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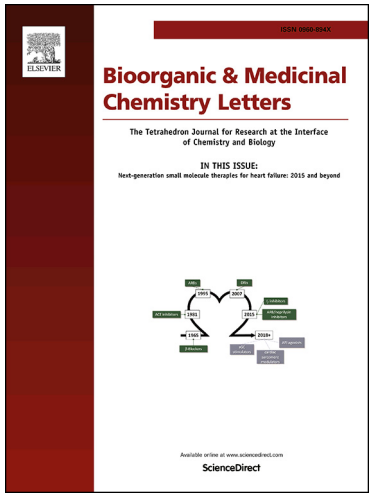

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Synthesis of novel dihydrotriazin derivatives bearing 1,3-diaryl pyrazole moieties as potential antibacterial agents

Tian-Yi Zhang [a,c,*], Chang-Ji Zheng [b,c], Jie Wu [b], Liang-Peng Sun [b], Hu-Ri Piao [b,*]

[a]*Department of Pharmacy, Jilin Medical University, Jilin, Jilin Province 132013, PR China*

[b]*Key Laboratory of Natural Resources and Functional Molecules of the Changbai Mountain, Affiliated Ministry of Education; Yanbian University College of Pharmacy, Yanji, Jilin Province 133002, PR China*

*Correspondence Author: Tel: + 86(433)243-5003; Fax: + 86(433)243-5026.

E-mail: piaohr@ybu.edu.cn (H. R. Piao).

*Correspondence Author: Tel: + 86(432)64561064;

E-mail: tianyizhang@126.com (T. Y. Zhang).

[c] These authors contributed equally to this work.

Abstract

Three novel series of dihydrotriazin derivatives bearing 1,3-diaryl pyrazole moieties were designed, synthesized and evaluated in terms of their antibacterial and antifungal activities. Most of the synthesized compounds showed potent inhibition of several Gram-positive bacterial strains (including multidrug-resistant clinical isolates) and Gram-negative bacterial strains with minimum inhibitory concentration values in the range of 1–64 μg/mL. Compounds **4b** and **4c** presented the most potent inhibitory activity against Gram-positive bacteria (*S. aureus* 4220, MRSA 3167, QRSA 3519) and Gram-negative bacteria (*E. coli* 1924), with minimum inhibitory concentration values of 1 or 2 μg/mL. Compared with previous studies, these compounds exhibited a broad spectrum of inhibitory activity. The cytotoxic activity of the compounds **4a**, **4b**, **4c** and **11n** were assessed in L02 cells. *In vitro* enzyme study implied that compound **4c** exerted its antibacterial activity through DHFR inhibition.

Keywords: Pyrazole; Dihydrotriazine; Antibacterial activity; Antifungal activity; Cytotoxicity; DHFR inhibition

Infections caused by multidrug-resistant (MDR) bacteria, particularly by Gram-negative pathogens, represent a serious and growing threat to human health. The“ESKAPE”pathogens, such as *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, are emerging as threatening pathogens.[1,2] Current bacterial infection treatments have become inadequate and are often associated with higher healthcare costs and increased morbidity and mortality.[3,4] Furthermore, fungal infections pose a serious threat to human health, especially to immunocompromised patients.[5,6] More than 90% of the life-threatening invasive fungal infections (IFIs) are caused by the *Candida*, *Cryptococcus* and *Aspergillus species*. The *Candida species*, particularly *Candida albicans* (*C. albicans*), are the most common cause of IFIs and are ranked as the fourth most common cause of nosocomial bloodstream infections in modern hospitals with approximately 40% mortality.[7,8] Therefore, there is an urgent need for the development of new antibacterial agents with divergent and unique structures and mechanisms of action that differ from those of existing antimicrobial agents.[9]

Heterocyclic chemistry has become one of the most important fields of research in pharmaceutical industry due to their many fold applications. Pyrazoles and its derivatives are important nitrogen containing heterocyclic compounds.[10] Pyrazoles constitute the core structures of natural products and pyrazole based well known drugs are available in the market such as celebrex, viagra and acomplia.[11] Medicinal chemistry studies have shown that a 1,3,5-triazine scaffold is an outstanding pharmacophore, and many molecules with this scaffold have been reported as antibacterial agents. 1,2-Dihydro-1,3,5-triazine (Baker triazines) compounds are by far the best known, with several studies exploring their potential as inhibitors of eukaryotic dihydrofolate reductase (DHFR), an important enzyme in the de novo pathway of purine and thymidine synthesis, and small molecules targeting this enzyme have demonstrated utility as potential antibiotics.[12,13] In our previous work, we reported the identification of a series of 1,3-diphenyl-1*H*-pyrazoles functionalized with rhodanine derivatives, and demonstrated that all of the compounds belonging to this series showed outstanding bacteriostatic activity against Gram-positive bacteria,

