Med Chem Res (2014) 23:3793–3802
DOI 10.1007/s00044-014-0960-x

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Identification of novel bacterial RNA polymerase "Switch Region" inhibitors using pharmacophore model based on multi-template and similarity research

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Received: 11 November 2013 / Accepted: 14 February 2014 / Published online: 1 March 2014

Abstract Bacterial RNA polymerase, which is a complex molecular machine for RNA synthesis in all cellular organisms, appears to be a new discovered and potential protein. Switch Region of bacterial RNA polymerase turns out to be an ideal target for antibiotics in consequence of highly conserved in gram-positive/negative bacterial and non-conserved in human RNAP. Present study collected recently discovered bacterial RNAP inhibitors and generated a pharmacophore query in combination with similarity research for new antibiotics identification. The generated query is consisted of three features: one hydrophobic site and two acceptor atoms. Then, pharmacophore and similarity research as two different strategies were used against to 1,623,646 compounds from ZINC database. Finally, ten compounds were filtered out as potential antibiotics. This work could be less limitation in various scaffold research and more accuracy in antibiotics discovery by applying novel inhibitors.

Keywords Bacterial RNA polymerase · Switch Region · Pharmacophore model · Similarity research · Antibiotics

Introduction

RNA polymerase (RNAP), also called DNA-dependent RNA polymerase, is a complex molecular machine for RNA synthesis in all cellular organisms. The bacterial RNAP "core enzyme" consists of five subunits with total molecular mass of around 400 kDa. These subunits in bacteria are highly conserved and identified as β', β, α^{I}, α^{II}, and ω in order of molecular mass. (Sekine *et al*., 2012; Richard and Bright, 2000; Saecker and Record, 2011; Iyer *et al*., 2004; Darst, 2001). RNAP resembles a crab claw with two pincers that participate in regulation of DNA into the catalytic cleft. Generally, the largest β' subunit in bacterial RNAP form one pincer "clamp" and second-largest β form the other pincer. Two pincers form the positively charged active-center cleft containing a determinant which can interact with unwounded DNA in transcription. As to the ω subunit, it stabilizes its connection with α_2-β sub-structures assembly. The primary function of sigma factor is identification of a specific promoter located on DNA sequences and essentially serves to assemble "core enzyme" together as "holoenzyme" (Darst, 2001; Campbell *et al*., 2008; Feklistov and Darst, 2011; Tuske *et al*., 2005; James *et al*., 2012; Borukhov and Konstantin, 2002). Moreover, two special channels (secondary channel and RNA-exit channel) exist in RNAP with different functions. The secondary channel mediates the entrance of nucleotide triphosphate while RNA-exit channel charges of egress of nascent RNA from the active-center cleft (Tuske *et al*., 2005).

In vivo, RNAP is responsible for regulation of transcription (Darst, 2001; Belogurov *et al*., 2009). In initiation step, a single polypeptide is required to bind to the RNAP for holoenzyme formation. The holoenzyme locates the promoters and melts the DNA transcription start site for synthesis of RNA chain. As the RNA chain grows as long as ten nucleotides or so, the polypeptide is released and core RNAP elongates the RNA. In the end, RNAP separates itself from DNA template after engaging a

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termination signal. In context of biological progress, each clamp conformational state was defined and the difference between opening and closing states, surprisingly, turned out to be 20° (Sekine *et al*., 2012; Chakraborty *et al*., 2012).

After unlocking crystal structure of bacterial RNAP, it is certified that four binding sites are essential to biological function and inhibition of current protein: Rifamycins binding site, Lipiarmycin binding site, Streptolydigin binding site, and recently discovered Switch Region. Even various binding sites being explored, the clinical utility of most inhibitors are greatly limited by resistance as consequence of residues substitution (Tuske *et al*., 2005; Srivastava *et al*., 2011; Mukhopadhyay *et al*., 2008; Agarwal *et al*., 2008; Darst, 2004; Doundoulakis *et al*., 2004; Lira *et al*., 2007).

