Trademark Office

Kaplan A, Gaschler MM, Dunn DE, Colligan R, Brown LM, Palmer AG, Stockwell BR (2015) Small molecule-induced oxidation of protein disulfide isomerase is neuroprotective. PNAS 112:E2245–E2252

Karakaya I, Karabuga S, Ulukanli Z, Ulukanli S (2013) Synthesis and antifungal evaluation of imines derived from 3-amino-2-isopropyl-3H-quinazoline-4-one. Org Commun 6:139–147

Kasai S (2014) A novel Parkinson's disease drug, istradefylline. BIO Clin 29:1301–1307

Kasai S, Igawa H, Takahashi M, Maekawa T, Kakegawa K, Yasuma T (2013) Preparation of benzimidazole and imidazopyridine derivatives and analogs as MCH receptor antagonists for treating obesity. PCT Int. Appl. WO 2013105676 A1 20130718

Kawaminami E, Takahashi T, Kanayama T, Sakamoto K (2012) Preparation of heterocycle-carboxamide compounds as LPA receptor antagonists. PCT Int. Appl. WO 2012039460 A1 20120329

Khafagy MM, El-Wahab AHA, Eid FA, El-Agrody AM (2002) Synthesis of halogen derivatives of benzo [h] chromene and benzo [a] anthracene with promising antimicrobial activities. II. Farmaco 57:715–722

Khan NA, Siddiqui R (2009) *Acanthamoeba* affects the integrity of human brain microvascular endothelial cells and degrades the tight junction proteins. Int J Parasitol 39:1611–1616

Khan NA, Osman K, Goldsworthy G (2008) Lysates of *Locusta migratoria* brain exhibit potent broad spectrum antibacterial activity. J Antimicrob Chemother 62:634–635

Kim HD, Lee JM (2015) Perfume composition for masking odorous smell in formulation comprising amine. Repub Kor Kong Taeh Kong KR 2015070937 A 20150625

Kiyama R, Kanda Y, Tada Y, Fujishita T, Kawasuji T, Takechi S, Fuji M (2003) Preparation of heterocyclic compounds as integrase inhibiting antiviral agents. WO2003016275

Kon T, Kato S, Morie T, Harada H (1991) Preparation of indazole-3-carboxamidohexahydro-1,4-diazepines as serotoninergic S3 antagonists. Jpn Kok Tok Koh JP 03223280 A 19911002

Kormann EC, de Aguiar Amaral P, David M, Eifler-Lima VL, Cechinel Filho V, de Campos Buzzi F (2012) Kavain analogues as potential analgesic agents. Pharmacol Rep 64(6):1419–1426

Korthout HA (2012) Medical use for acidic cannabinoids for increasing natural resistance in an animal or enhancing cellular resistance for use in therapy. PCT Int. Appl. WO 2012144892 A1 20121026

Kosakai H, Hirose A (2015) Ethanol-containing food preservative and food preservation method using it. Jpn Kok Tok Koh JP 2015123062 A 20150706

Kouznetsov VV, Vargas Mendez LY, Milena Leal S, Mora Cruz U, Andres Coronado C, Melendez Gomez CM, Escobar Rivero P (2007) Target-oriented synthesis of antiparasitic 2-hetaryl substituted quinolines based on imino Diels-Alder reactions. Lett Drug Desig Discov 4:293–296

Kouznetsov VV, Rojas Ruiz A, Vargas Mendez LY, Gupta M (2012) Simple C-2-substituted quinolines and their anticancer activity. Lett Drug Desig Discov 9:680–686

Kumar P, Rawat A, Keshari AK, Singh AK, Maity S, De A, Saha S (2015) Antiproliferative effect of isolated isoquinoline alkaloid from *Mucuna pruriens* seeds in hepatic carcinoma cells. Nat Prod Res 30: 460–463

La J, Latham CF, Tinetti RN, Johnson A, Tyssen D, Huber KD, Tachedjian G (2015) Identification of mechanistically distinct inhibitors of HIV-1 reverse transcriptase through fragment screening. PNAS 112:6979–6984

Lack NA, Axerio-Cilies P, Tavassoli P, Han FQ, Chan KH, Feau C, Cherkasov A (2011) Targeting the binding function 3 (BF3) site of the human androgen receptor through virtual screening. J Med Chem 54:8563–8573

Le BV, Klöck C, Schatz A, Nguyen JB, Kakani EG, Catteruccia F, Baxter RH (2014) Dihydroisoxazole inhibitors of *Anopheles gambiae* seminal transglutaminase AgTG3. Malar J 13:210

Leal KW, Troupin AS (1977) Clinical pharmacology of anti-epileptic drugs: a summary of current information. Clin Chem 23:1964–1968

Lee S, Duce I, Atkins H, Khan NA (2011) Cockroaches and locusts: physicians' answer to infectious diseases. Int J Antimicrob Agents 37:279–280