as exemplified by compounds **A** and **B** (MIC = 2 µg/mL and 16 µg/mL, respectively) (Fig. 1).[14,15] Unfortunately, compounds belonging to this series did not show any bacteriostatic activity against Gram-negative bacteria. In contrast, we synthesized a series of dihydrotriazine derivatives containing benzyl naphthalene moieties. Compounds **C** and **D** were found to be the most potent of all of the compounds tested, with an MIC value of 0.5 µg/mL or 1 µg/mL against several Gram-positive (*S. aureus* 4220 and QRSA CCARM 3505) and Gram-negative (*E. coli* 1924) strains of bacteria. (Fig. 1).[16,17] In this study, we designed and synthesized three novel series of compounds (**4a-c**, **8a-i**, **11a-p**) (Fig. 2) using a hybrid strategy with compounds **A**-**D** as the lead compounds, in which the rhodamine moiety was replaced by a dihydrogentriazine scaffold. Simultaneously changing the substituents on the phenyl ring of the pyrazole, to investigate their effects on activity. Inspired from existing antibacterial agents bearing nitro groups, such as chloramphenicol that operates via inhibition of bacterial protein synthesis after the nitro group is metabolized to a hydroxyamino group, nitro group was introduced into the phenyl ring on the N^1 position of the pyrazole. Thus, three series of 28 dihydrotriazin derivatives bearing 1,3-diaryl pyrazoles were synthesized, characterized and screened.

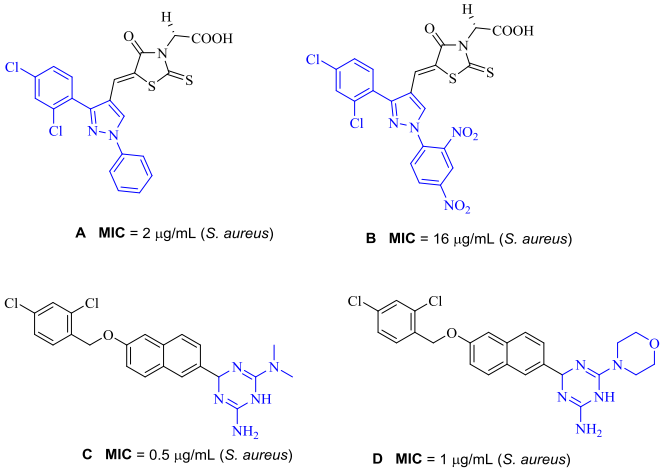


Figure 1. Previously reported antibacterial compounds

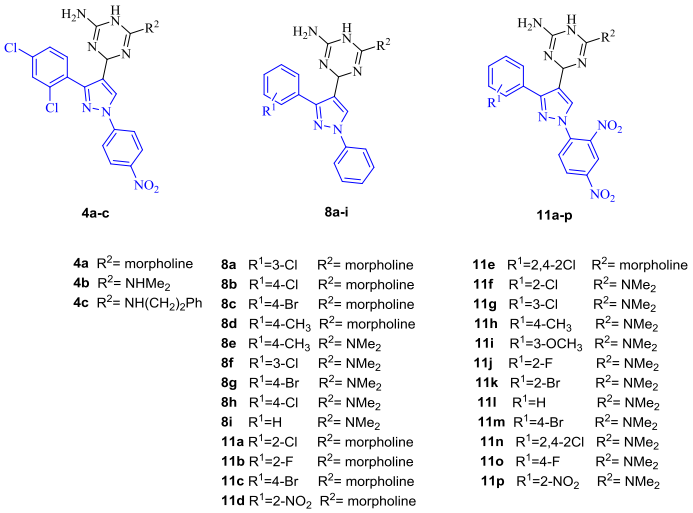
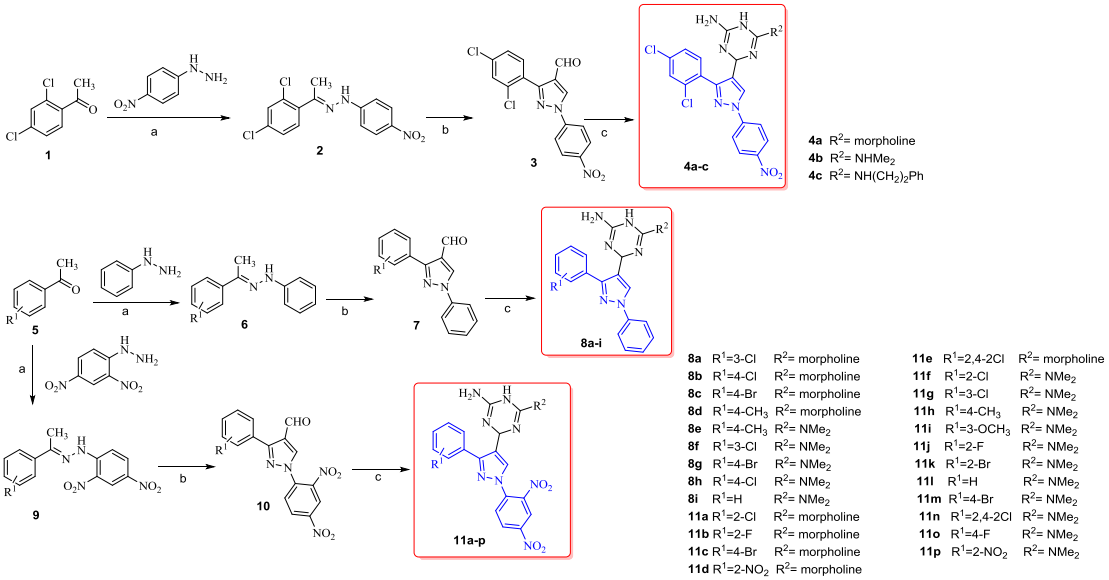