Among these binding sites, RNAP Switch Region shows its potential in antibacterial therapy as following: (a) locates in a completely different regions to other sites so that its inhibitors having no cross resistances with others; (b) residues in Switch Region are highly conserved in Gram-positive/negative bacteria RNAP, which is an advantage on broad-spectrum bacterial inhibition; (c) Switch Region contains residues that are not conserved in human RNAP, which provides a basis for therapeutic selectivity; (d) indispensability for the only transcription channel in bacterial and highly efficiency in antimicrobial. So far, only several Switch Region inhibitors were explored, namely myxopyronin series, ripostatin, squaramides series, and a hybrid-type agent. Myxopyronin, and its 197 analogs were covered by patent; squaramides series containing 9 analogs were newly discovered by Buurman, and a hybrid-type agent was synthesized by Fumika Yakushiji team (Srivastava *et al*., 2011; Mukhopadhyay *et al*., 2008; Buurman *et al*., 2012; Yakushiji *et al*., 2013; Li *et al*., 2011). Here, myxopyronin, corallopyronin, ripostatin, squaramides-1, and hybrid-type agent were selected as five templates for the study.

More comprehensive perspective than previously reported work, present study makes a good use of these new inhibitors in pharmacophore modeling and structural similarity method to explore new scaffolds antibacterial RNAP agents (Li *et al*., 2011). In pharmacophore generation, these inhibitors were calculated using docking program to obtain reasonable and optimized conformation. Based on their affinities with Switch Region pocket, three pharmacophore features were defined in a specific arrangement. The reliability of generated model was test by large numbers patent compounds. Using the best model, 1,623,646 compounds from ZINC database were screened for new candidates. Considering the essential roles played by molecular structure in protein–ligand contact, filtered candidates were subjected to structures similarity research with five template inhibitors. The final compounds were picked out as potential inhibitors to Switch Region and expected to be useful in antibacterial therapy.

Materials and methods

Ligand and protein preparation

Initially, 3D structures of five inhibitors were built in ChemBioOffice 2010 followed by modification of atom types, energy minimization, and optimization in Sybyl-X 1.3 (Tripos Associates, Inc., St Louis, MO, USA). The crystal structure of bacterial RNAP (PDB ID: 3DXJ) was downloaded directly from Protein Data Bank. The protein was modified by energy minimization and optimization as well, and the docking site was defined by collection of residues around ligand site (Mukhopadhyay *et al*., 2008; Li *et al*., 2011; Chen and Reynolds, 2002). In order to obtain the most reasonable conformation, each inhibitor was docked into RNAP Switch Region by Gold 5.0 program (Cambridge Crystallographic Data Center, UK). Taking the steric and electric factors into consideration, reasonable conformation of each compound was picked out for later process.

Pharmacophore generation and database filtration

According to interaction and specific structures of inhibitors, pharmacophore features were selected and a common pharmacophore model was developed. The reliability of model was further tested by examining existed Switch Region inhibitors. As most applied technique in virtual screening, this pharmacophore was used as query to search pharmacophore-matched compounds.

Similarity research

Quantitative measurement of chemical similarity leads a significant role in drug discovery techniques which can be identified by its application in database researching, QSAR analysis, and diversity analysis. In this technique, the similar property principle is emphasized for the states that similar structures lead to similar physicochemical and biological properties significantly. All inhibitors candidates in this step were carried out similarity research based on five templates compounds using similarity research protocol in Discovery Studio 2.5 (Srivastava *et al*., 2011; Mukhopadhyay *et al*., 2008; Yakushiji *et al*., 2013; Buurman *et al*., 2012). In research progress, one basic principle, which is matching at least four templates and structural similarity within top 2 %, was applied for compounds selection.

Docking

To assess, if these compounds are suitable for target or not, docking calculation was carried out using GOLD 5.0 program (Cambridge Crystallographic Data Center, UK). The numbers of operations in docking were set to 100,000, and gold score was chosen as score function. Other parameters were kept at their default values. In order to certify logical parameters, redock step was carried out, and RMSD value was 1.831. The alignment of docked conformation and reference molecule showed that a slight difference occurred in hydrophobic. Whereafter, compounds that had better scores and reasonable conformations were selected. The whole work flow is concisely represented in Fig. 1.