Levy SB, Alekshun MN, Podlogar BL, Ohemeng K, Verma AK, Warchol T, Bhatia B, Bowser T Grier M (2005) Substituted benzoimidazole compounds as transcription factor-modulating compounds useful as anti-infectives. US Patent Appl. 2005124678, pA120050609

Li H, Shinde PB, Lee HJ, Yoo ES, Lee CO, Hong J, Jung JH (2009) Bile acid derivatives from a sponge-associated bacterium Psychrobacter sp. Arch Pharm Res 32:857–862

Lima TC, Santos ADC, Costa DT, Souza RJ, Barison A, Steindel M, Biavatti MW (2015) Chromenes from leaves of *Calea pinnatifida* and evaluation of their leishmanicidal activity. Rev Bras Farmaco 25:7–10

Liou SF, Hsu JH, Chu HC, Lin HH, Chen IJ, Yeh JL (2015) KMUP-1 promotes osteoblast differentiation through cAMP and cGMP pathways and signaling of BMP-2/Smad1/5/8 and Wnt/β-catenin. J Cell Physiol 230:2038–2048

Liu G, Wu Y, Xu H, Liu H (2013) A green route for the synthesis of antiepileptic drug Losigamone and its analogues. Chin. J Org Chem 33(7):1527–1539

Lujan SA, Guogas LM, Ragonese H, Matson SW, Redinbo MR (2007) Disrupting antibiotic resistance propagation by inhibiting the conjugative DNA relaxase. PNAS 104:12282–12287

Ma M, Feng J, Li R, Chen SW, Xu H (2015) Synthesis and antifungal activity of ethers, alcohols, and iodohydrin derivatives of sclareol against phytopathogenic fungi in vitro. Bioorg. Med Chem Lett 25(14):2773–2777

Macias WL (2001) Compositions containing potential secretory phospholipase A2 (sPLA2) inhibitors for the treatment of pain. PCT Int. Appl. WO 2001066111 A1 20010913

Macias WL, Meador VP (2001) Methods and formulations containing secretory phospholipase A2 (sPLA2) inhibitors for the treatment of renal dysfunction. PCT Int. Appl. WO 2001066110 A2 20010913

Mackmull MT, Iskar M, Parca L, Singer S, Bork P, Ori A, Beck M (2015) Histone deacetylase inhibitors (HDACi) cause the selective depletion of bromodomain containing proteins (BCPs). Mol Cell Proteo 14:1350–1360

Makowski CT, Rissmiller RW, Bullington WM (2015) Riociguat: a novel new drug for treatment of pulmonary hypertension. Pharmacotherapy. J Hum Pharm Drug Ther 35:502–519

Mareddy J, Nallapati SB, Anireddy J, Devi YP, Mangamoori LN, Kapavarapu R, Pal S (2013) Synthesis and biological evaluation of nimesulide based new class of triazole derivatives as potential PDE4B inhibitors against cancer cells. Bioorg Med Chem Lett 23(24):6721–6727

Mashhoon N, Pruss C, Carroll M, Johnson PH, Reich NO (2006) Selective inhibitors of bacterial DNA adenine methyltransferases. J Biomol Screen 11:497–510

Mautino M, Jaipuri F, Marcinowicz-Flick A, Kesharwani T, Waldo J (2009) Preparation and disclosure of indoleamine 2,3-dioxygenase (IDO) inhibitors. PCT Int. Appl. WO 2009073620 A2 20090611

Mayhoub AS, Khaliq M, Botting C, Li Z, Kuhn RJ, Cushman M (2011) An investigation of phenylthiazole antiflaviviral agents. Bioorg Med Chem 19:3845–3854

Mehetre D (2013) Synthesis and evaluation of antimicrobial activity of gamma butyrolactone. Int J Pharmaceut Phytopharmacol Res 2: 412–414

Metz-Boutigue MH, Goumon Y, Strub JM, Lugardon K, Aunis D (2003) Antimicrobial chromogranins and proenkephalin-A-derived peptides: antibacterial and antifungal activities of chromogranins and proenkephalin-A-derived peptides. Ann N Y Acad Sci 992:168–178

Mharti FZ, Lyoussi B, Abdellaoui A (2011) Antibacterial activity of the essential oils of *Pistacia lentiscus* used in Moroccan folkloric medicine. Nat Prod Commun 6:1505–1506

Mihailovic V, Vukovic N, Niciforovic N, Solujic S, Mladenovic M, Maškovic P, Stankovic MS (2011) Studies on the antimicrobial activity and chemical composition of the essential oils and alcoholic extracts of *Gentiana asclepiadea* L. J Med Plant Res 5:1164–1174

Miliukienė V, Nivinskas H, Čėnas N (2014) Cytotoxicity of anticancer aziridinyl-substituted benzoquinones in primary mice splenocytes. Acta Biochim Pol 61(4):833–836