Figure 2. Designed target compounds

The targets were synthesized according to the route depicted in Scheme 1. Hydrazone derivatives (compounds **2**, **6** and **9**) were prepared by reacting substituted acetophenones with phenylhydrazine, 4-nitrophenylhydrazine or 2,4-dinitrophenylhydrazine in the presence of glacial acetic acid in ethanol.[18] A series of intermediates (**2**, **6** and **9**) reacted under Vilsmeier-Haack (DMF-$POCl_3$) conditions and afforded corresponding 4-carboxaldehyde functionalized pyrazole intermediates (**3**, **7** or **10)**.[19,20] Then, the intermediates were reacted with moroxydine hydrochloride, metformin hydrochloride or phenformin hydrochloride in acetic acid to generate the target compounds.[17] The structures of the synthesized dihydrotriazine compounds were characterized by ^{1}H NMR, ^{13}C NMR, MS and HRMS analyses. The purity (≥95%) of the compound is verified by the HPLC study performed on Develosil C18 (4.6 mm×250 mm, 5 μm) column using a mixture of solvent 0.1FA acetonitrile/0.1FA water at the flow rate of 1 mL/min and peak detection at 311 nm under UV.[21]



Scheme 1. Synthetic scheme for the synthesis of the target compounds. Reagents and conditions: (a) EtOH, AcOH or AcONa, Reflux 5-7 h, (b) $POCl_3$, DMF, 0℃, 0.5 h, 70℃, 6h, (c) Moroxydine hydrochloride or metformin hydrochloride or phenformin hydrochloride, AcOH, 120℃, 4-8 h.

The MIC values of the synthesized compounds were determined against *S. aureus*, *E. coli*, *Candida albicans*, *Streptococcus mutans* and the clinical isolates of multidrug-resistant Gram-positive bacterial strains (Tables 1 and 2).[22] Gatifloxacin, moxifloxacin, norfloxacin, and oxacillin were used for the antibacterial activity, fluconazole and itraconazole for the antifungal activity as positive controls.

As shown in Table 1, most of the synthesized compounds showed good inhibitory activities against the different bacteria and the one fungus tested in the current study with MICs ranging from 1-64 μg/mL. Compound **4c** had the highest activity against the two different types of Gram-positive bacteria, with an MIC value of 1 μg/mL, this was slightly lower than gatifloxacin (MIC = 0.25 μg/mL) and moxifloxacin (MIC = 0.25 μg/mL). Against the Gram-negative *E. coli* 1924, compounds **4b** and **4c** were equipotent or more potent than the positive controls gatifloxacin and moxifloxacin (MIC = 2 μg/mL), with an MIC of 1 μg/mL. In terms of its activity towards the fungus *C. albicans* 7535, compound **4c** displayed the strongest potency of all of the compounds synthesized in series **4** with an MIC value

of 1 μg/mL, which was equal to that of fluconazole. Compounds **4a** and **4b** also displayed good potency, with an MIC of 4 μg/mL, which was slightly lower than that of fluconazole (MIC = 1 μg/mL).