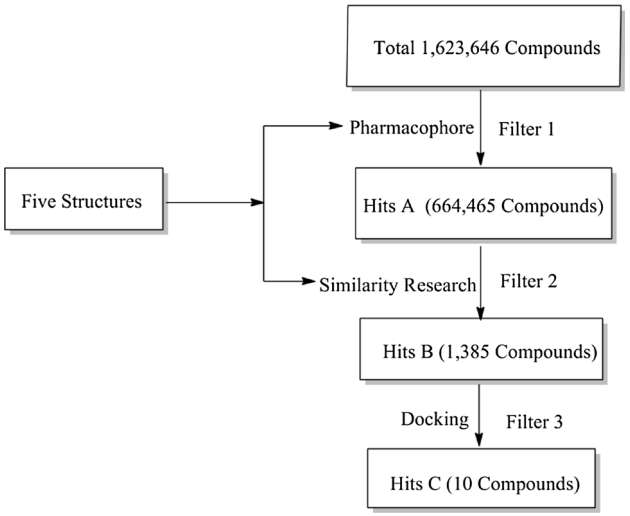


Fig. 1 The diagram of current work flow

Results and discussion

Pharmacophore generation and database filtration

In model generation, binding affinities of five template inhibitors were first concerned, which were also significant in filtering candidates (Fig. 2). Each agent contains various types of carbonic rings as well as no bifurcation occurs in main chain. It is known to all that Switch Region is mostly buried with a little surface accessibility for entrance of