Minami S, Shono T, Matsumoto JI (1971) Pyrido [2, 3-d] pyrimidine antibacterial agents. I. 8-alkyl-5, 8-dihydro-5-oxopyrido [2, 3-d]-pyrimidine-6-carboxylic acids and related compounds. Chem Pharm Bull 19(7):1482–1486

Miyazawa M, Shimabayashi H, Hayashi S, Hashimoto S, Nakamura SI, Kosaka H, Kameoka H (2000) Synthesis and biological activity of α-methylene-γ-lactones as new aroma chemicals. J Agri Food Chem 48:5406–5410

Mjalli AM, Sarshar S, Zhang C (1998) U.S. Patent No. 5,723,451. Washington, DC: U.S. Patent and Trademark Office

Moinet G, Correc JC, De Vacqueur Arbellot A (2005) Acidic quinolines as antihyperglycemics and their preparation. Fr. Demande FR 2864535 A1 20050701

Mootha VK, Gohil V, Sheth S, Ji Y (2010) U.S. Patent Application 13/320,348

Morgan CA, Hurley TD (2015) Characterization of two distinct structural classes of selective aldehyde dehydrogenase 1A1 inhibitors. J Med Chem 58:1964–1975

Murthy YLN, Rajack A, Ramji MT, Praveen C, Lakshmi KA (2012) Design, solvent free synthesis, and antimicrobial evaluation of 1, 4 dihydropyridines. Bioorg Med Chem Lett 22:6016–6023

Musad EA, Mohamed R, Saeed BA, Vishwanath BS, Rai KL (2011) Synthesis and evaluation of antioxidant and antibacterial activities of new substituted bis (1, 3, 4-oxadiazoles), 3, 5-bis (substituted) pyrazoles and isoxazoles. Bioorg Med Chem Lett 21(12):3536–3540

Nagarajan S, Choi MJ, Cho YS, Min SJ, Keum G, Kim SJ, Pae AN (2015) Tubulin inhibitor identification by bioactive conformation alignment pharmacophore-guided virtual screening. Chem Biol Drug Design 86:998–1016

Naseem T, Farrukh MA (2015) Antibacterial activity of green synthesis of iron nanoparticles using *Lawsonia inermis* and *Gardenia jasminoides* leaves extract. J Chem

Nemeikaitė-Čėnienė A, Jarašienė R, Nivinskas H, Šarlauskas J, Čėnas N (2015) Cytotoxicity of anticancer aziridinyl-benzoquinones in murine hepatome MH22a cells: the properties of RH1-resistant subline. Chemija 26(1):46

Niaz H, Kashtoh H, Khan JA, Khan A, Alam MT, Khan KM, Choudhary MI (2015) Synthesis of diethyl 4-substituted-2, 6-dimethyl-1, 4-dihydropyridine-3, 5-dicarboxylates as a new series of inhibitors against yeast α-glucosidase. Eur J Med Chem 95:199–209

Nidorf M (2015) U.S. Patent Application 14/603,085

Nordmann P, Naas T, Fortineau N, Poirel L (2007) Superbugs in the coming new decade; multidrug resistance and prospects for treatment of *Staphylococcus aureus*, *Enterococcus* spp. and *Pseudomonas aeruginosa* in 2010. Curr Opin Microbiol 10:436–440

Oberbauer E, Urmann C, Steffenhagen C, Bieler L, Brunner D, Furtner T, Aigner L (2013) Chroman-like cyclic prenylflavonoids promote neuronal differentiation and neurite outgrowth and are neuroprotective. J Nutri. Biochemist 24:1953–1962

Ohkawa S, Naruo K, Morimoto S, Nagase Y, Miwatashi S (2002) Medicinal compositions as p38MAP kinase and/or TNF-a production inhibitor for pain. PCT Int. Appl. WO 2002100433 A1 20021219

Okabe B (2015) Skin-whitening agent and melanin production inhibitor containing dihydroactinidiolide. Jpn. Kokai Tokkyo Koho JP 2015063496 A 20150409

O'Mahony MJ, West PJ, Lindell SD, Macritchie JA (1997) Preparation of fungicidal pyridopyrimidines. Brit. UK Pat. Appl. GB 2307177 A 19970521

Ontoria JM, Altamura S, Di Marco A, Ferrigno F, Laufer R, Muraglia E, Jones P (2009) Identification of novel, selective, and stable inhibitors of class II histone deacetylases. Validation studies of the inhibition of the enzymatic activity of HDAC4 by small molecules as a novel approach for cancer therapy. J Med Chem 52:6782–6789

Orabi MA, Aoyama H, Kuroda T, Hatano T (2014) Structures of new phenolics isolated from licorice, and the effectiveness of licorice phenolics on vancomycin-resistant enterococci. Molecul 19: 13027–13041

Orhan I, Özçelik B, Karaoğlu T, Şener B (2007) Antiviral and antimicrobial profiles of selected isoquinoline alkaloids from Fumaria and Corydalis species. Zeit Natur 62:19–26