As indicated in Table 2, all of the synthesized compounds were also tested for their inhibitory activities against the clinical isolates of several different multidrug-resistant Gram-positive bacterial strains (MRSA CCARM 3167 and 3506, QRSA CCARM 3505 and 3519). Compound **4c** showed potent activity against the MRSA (3167 and 3506) strains, with an MIC value of 1 μg/mL. This was equivalent to moxifloxacin (MIC = 1 μg/mL) and greater than gatifloxacin (MIC = 2 μg/mL), oxacillin (MIC > 64 μg/mL) and norfloxacin (MIC = 8 μg/mL for MRSA 3167 and 4 μg/mL for MRSA 3056). Compounds **4a** and **4b** showed the same potenty as gatifloxacin (MIC = 2 μg/mL) against the MRSA (3167 and 3506) strains. For the QRSA (CCARM 3505 and 3519) strains, compound **4c** also had the greatest inhibitory effect, with an MIC value of 1 μg/mL. This was equivalent to oxacillin (MIC = 1 μg/mL) and stronger than moxifloxacin (MIC = 4 μg/mL), norfloxacin (MIC > 64 μg/mL) and gatifloxacin (MIC = 8 μg/mL against CCARM 3505 and 4 μg/mL against CCARM 3519). Compounds **4a**, **4b**, **11g** and **11m** were equipotent to the positive controls moxifloxacin (MIC = 4 μg/mL for QRSA 3505), with an MIC of 4 μg/mL.

Based on the present data of the synthesized compounds, simple structure-activity relationships (SAR) could be proposed. The introduction of a dihydrotriazin moiety resulted in moderate to good levels of inhibition against the Gram-negative strains. Comparing the antibacterial activity of the compounds in series **4**, **8** and **11**, compounds in series **4** showed better activity than those in series **8** and **11** against most of the test strains, which suggested that the 4-nitrophenyl moiety at the N^1 position of the pyrazole is critical. Nevertheless, the introduction of a 2-nitrophenyl moiety on the phenyl ring, as exemplified by the compounds **11d** and **11p**, resulted in a significant difference in the activity, which indicated that the increase of 2-nitrophenyl moiety on the phenyl ring did not exhibit a positive impact on the activity. Furthermore, no clear pattern was found for the SAR between the

antibacterial activity and the position and physicochemical properties of different substituents on the phenyl ring, indicating that the electronic effect of the substituent on the benzene ring is not critical. Isosteric replacement with a phenethyl group at the *N*-position of the dihydro-1,3,5-triazine ring, as exemplified by the compounds in series **4**, resulted in a significant difference in the activity, indicating that the phenethyl group was critical to the activities of these compounds.

Table 1. Inhibitory activity (MIC, μg/mL) of compounds **4a**–**c**, **8a**–**i** and **11a**–**p** against various bacteria.

Compound	R^1	R^2	Gram-positive strains		Gram-negative strains	Fungus
			4220[a]	3289[b]	1924[c]	7535[d]
4a	2,4-di-Cl	morpholine	2	8	4	4
4b	2,4-di-Cl	$NHMe_2$	2	4	2	4
4c	2,4-di-Cl	$NH(CH_2)_2Ph$	1	1	1	1
8a	3-Cl	morpholine	16	32	16	16
8b	4-Cl	morpholine	16	32	16	16
8c	4-Br	morpholine	8	32	16	16
8d	4-CH_3	morpholine	64	64	64	64
8e	4-CH_3	$NHMe_2$	32	64	32	32
8f	3-Cl	$NHMe_2$	4	16	8	8
8g	4-Br	$NHMe_2$	8	16	8	8
8h	4-Cl	$NHMe_2$	8	32	8	8
8i	H	$NHMe_2$	32	>64	64	>64
11a	2-Cl	morpholine	32	64	64	64
11b	2-F	morpholine	64	>64	64	64
11c	4-Br	morpholine	8	16	8	8
11d	2-NO_2	morpholine	>64	>64	>64	>64
11e	2,4-di-Cl	morpholine	16	16	8	8
11f	2-Cl	$NHMe_2$	32	64	32	64
11g	3-Cl	$NHMe_2$	4	8	8	8
11h	4-CH_3	$NHMe_2$	16	16	16	64
11i	3-OCH_3	$NHMe_2$	32	64	32	32
11j	2-F	$NHMe_2$	64	64	32	32
11k	2-Br	$NHMe_2$	32	32	32	64
11l	H	$NHMe_2$	32	64	32	32
11m	4-Br	$NHMe_2$	8	16	8	8
11n	2,4-di-Cl	$NHMe_2$	8	8	8	8
11o	4-F	$NHMe_2$	32	32	32	32
11p	2-NO_2	$NHMe_2$	>64	>64	>64	>64
Gatifloxacin			0.25	0.25	2	n.d

Moxifloxacin	0.25	0.25	2	n.d
Fluconazole	n.d	n.d	n.d	1
Itraconazole	n.d	n.d	n.d	0.6

[a] *Staphylococcus aureus RN* 4220. [b] *Streptococcus mutans* 3289.