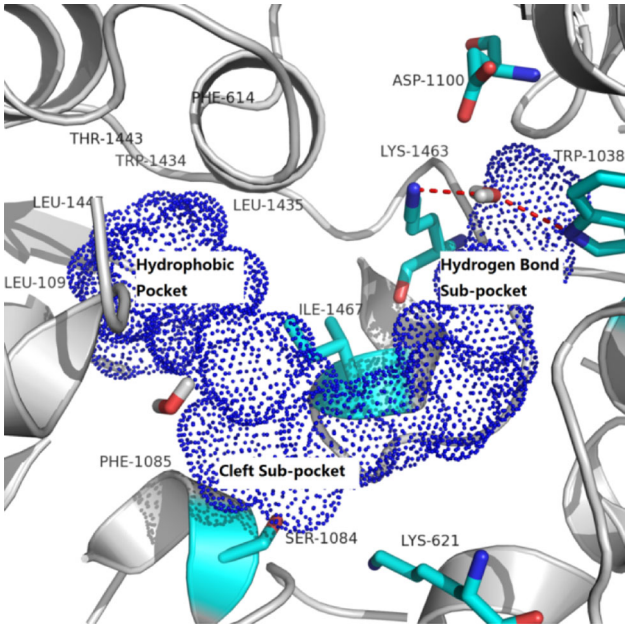
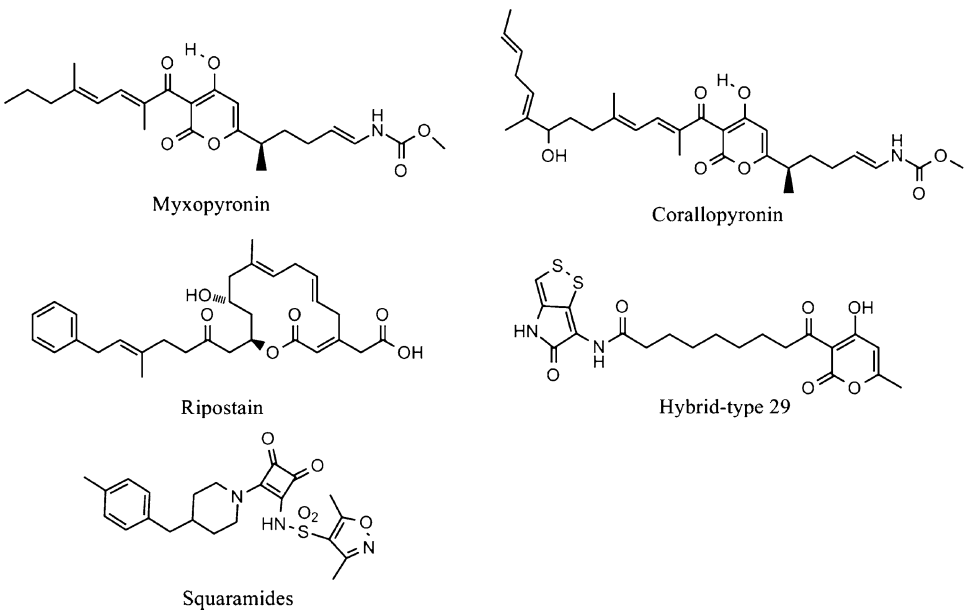
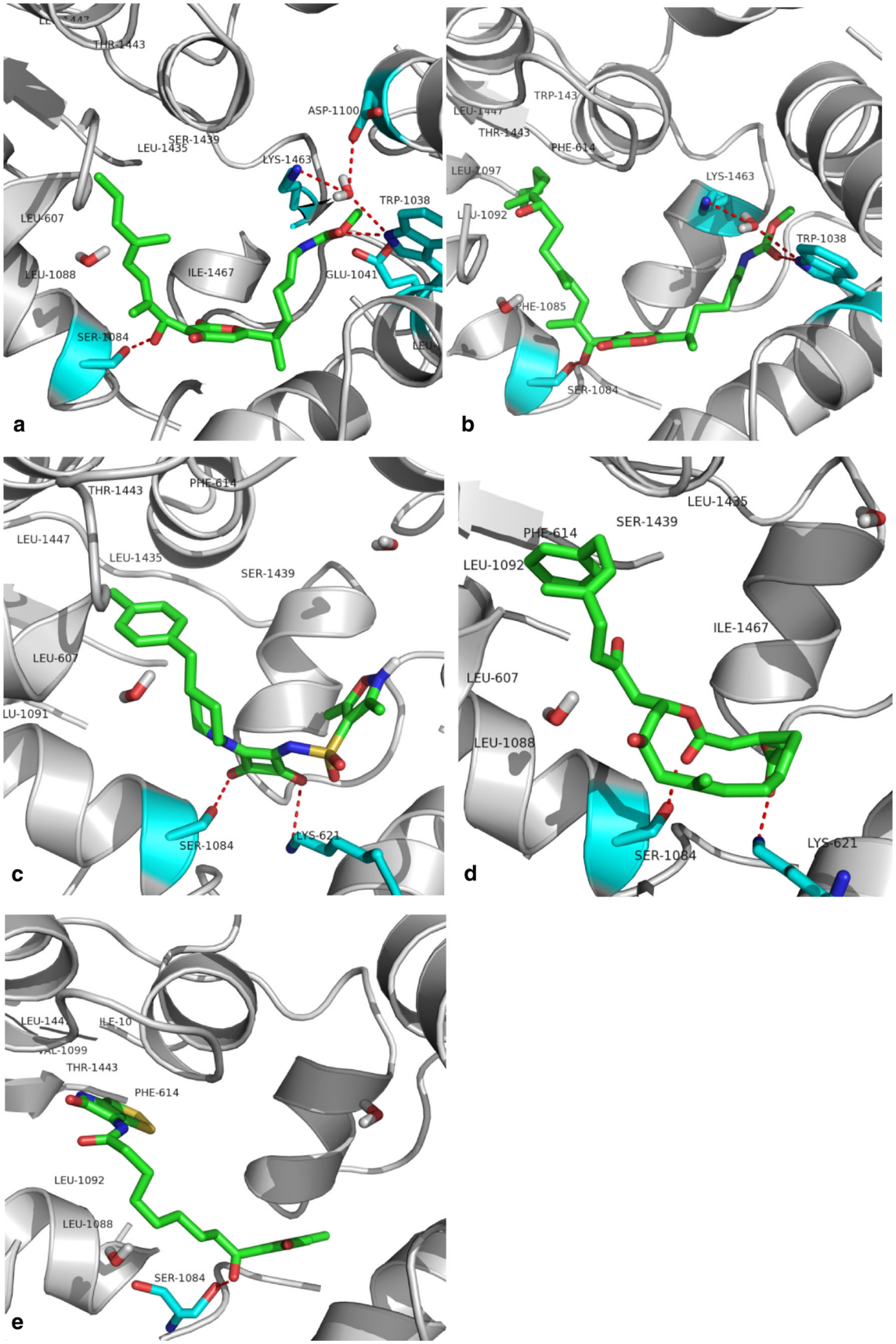


Fig. 3 The diagram of three sub-pockets. Cavity of binding is color by *blue* (Color figure online)