Özbek N, Katırcıoğlu H, Karacan N, Baykal T (2007) Synthesis, characterization and antimicrobial activity of new aliphatic sulfonamide. Bioorg Med Chem 15:5105–5109

Özkay Y, Işıkdağ İ, İncesu Z, Akalın G (2010) Synthesis of 2-substituted-N-[4-(1-methyl-4, 5-diphenyl-1H-imidazole-2-yl) phenyl] acetamide derivatives and evaluation of their anticancer activity. Eur J Med Chem 45:3320–3328

Pantosti A, Venditti M (2009) What is MRSA? Eur Respir J 34:1190–1196

Park KW, Kundu J, Chae IG, Kim DH, MH Y, Kundu JK, Chun KS (2014) Carnosol induces apoptosis through generation of ROS and inactivation of STAT3 signaling in human colon cancer HCT116 cells. Int J Oncol 44:1309–1315

Parmar VS, Prasad AK, Raj HG, Bose M, Sharma SK, Tandon R, Baghel A, Kathuria A, Gupta G, Aggarwal Neha (2012) Coumarin compounds for the treatment of mycobacterial infections. Indian Pat. Appl. IN 2011DE00983 A 20121019

Pawelczap M, Nowak K, Kafarski P (1998) Synthesis of phosphono dipeptides, inhibitors of cathepsin C. Phospho Sulf Silic Rel Element 132:65–71

Pawellek A, McElroy S, Samatov T, Mitchell L, Woodland A, Ryder U, Lamond AI (2014) Identification of small molecule inhibitors of pre-mRNA splicing. J Biol Chem 289:34683–34698

Pellecchia M (2008) Inhibitors of JNK, methods for identifying inhibitors of the JNK interaction with JIP (JNK-interacting protein), and use. PCT Int. Appl. WO 2008118626 A2 20081002

Perwitasari O, Johnson S, Yan X, Howerth E, Shacham S, Landesman Y, Tripp RA (2014) Verdinexor, a novel selective inhibitor of nuclear export, reduces influenza a virus replication *in vitro* and *in vivo*. J Virol 88:10228–10243

Pery E, Sheehy A, Nebane NM, Brazier AJ, Misra V, Rajendran KS, Gabuzda D (2015) Identification of a novel HIV-1 inhibitor targeting Vif-dependent degradation of human APOBEC3G protein. J Biol Chem 290:10504–10517

Peter OO, Lucky OO (2014) Design, synthesis and bioassay of novel metal complexes of 3-amino-6, 8-dibromo-2-methyl quinazolin-4 (3H)-one. Pharm Chem J 48:718–721

Peyman A, Uhlmann E, Budt K, Knolle J, Winkler I, Helsberg M (1991) Preparation of benzylphosphonates as virucides. Eur. Pat. Appl. EP 440148 A1 19910807

Philip K (2014) *In vitro* antifungal activity screening of some new glutamoyl derivatives. Res. J Chem Sci 4:17–24

Piazza GA (2015) Treatment and diagnosis of cancer and precancerous conditions using pde10a inhibitors and methods to measure pde10a expression. PCT Int. Appl. WO 2015006689 A1 20150115

Pisanenko DA, Smirnov-Zamkov YI, Novikov IN, Kovtun VK, Grib OK, Abramova KA (1986) Synthesis and pesticidal activity of esters of bis[4-(carboxymethoxy)phenyl] sulfone. Vest Kiev Politek Ins Khim Mash Tekhnol 23:21–23

Puig-Basagoiti F, Qing M, Dong H, Zhang B, Zou G, Yuan Z, Shi PY (2009) Identification and characterization of inhibitors of West Nile virus. Antivir Res 83(1):71–79

Rademacher C, Guiard J, Kitov PI, Fiege B, Dalton KP, Parra F, Peters T (2011) Targeting norovirus infection—multivalent entry inhibitor design based on NMR experiments. Chem-Eur J 17:7442–7453

Raffa D, Maggio B, Cascioferro S, Raimondi MV, Daidone G, Plescia S, Tolomeo M (2009) N-(Indazolyl) benzamido derivatives as CDK1 inhibitors: design, synthesis, biological activity, and molecular docking studies. Arch Pharmaz 342:265–273

Rajagopal L, Howard KB, Whidbey C (2013) Kinase inhibitors capable of increasing the sensitivity of bacterial pathogens to b-lactam antibiotics. PCT Int. Appl. WO 2013066469 A2 20130510

Ramdani G, Naissant B, Thompson E, Breil F, Lorthiois A, Dupuy F, Cummings R, Duffier Y, Corbett Y, Mercereau-Puijalon O, Vernick K (2015) cAMP-signalling regulates gametocyte-infected erythrocyte deformability required for malaria parasite transmission. PLoS Pathog 11(5):e1004815