[c] *EscherichiaColiKCTC* 1924. [d] *Candida albicans* 7535.

S. aureus RN 4220 is a genotype of *S. aureus*. KCTC, Korean Collection for Type Cultures; CCARM, Culture Collection of Antimicrobial Resistant Microbes; n.d.: Not determined

Table 2. Inhibitory activity (MIC, μg/mL) of compounds **4a–c**, **8a–i** and **11a–p** against clinical isolates of multidrug-resistant Gram-positive strains.

Compound	R^1	R^2	Multidrug-resistant Gram-positive strains			
			MRSA		QRSA	
			3167[a]	3506[b]	3505[c]	3519[d]
4a	2,4-di-Cl	morpholine	2	2	4	4
4b	2,4-di-Cl	$NHMe_2$	2	2	4	2
4c	2,4-di-Cl	$NH(CH_2)_2Ph$	1	1	1	1
8a	3-Cl	morpholine	16	16	16	16
8b	4-Cl	morpholine	16	16	16	16
8c	4-Br	morpholine	8	4	16	8
8d	4-CH_3	morpholine	32	32	64	64
8e	4-CH_3	$NHMe_2$	16	32	64	64
8f	3-Cl	$NHMe_2$	16	16	32	32
8g	4-Br	$NHMe_2$	4	4	16	16
8h	4-Cl	$NHMe_2$	16	8	16	16
8i	H	$NHMe_2$	32	32	32	64
11a	2-Cl	morpholine	32	32	32	64
11b	2-F	morpholine	64	32	64	64
11c	4-Br	morpholine	8	4	8	8
11d	2-NO_2	morpholine	>64	>64	>64	>64
11e	2,4-di-Cl	morpholine	8	8	8	16
11f	2-Cl	$NHMe_2$	32	64	32	64
11g	3-Cl	$NHMe_2$	4	4	4	16
11h	4-CH_3	$NHMe_2$	8	8	8	16
11i	3-OCH_3	$NHMe_2$	32	32	64	64
11j	2-F	$NHMe_2$	64	32	64	64
11k	2-Br	$NHMe_2$	32	32	32	64
11l	H	$NHMe_2$	32	64	32	64
11m	4-Br	$NHMe_2$	8	4	4	8
11n	2,4-di-Cl	$NHMe_2$	4	4	8	16
11o	4-F	$NHMe_2$	32	32	64	64
11p	2-NO_2	$NHMe_2$	>64	>64	>64	>64
Gatifloxacin			2	2	8	4

Moxifloxacin	1	1	4	4
Norfloxacin	8	4	>64	>64
Oxacillin	>64	>64	1	1

[a] *Methicillin-resistant S. aureus CCARM* 3167. [b] *Methicillin-resistant S. aureus CCARM* 3506. [c] *Quinolone-resistant S. aureus CCARM* 3505. [d] *Quinolone-resistant S. aureus CCARM* 3519.

To determine whether the antibacterial and antifungal activities of the synthesized compounds were selectively toxic towards bacteria and the fungus, we evaluated the cytotoxicity of the compounds **4a**, **4b**, **4c** and **11n** using a standard technique.[23] As shown in Table 3, the result indicated that the compounds **4a**, **4b** and **11n** showed any appreciable cytotoxic activity (IC_{50} > 100 μmol/L against L02 cells), suggesting that the promising antibacterial activity of these compounds is not due to their toxicity, but some unknown mechanism of action.