Fig. 2 The 2D structures of five template inhibitors




THR-1443
ASP-1100
SER-1439
LEU-1435
LYS-1463
TRP-1038
LEU-607
LEU-1088
ILE-1467
GLU-1041
SER-1084
a
TRP-143
LEU-1447
THR-1443
PHE-614
LEU-1097
LYS-1463
TRP-1038
PHE-1085
SER-1084
b
THR-1443
PHE-614
LEU-1447
LEU-1435
SER-1439
LEU-607
LU-1091
SER-1084
LYS-621
c
LEU-1435
SER-1439
PHE-614
LEU-1092
ILE-1467
LEU-607
LEU-1088
SER-1084
LYS-621
d
LEU-144
ILE-10
VAL-1099
THR-1443
PHE-614
LEU-1092
LEU-1088
SER-1084
e

◀**Fig. 4** Binding affinities of five inhibitors with RNAP Switch Region. **a** Myxopyronin, **b** corallopyronin, **c** squaramides-1, **d** ripostatin, and **e** hybrid-type agent 29

agents, which appears to be more limitation in shapes of inhibitors. To get an impressive insight of binding model, binding site in Switch Region could be further subdivided into three sub-pockets: hydrophobic sub-pocket, cleft and hydrogen bond sub-pocket. As depicted in Fig. 3, three sub-pockets lies in a way of half curve, residues (LEU-1447, TRP-1434, LEU-1435, LEU-1097, PHE-614, and PHE-1085) predominantly form a huge and deep hydrophobic surface in left side. In the middle of half-curved binding site, cleft sub-pocket is closes to entrance and sustained by SER-1084, LYS-62, and ILE-1467 together with surrounding residues. The hydrogen bond pocket, as the name, is involved in hydrogen bond formation: LYS-1463, TRP-1038, ASP-1100, and water molecule. Critical characteristics are considered in further study based on these residues.

Therefore, various binding affinities based on inhibitors are shown in Fig. 4. As depicted in Fig. 4a, myxopyronin (Myx) located in Switch Region pocket in a half-curved manner, which is dominated by shape of pocket. Myx occupies the whole binding pocket: alkyl chain expands into hydrophobic area; a hydrogen bond between a ketonic oxygen with SER-1084 forces the pyrone lay in a plane in cleft region. In terms of hydrogen bond sub-pocket, ketonic oxygen in terminal interacts directly with TRP-1038 besides three formed hydrogen connection via water molecule. Corallopyronin (Cor), a polyketide-derived a-pyrone antibiotic structurally related to Myx, makes the same interactions in hydrophobic and cleft part but a slightly difference in hydrogen bond pocket (Fig. 4b). Squaramides-1 produces an additional hydrogen bond with LYS-621, which favor squaramide core to mimic the pyrone ring in myx and cor. Moreover, the interaction of oxazole ring in hydrogen bond pocket is limited by its length (Fig. 4c).

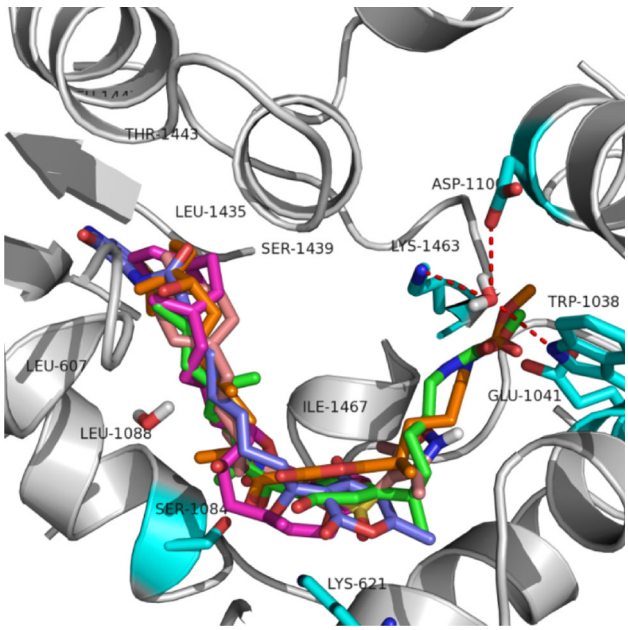


Fig. 5 Alignment of five inhibitors in binding pocket. Each agent is colored. *Green* myxopyronin, *Oranges* corallopyronin, *Deep salmon* squaramides 1; *Magenta* ripostatin; *Blue* hybrid agent 29 (Color figure online)