Rappai JP, Raman V, Unnikrishnan PA, Prathapan S, Thomas SK, Paulose CS (2009) Preliminary investigations on the synthesis and antitumor activity of 3 (2H)-furanones. Bioorg Med Chem Lett 19: 764–765

Rathore D, Jani D, Nagarkatti R (2007) HDP (heme detoxification protein) involved in hemozoin formation in *Plasmodium* and *Theileria* as an anti-protozoal target, and high-throughput screening for antimalarial HDP inhibitors. U.S. Pat. Appl. Publ. US 20070148185 A1 20070628

Rauf A, Uddin G, Khan H, Raza M, Zafar M, Tokuda H (2015) Anti-tumour-promoting and thermal-induced protein denaturation inhibitory activities of β-sitosterol and lupeol isolated from *Diospyros lotus* L. Nat Prod Res 30:1205–1207

Ray A, Boyle SM (2011) *In silico* screening method for identifying ligands for odor receptors and olfactory neurons for use as repellents in traps or other media. PCT Int. Appl. WO 2011130726 A2 20111020

Ren G, Sha T, Guo J, Li W, Lu J, Chen X (2015) Cucurbitacin B induces DNA damage and autophagy mediated by reactive oxygen species (ROS) in MCF-7 breast cancer cells. J Nat Med 69:522–530

Richardson P, Campbell B (2015) Drug combination and its use in therapy of obesity comprising (2R)-Methyl-1-{3-[2-(3-pyridinyloxy)ethoxy]-2-pyrazinyl}piperazine or vabicaserin and a sympathomimetic. PCT Int. Appl. WO 2015001359 A1 20150108

Richters A, Basu D, Engel J, Ercanoglu MS, Balke-Want H, Tesch R, Rauh D (2014) Identification and further development of potent TBK1 inhibitors. ACS Chem Biol 10:289–298

Rico A, Van den Brink PJ (2015) Evaluating aquatic invertebrate vulnerability to insecticides based on intrinsic sensitivity, biological traits and toxic mode-of-action. Environ Toxicol Chem 34:1907–1917

Riscoe MK, Kelly JX, Winter RW, Hinrichs DJ, Smilkstein MJ, Nilsen A (2011) U.S. Patent Application 13/153,347

Rosatelli E, Carotti A, Ceruso M, Supuran CT, Gioiello A (2014) Flow synthesis and biological activity of aryl sulfonamides as selective carbonic anhydrase IX and XII inhibitors. Bioorg Med Chem Lett 24:3422–3425

Roy NK, Taneja H (1989) Synthesis of aroyl phosphonates and oximes and their antifungal activity. Int J trop. Agri 6:142–146

Ruckli R, Hesse K, Glauser G, Rusterholz HP, Baur B (2014) Inhibitory potential of naphthoquinones leached from leaves and exuded from roots of the invasive plant *Impatiens glandulifera*. J Chem Ecol 40(4):371–378

Ryder S (2010) U.S. Patent Application 12/823,905

Sadek B, Al-Tabakha MM, Fahelelbom KMS (2011) Antimicrobial prospect of newly synthesized 1, 3-thiazole derivatives. Molecul 16: 9386–9396

Sagheer M, Siddiqui R, Iqbal J, Khan NA (2014) Black cobra (*Naja naja karachiensis*) lysates exhibit broad-spectrum antimicrobial activities. Pathogen Glob Health 108:129–136

Şahin G, Palaska E, Ekizoğlu M, Özalp M (2002) Synthesis and antimicrobial activity of some 1, 3, 4-oxadiazole derivatives. Il. Farmaco 57:539–542

Sakunphueak A, Panichayupakaranant P (2012) Comparison of antimicrobial activities of naphthoquinones from *Impatiens balsamina*. Nat Prod Res 26(12):1119–1124

Salas Vazquez DI, Rodriguez Jerez JJ, Osset Hernandez M, Montanes Izquierdo V (2014) Composition, kit and methods for control and elimination of biofilms. Span. ES 2464872 A1 20140604

Salzet M (2001) Vertebrate innate immunity resembles a mosaic of invertebrate immune responses. Trends Immunol 22:285–288

Samadhiya P, Sharma R, Srivastava SK, Srivastava SD (2014) Synthesis and biological evaluation of 4-thiazolidinone derivatives as antitubercular and antimicrobial agents. Arab J Chem 7:657–665

Sanchez TW, Debnath B, Christ F, Otake H, Debyser Z, Neamati N (2013) Discovery of novel inhibitors of LEDGF/p75-IN protein–protein interactions. Bioorg Med Chem 21:957–963

Sasaki T, Myata H, Morikawa K (1996) Preparation of phosphonic acids as herbicide materials. Jpn. Kok Tok Koh JP 08034790 A 19960206

Savage PB, Li C (2000) Cholic acid derivatives: novel antimicrobials. Expert Opin Invest Drug 9:263–272