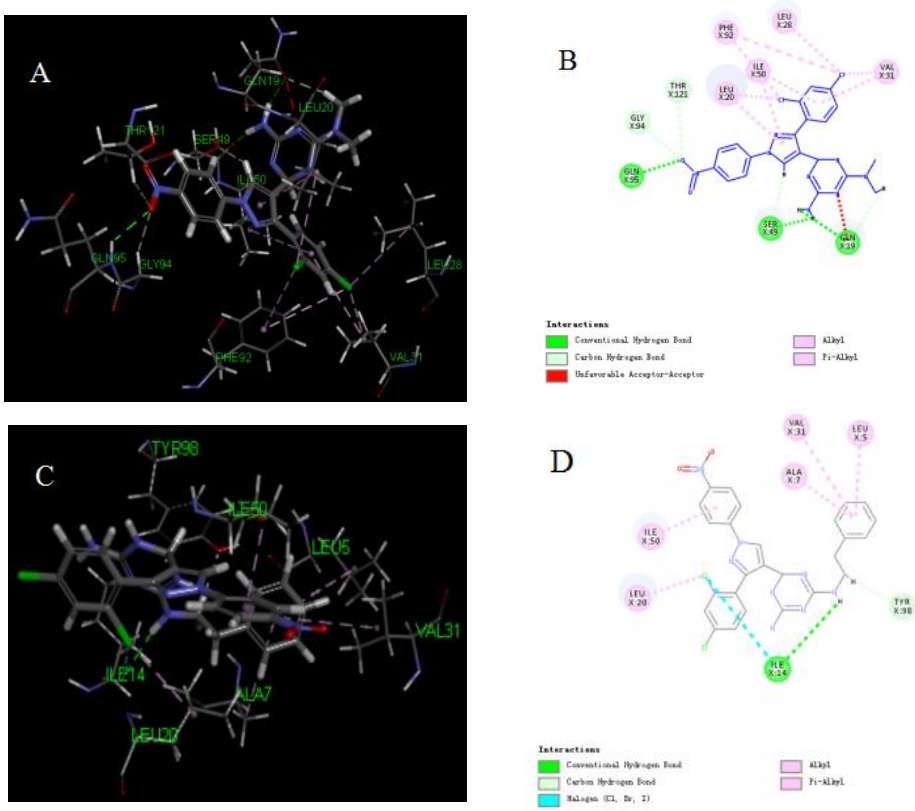
Table 3. Antibacterial activity and cytotoxicity for **4a**, **4b**, **4c** and **11n**

	Test organisms	4a	4b	4c	11n
MIC (μmol/L)	*S. aureus* 4220	3.9	4.2	1.8	15.5
	MRSA 3167	3.9	4.2	1.8	7.7
IC_{50}[a] (μmol/L)	L02[b]	>100	>100	50.46	>100

[a] IC_{50} is the concentration required to inhibit the cell growth by 50%. Data represent the average of three independent experiments running in triplicate. Variation was generally between 5–10%. [b] Human normal hepatic cells.

Molecular docking is a significant computational method used to forecast the binding of the ligand to the receptor binding site by varying position and conformation of the ligand keeping the receptor rigid. To rationalize the observed antibacterial activity and understand the possible mechanism of action of these compounds, a libdocking investigation was undertaken. The crystal structure data (*S. aureus* DHFR) were obtained from the protein data bank (PDB ID: 3fra).[24,25] The water molecules and heavy atom in protein were removed and the protein was prepared by adding hydrogen and correcting incomplete residues using Clean Protein tool of DS, then the protein was refined with CHARMm. The structures of **4b**, **4c** and **11l** were sketched in 2D and converted into 3D using the DS molecule editor (Fig. 3). Fragment A of **4b** is bound into the active site, in which the benzene ring formed pi-alkyl bond with Phe 92. The pyrazole N atom of **4b** formed alkyl bond with Leu 20

and nitro group of **4b** formed hydrogen bond with the backbone of Gly 94 and Gln 95. The dihydrotriazin ring N atom of **4b** interacted with Gln 19 *via* Conventional hydrogen bond. Fragment B of **4c** is bound into the active site, in which the benzene ring formed alkyl bond with Leu 5, Val 31 and Ala 7. The Cl atom of **4c** interacted with the backbone of Ile 14 and Leu 20. Fragment C of **11l** is bound into the active site where the pyrazole N atom shows interaction with Gln 95 *via* Conventional hydrogen bond. Nitro group of **11l** also formed Conventional hydrogen bond with the backbone of Gly 94 and Thr 96. The benzene ring of **11l** formed pi-alkyl bond with Ile 14. Our docking results indicated that more active compounds **4b** and **4c**, showed the more favorable intermolecular interactions with the DHFR active site than compound **11l**. The preliminary docking results imply that compounds **4b**, **4c** and **11l** possibly display their antibacterial activity through the interaction with DHFR protein by targeting residues of the active cavities of DHFR.