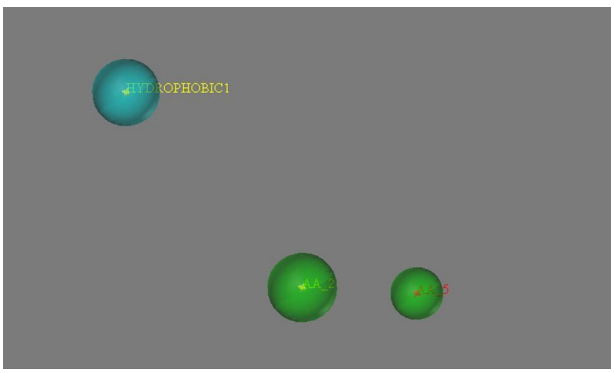


Fig. 6 The generated pharmacophore model based on inhibitors. All features are coded with color. *Cyan* hydrophobic; *Green* acceptor atom (AA) (Color figure online)

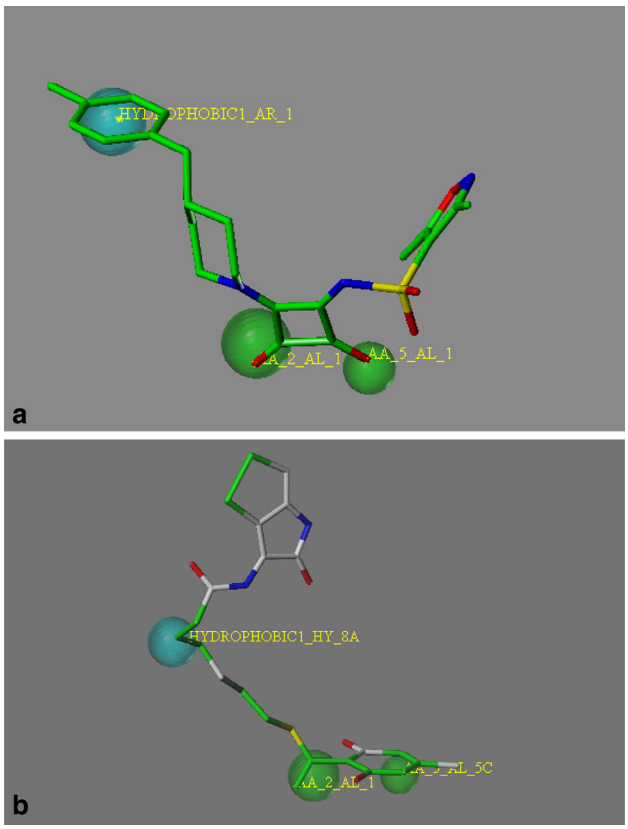


Fig. 7 Two agents superposed to features. **a** Squaramides-1; **b** hybrid agents 29

Table 1 The 2D structures and docking scores of 10 final compounds

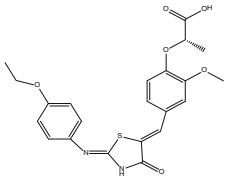
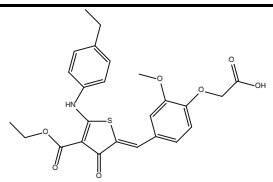
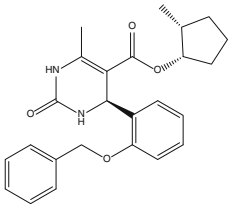
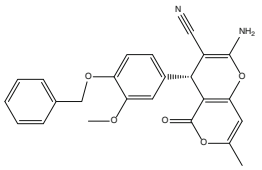
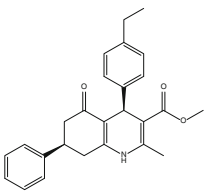
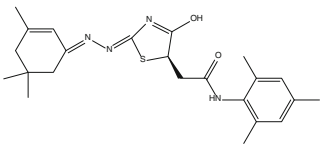
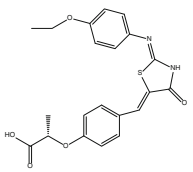
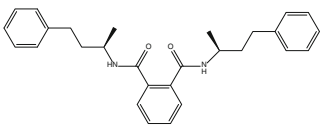
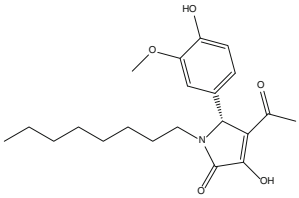
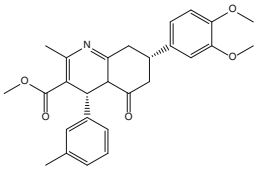
Number	Structure	Number	Structure
1	 ZINC02098042 (61.63)	2	 ZINC02969188 (50.17)
3	 ZINC04066604 (53.39)	4	 ZINC00989042 (61.72)
5	 ZINC04349703 (52.17)	6	 ZINC04576721 (53.92)
7	 ZINC12411694 (58.91)	8	 ZINC16225971 (65.56)