Schlewer G, Benezra C, Beck G, Beck JP (1979) The cytotoxic properties of g-mono-, b,g- and g,g-disubstituted a-methylene- g-butyrolactones. Toxicol Eur Res 2:223–226

Schnatterer S, Maier M, Petry F, Knauf W, Seeger K (2009) Pesticidal substituted piperidines and their preparation. U.S. Pat. Appl. Publ. , US 20090082389 A1 20090326

Seo YH, Han CH, Lee JM, Choi SM, Moon KD (2012) Effects of *Opuntia ficus indica* extracts on inactivation of *Escherichia coli* O157: H7 and *Listeria monocytogenes* on fresh-cut apples. J Kor Soc. Food Sci Nutr 41:1009–1013

Shin HB, Choi MS, Ryu B, Lee NR, Kim HI, Choi HE, Inn KS (2013) Antiviral activity of carnosic acid against respiratory syncytial virus. Virol J 10:303

Shiota C, Abe T, Kawai N, Ohno A, Teshima-Kondo S, Mori H, Nikawa T (2015) Flavones inhibit LPS-induced Atrogin-1/MAFbx expression in mouse C2C12 skeletal myotubes. J Nutr Sci Vitam 61:188–194

Simon WA, Postius S, Riedel R, Senn-Bilfinger J, Grundler G (1998) Preparation of 7,8,9,10-tetrahydroimidazo[1,2-h][1,7]naphthyridines for the prevention and treatment of. PCT Int. Appl. WO 9842707 A1 19981001

Sinam YM, Kumar S, Hajare S, Gautam S, Chatterjee S, Variyar PS, Sharma A (2012) Isolation and identification of antibacterial compound from Indo–Himalayan *Aconitum nagarum*. Asia Pac. J Trop Dis 2:S878–S882

Singh U, Raju B, Lam S, Zhou J, Gadwood RC, Ford CW, Zurenko GE, Schaadt RD, Morin SE, Adams WJ, Friis JM (2003) New antibacterial tetrahydro-4 (2H)-thiopyran and thiomorpholine S-oxide and S, S-dioxide phenyloxazolidinones. Bioorg Med Chem Lett 13(23): 4209–4212

Sit SY, Xie K (2003) Bisarylimidazolyl fatty acid amide hydrolase inhibitors U.S. Patent No. 6,562,846

Smetana H (1928) Studies upon the physiological action of hematoporphyrin. J Exp Med 47(4):593–610

Strobel H, Wohlfart P, Kleemann HW, Zoller G, Will DW (2008) Heteroarylacrylamides as endothelial nitric oxide synthase transcription modulators and their preparation and use as. PCT Int. Appl. WO 2008074413 A2 20080626

Su Z, Huang H, Li J, Zhu Y, Huang R, Qiu SX (2013) Chemical composition and cytotoxic activities of petroleum ether fruit extract of fruits of *Brucea javanica* (Simarubaceae. Trop J Pharm Res 12:735–742

Sun JF, Lin X, Zhou XF, Wan J, Zhang T, Yang B, Yang XW, Tu Z, Liu Y (2014a) Pestalols A–E, new alkenyl phenol and benzaldehyde derivatives from endophytic fungus *Pestalotiopsis* sp. AcBC2 isolated from the Chinese mangrove plant *Aegiceras corniculatum*. J Antibiot 67(6):451–457

Sun L, Quan H, Xie C, Wang L, Hu Y, Lou L (2014b) Phosphodiesterase 3/4 inhibitor Zardaverine exhibits potent and selective antitumor activity against hepatocellular carcinoma both in vitro and in vivo independently of phosphodiesterase inhibition. PLoS One 9(3): e90627

Sun XP, Cao F, Shao CL, Wang M, Zhang XL, Wang CY (2015) Antibacterial D1-3-ketosteroids from the South China Sea gorgonian coral *Subergorgia rubra*. Chem Biodiv 12:1068–1074

Sunduru N, Agarwal A, Katiyar SB, Goyal N, Gupta S, Chauhan PM (2006) Synthesis of 2, 4, 6-trisubstituted pyrimidine and triazine