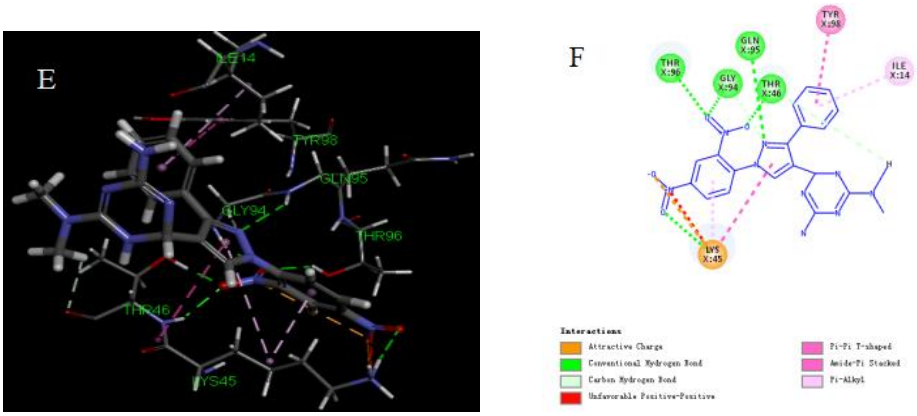


Figure 3. Docking result of compound **4b**, **4c** and **11l**. (A) Key residues in binding site surrounding **4b**. (B) 2D molecular docking modeling of compound **4b** with 3fra. (C) Key residues in binding site surrounding **4c**. (D) 2D molecular docking modeling of compound **4c** with 3fra. (E) Key residues in binding site surrounding **11l**. (F) 2D molecular docking modeling of compound **11l** with 3fra.

In order to confirm this phenomenon, compound **4c (**MIC= 1 μg/mL**)** was tested for its ability to inhibit DHFR activity *in vitro* enzyme assays (Fig. 4).[26] The test molecule rendered a inhibitory against the dihydrofolate reductase at 10 μmol/L, comparably indicated its cause 92% decrease than that of the control group. The results implied that compound **4c** exerted its antibacterial activity through DHFR inhibition.

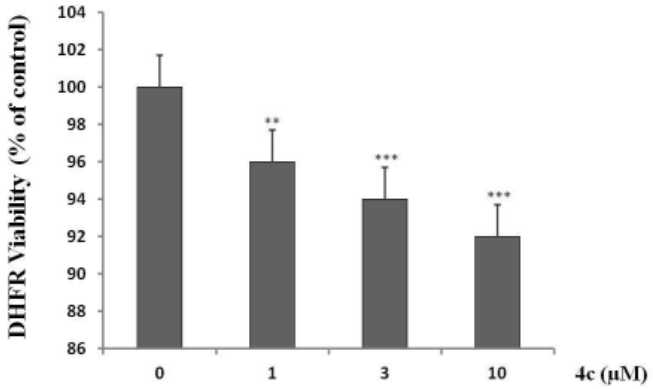


Figure 4. Inhibition of DHFR activities *in vitro*.

In summary, we have synthesized three novel series of dihydrotriazin derivatives bearing 1,3-diaryl pyrazole moieties and evaluated their antibacterial and antifungal activities. The results showed that most compounds exhibited moderate to good levels of antibacterial activities. In particular, all of the compounds in series **4** exhibited good levels of antibacterial activities against Gram-negative strains (*E. coli* 1924) and

antifungal activity (*C. albicans* 7535). These results suggested that the dihydrotriazine derivatives bearing 1,3-diaryl pyrazole moieties, which play a critical role in increasing the antibacterial properties of the compounds, represented promising lead compounds for the development of novel antibacterial agents. *In vitro* enzyme study implied that compound **4c** exerted its antibacterial activity through DHFR inhibition.

Acknowledgment

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21. *Preparation of **4b***: Synthesized intermediate compounds (1 mmol) and Metformin hydrochloride (1 mmol) were refluxed in glacial acetic acid (7 mL) at 120^{o}C for 4–8 h. The whole processes of the reactions were traced by TLC, then removed solvent under reduced pressure. The crude products were purified by column chromatography (dichloromethane : methanol = 20 : 1). Yield 50%; m.p. 234-236 ^{o}C. ^{1}H NMR (DMSO-d_6, 300 MHz, ppm): δ 9.06 (s, 1H, NH), 8.86 (s, 1H, NH), 8.59 (s, 1H, NH), 8.41 (d, *J* = 9.1 Hz, 2H, Ar-H), 8.18 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.78 (s, 1H, Ar-H), 7.55 (s, 2H, Ar-H), 7.37 (s, 1H, CH), 5.82 (s, 1H, CH),2.90 (s, 6H, CH_3). ^{13}C NMR (126 MHz, DMSO) δ 157.64, 155.90, 149.62, 145.77, 143.83, 135.06, 134.65, 133.86, 130.35, 129.64, 129.46, 127.80, 126.07, 125.15, 119.19, 56.50. HRMS (ESI) m/z calcd for $C_{20}H_{19}Cl_2N_8O_2$ (M+H) 473.10025, found 473.10022. HPLC purity of 95.34% (retention time = 13.04 min).

22. *Evaluation of anti-bacterial activity in vitro*: The micro-organisms used in the present study were *S. aureus* 4220, *S.mutans* 3289, *E. Coli* 1942 and *C. Albicans* 7535. The strains of multidrug-resistant clinical isolates were methicillin-resistant *S. aureus* (MRSA CCARM 3167 and 3506) and quinolone-resistant *S. aureus* (QRSA CCARM 3505 and 3519). Clinical isolates were collected from various patients hospitalized in several clinics. Test bacteria were grown to mid-log phase in MuellereHinton broth (MHB) and diluted 1000-fold in the same medium. The bacteria of 10^5 CFU/mL were inoculated into MHB and dispensed at 0.2 mL/well in a 96-well microtiter plate. As positive controls, oxacillin and norfloxacin were used. Test compounds were prepared in DMSO, the final concentration of which did not exceed 0.05%. A two-fold serial dilution technique was used to obtain final concentrations of 64-0.25 μg/mL. The MIC was defined as the concentration of a test compound that completely inhibited

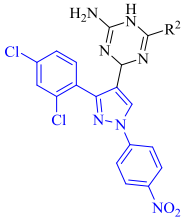
bacteria growth during 24 h incubation at 37 ^{o}C. Bacteria growth was determined by measuring the absorption at 650 nm using a microtiter enzyme-linked immunosorbent assay (ELISA) reader. All experiments were carried out three times.

23. *Cytotoxicity on human cells*: The cytotoxicity test of selected compounds was measured through the colorimetric MTT assay. Human normal liver cells (L02) suspension in DMEM medium supplemented with 10% FBS and antimycotic was added in 96-well microplates at 1.8×10^4 cells/well. A variety of concentrations of the test compounds (200, 100, 50, 25, 12.5, 6.25, 3.125, 1.625 μM/L) dissolved by distilled 10% DMSO was added to each well. Incubation for 24h at 37℃ under 5% CO_2, 2.5mg/mL of MTT solution was added to each well. Further the plate was incubated for 4h. Then, the medium was removed and the resulting formazan crystals were dissolved with 100 μL DMSO. After shaking 10 min, the optical density was measured at 570 nm using a microtiter ELISA reader. The selected compounds were used as positive control, whereas untreated cells were used as negative controls. The IC_{50} values were defined as the concentrations inhibiting 50% of cell growth. All experiments were performed in triplicate.

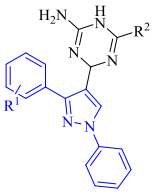
24. Lam T, Hilgers MT, Cunningham ML, et al. *J Med Chem*. 2014;57:651.

25. Vijesh AM, Isloor AM, Peethambar SK, et al. *Eur J Med Chem*. 2011;46:5591.

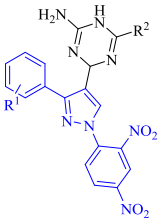
26. *Inhibition of DHFR activities in vitro:* The test of compound **4c** was measured through the ELISA assay. Solid-phase antibody was prepared by coating the microtiter plate wells with purified human dihydrofolate reductase (DHFR) antibody. A variety of concentrations of the test compound (0, 1, 3, 10 μmol/L) was combined with DHFR. Incubation for 1.5 h at 37℃, HRP labeled was added to become antibody-antigen-enzyme-antibody complex. After washing completely, TMB substrate was added, TMB substrate was becoming blue color at HRP enzyme-catalyzed. Reaction was terminated by the addition of a sulphuric acid solution and the color change was measured spectrophotometrically at a wavelength of 450 nm. The concentration of DHFR activity was calculated by a standard curve.



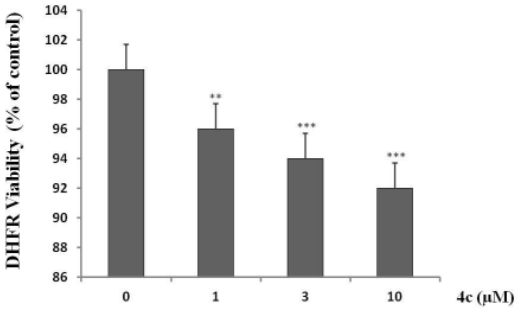
4a-c



8a-i



11a-p



Three novel series of dihydrotriazine derivatives were designed, synthesized, and evaluated for their antibacterial and antifungal activity.