heterocycles as antileishmanial agents. Bioorg Med Chem 14:7706–7715
Suzuki M, Ueno M, Fukutomi R, Satoh H, Kikuchi H, Hagihara K, Noguchi Y (2000) U.S. Patent No. 6,096,746. Washington, DC: U.S. Patent and Trademark Office
Take Y, Inouye Y, Nakamura S, Allaudeen HS, Kubo A (1989) Comparative studies of the inhibitory properties of antibiotics on human immunodeficiency virus and avian myeloblastosis virus reverse transcriptases and cellular DNA polymerases. J Antibiot 42(1):107–115
Tamao K, Minato A, Suzuki K, Kumada M, Tsujimoto K, Hamada M (1986) Heteroallene oligomer derivatives as fungicides. Jpn Kok Tok Koh JP 61037705 A 19860222
Tang Y, Ling J, Zhang P, Zhang X, Zhang N, Wang W, Li N (2015) Potential therapeutic agents for circulatory diseases from *Bauhinia glauca* Benth. subsp. Pernervosa.(Da Ye Guan Men. Bioorg Med Chem Lett 25:3217–3220
Tangdenpaisal K, Worayuthakarn R, Karnkla S, Ploypradith P, Intachote P, Sengsai S, Chittchang M (2015) Designing new analogs for streamlining the structure of cytotoxic lamellarin. Nat Prod Chem–Asia J 10:925–937
Tapia RA, Cantuarias L, Cuéllar M, Villena J (2009) Microwave-assisted reaction of 2, 3-dichloronaphthoquinone with aminopyridines. J Braz Chem Soc 20:999–1002
Taylor PL, Rossi L, De Pascale G, Wright GD (2012) A forward chemical screen identifies antibiotic adjuvants in *Escherichia coli*. ACS Chem Biol 7:1547–1555
Tiuman TS, Ueda-Nakamura T, Alonso A, Nakamura CV (2014) Cell death in amastigote forms of *Leishmania amazonensis* induced by parthenolide. BMC Microbiol 14:152
Tomizawa K, Wei F, Inoue K, Okawara T (2014) Therapeutic agent for type 2 diabetes containing specified benzene compound. PCT Int. Appl. WO 2014156196 A1 20141002
Tracey KJ, Al-Abed Y, Ivanova S, Bucala RJ (2000) Compounds and compositions for treating tissue ischemia. PCT Int. Appl. WO 2000003711 A1 20000127
Uesugi M, Wakil SJ, Al-Elheiga L, Watanabe M (2013a) U.S. Patent Application 14/052,074
Uesugi M, Wakil SJ, Al-Elheiga L, Watanabe M (2013b) U.S. Patent Application 14/013,918
Vance W, Kambam S (2007) U.S. Patent Application 11/676,805
Vassilev GN (1995) Growth regulating and herbicidal activities of benzylphosphonic acid derivatives obtained by the Ivanov reaction. Bulg. Chem Comm 28:231–245
Vennerstrom JL, Makler MT, Angerhofer CK, Williams JA (1995) Antimalarial dyes revisited: xanthenes, azines, oxazines, and thiazines. Antimicrob Agents Chem 39:2671–2677
Verbitskiy EV, Cheprakova EM, Slepukhin PA, Kravchenko MA, Skornyakov SN, Rusinov GL, Charushin VN (2015) Synthesis, and structure–activity relationship for C (4) and/or C (5) thienyl substituted pyrimidines, as a new family of antimycobacterial compounds. Eur J Med Chem 97:225–234
Vergara D, Simeone P, Bettini S, Tinelli A, Valli L, Storelli C, Maffia M (2014) Antitumor activity of the dietary diterpene carnosol against a panel of human cancer cell lines. Food Func 5:1261–1269
Villemagne B, Flipo M, Blondiaux N, Crauste C, Malaquin S, Leroux F (2014) Ligand efficiency driven design of new inhibitors of mycobacterium tuberculosis transcriptional repressor EthR using fragment growing, merging, and linking approaches. J Med Chem 57: 4876–4888
Wada K, Ohkoshi E, Zhao Y, Goto M, Morris-Natschke SL, Lee KH (2015) Evaluation of *Aconitum diterpenoid* alkaloids as antiproliferative agents. Bioorg Med Chem Lett 25:1525–1531
Wang XN, Jin T (2014) The clinical observation of ziprasidone and olanzapine for treating first-episode schizophrenia. Chong Yix 43: 3527–3529
Wang H, Liang F, Zhang L (2015a) Composition and anti-cyanobacterial activity of essential oils from six different submerged macrophytes. Pol J Environ Stud 24(1):333
Wang XD, Wei W, Wang PF, Yi LC, Shi WK, Xie YX, LZ W, Tang N, Zhu LS, Peng J, Liu C (2015b) Synthesis, molecular docking and biological evaluation of 3-arylfuran-2 (5H)-ones as anti-gastric ulcer agent. Bioorg Med Chem 23(15):4860–4865
Weaver JW, Jeroski EB, Goldstein IS (1959) Toxicity of dyes and related compounds to wood-destroying fungi. Appl Microbiol 7:145–149
Wei Y, Qiu G, Wang S (2015) Preparation of substituted 4,5-dihydropyrazolo[3,4-c]pyridine-2-one derivatives for treating serine protease-related disease. PCT Int. Appl. WO 2015081901 A1 20150611
Weitz JI (2014) Expanding use of new oral anticoagulants. F1000 prime reports 6
Wilcke M, Svensson B, Walse B, Bengtsson T (2008) The use of naphthoquinones and related compounds in the treatment and control of diabetes, insulin resistance and hyperglycemia. PCT Int. Appl. WO 2008008033 A1 20080117
Wilson R, Chen C, Ratcliffe NA (1999) Innate immunity in insects: the role of multiple, endogenous serum lectins in the recognition of foreign invaders in the cockroach, *Blaberus. discoidalis*. J Immunol 162:1590–1596
Wirth S, Rohbogner CJ, Cieslak M, Kazmierczak-Baranska J, Donevski S, Nawrot B, Lorenz IP (2010) Rhodium (III) and iridium (III) complexes with 1, 2-naphthoquinone-1-oximate as a bidentate ligand: synthesis, structure, and biological activity. JBIC J Biol Inorg Chem 15:429–440
Wood JE, Baryza JL, Brennan CR, Choi S, Cook JH, Dixon BR (2002) Preparation of 4-phenyl-pyrrolidine-2-ones as 17-b-hydroxysteroid dehydrogenase-II inhibitors. PCT Int. Appl. WO 2002026706 A2 20020404
World Health Organization. Mortality Report. (2002) available at http://www.who.org
Wynne GM, Wren SP, Lecci C (2008) Preparation of imidazopyridines and related compounds for the treatment of Duchenne muscular dystrophy. PCT Int. Appl. WO 2008029152 A2 20080313
Yan J, Xiao L (2015) One kind of moringa leaves flavonoids extraction methods and their use. Fam Zhuan Shenq CN 104758325 A 20150708
Yang JY, Lee HS (2015) Antimicrobial activities of active component isolated from *Lawsonia inermis* leaves and structure-activity relationships of its analogues against food-borne bacteria. J Food Sci Tech 52(4):2446–2451
Yang TC, Chao HF, Shi LS, Chang TC, Lin HC, Chang WL (2014) Alkaloids from Coptis chinensis root promote glucose uptake in C2C12 myotubes. Fitoterapia 93:239–244
Yang S, Zhang H, Beier RC, Sun F, Cao X, Shen J, Zhang S (2015) Comparative metabolism of Lappaconitine in rat and human liver microsomes and in vivo of rat using ultra high-performance liquid chromatography–quadrupole/time-of-flight mass spectrometry. J Pharm Biomed Anal 110:1–11
Yen CH, Chen SJ, Liu JT, Tseng YF, Lin PT (2013) Effects of water extracts of Graptopetalum paraguayense on blood pressure, fasting glucose, and lipid profiles of subjects with metabolic syndrome. BioMed Research Int 2013:809234
Yin TP, Cai L, Fang HX, Fang YS, Li ZJ, Ding ZT (2015) Diterpenoid alkaloids from *Aconitum vilmorinianum*. Phytochem 116:314–319
Youssef DT, Shaala LA, Alshali KZ (2015) Bioactive hydantoin alkaloids from the Red Sea marine sponge Hemimycale arabica. Marin Drug 13:6609–6619
Yuan CL, Wang XL (2012) Isolation of active substances and bioactivity of Aconitum sinomontanum Nakai. Nat Prod Res 26:2099–2102
Yuan Y, Xu J (2015) Compositions and methods for treating herpesvirus infection. PCT Int. Appl. WO 2015081199 A1 20150604
Yuzhakov A (2011) U.S. Patent Application 13/118,317
Zampini IC, Arias ME, Cudmani N, Ordoñez RM, Isla MI, Moreno S (2013) Antibacterial potential of non-volatile constituents of

Rosmarinus officinalis against 37 clinical isolates of multidrug-resistant bacteria. *Bol. latinoam*. Carib Plant Med Arom 12:201–208

Zarzycka B, Seijkens T, Nabuurs SB, Ritschel T, Grommes J, Soehnlein O, Nicolaes GA (2015) Discovery of small molecule CD40–TRAF6 inhibitors. J Chem Inform Mod 55:294–307

Zemtsova MN, Zimichev AV, Trakhtenberg PL, Klimochkin YN, Leonova MV, Balakhnin SM, Bormotov NI, Serova OA, Belanov EF (2011) Synthesis and antiviral activity of several quinoline derivatives. Pharm Chem J 45(5):267–269

Zender L, Wuestefeld T (2012) Small interfering RNA and other inhibitors of mitogen-activated protein kinase kinase 4 expression for liver regeneration and for treatment of liver failure. PCT Int. Appl. WO 2012136859 A1 20121011

Zhao Y, Yu QM, Wang JM (2014) The quantum chemical study on herbicidal activity of the ingredient from *Flaveria bidentis* (L) Kuntze. Guang Huag 42:12–14

Zheng Q, Wang S, Liu W (2014) Discovery and efficient synthesis of a biologically active alkaloid inspired by thiostrepton biosynthesis. Tetrahedron 70(42):7686–7690

Zhu M, Gao H, Wu C, Zhu T, Che Q, Gu Q, Li D (2015) Lipid-lowering polyketides from a soft coral-derived fungus *Cladosporium* sp. TZP29. Bioorg Med Chem Lett 25:3606–3609