Table 1 continued

Number	Structure	Number	Structure
9	 ZINC08438730 (50.64)	10	 ZINC6442961 (46.14)

Ripostatin (Rip) containing a macrocylic-lactone fully occupies the cleft pocket and tightly binds with SER-1084, LYS-621; the unique benzene ring extends to fit the hydrophobic interactions. Compared to previous inhibitors, its hydrogen bond part is totally missing (Fig. 4d). The last inhibitor, depicted in Fig. 4e, is a hybrid-type compound that a holothin moiety is added in left-hand of core α-pyrone. From the binding affinity, extended holothin part enhances the hydrophobic interaction but no contact in hydrogen bond sub-pocket.

Alignments of these agents are also shown in Fig. 5. All compounds place exactly in same manners within Switch Region pocket, especially the occupation in hydrophobic and cleft sub-pocket. Limited by length of some molecule, hydrogen bond pocket is connected by weaker interaction. It is speculated that hydrophobic pocket is indispensable for inhibitors' affinities, and any one of interactions in cleft sub-pocket is beneficial to stable compounds in a plane, while the hydrogen bond pocket is helpful in ligand–protein interaction but not necessary. Accordingly, a pharmacophore model containing a hydrophobic and two acceptors features were carefully developed (Fig. 6). Two acceptors features located in cleft pocket are supposed to restrain plane structures, while hydrophobic feature is deemed to interfere with hydrophobic surface. The spatial arrangement of three features is decided by shape of binding pocket. Squaramides and hybrid-type agent are overlapped to these features and shown in Fig. 7.

Unlike other generated quantitative queries, this pharmacophore model is qualitative one in which the validation is decided by the capability to identify potential inhibitors from large scale of compounds other than specific bioactivity value. Therefore, templates inhibitors and patent-covered compounds were mixed with large numbers database compounds to re-screen. Totally, 209 Switch Region inhibitors were collected from literatures (including patent compounds) and as many as 85 % were screened out by the model, which prove that the query can pick out potential agents excellently (Srivastava *et al*., 2011; Mukhopadhyay *et al*., 2008; Yakushiji *et al*., 2013; Buurman *et al*., 2012; Ebright and Ebright, 2012).

With tested Pharmacophore model, as large numbers as 1,623,646 commercial available compounds from ZINC database (Specs, Asinex, Innovapharm, Asischem, American custom chemical corp.) were submitted to feature research and match. Most of these compounds in database were narrow in shape and possess a hydrophobic moiety in their structures. Then, 664,465 of them were screened out as Hits A for next similarity research.

Similarity research

As mentioned previously, chemical similarity leads a critical role in drug exploration and database researching. The similar property is emphasized for the states that similar structures lead to similar physicochemical and biological properties significantly. To fortify the possibility of potential compounds, similarity research was carried out. In initiation step, 664,465 filtered compounds are matched to each template inhibitors. Then, top 2 % compounds from each match search are picked. In top cluster, it is noticed that these compounds that match at least 4 template inhibitors have better features in molecular shape as well as function group. On this principle, as many as 1,385 compounds (Hit B) are screened to further docking study.

Docking

By same filtering measure, Hits C containing ten final candidates was evaluated as potential antibiotics by RNAP inhibition (Table 1). In docking study, five templates inhibitors show same binding model with wide score range from 42.05 to 50.69 (myxopyronin = 42.05, corallopyronin = 50.69, squaramides = 50.43, Ripostatin = 48.05,

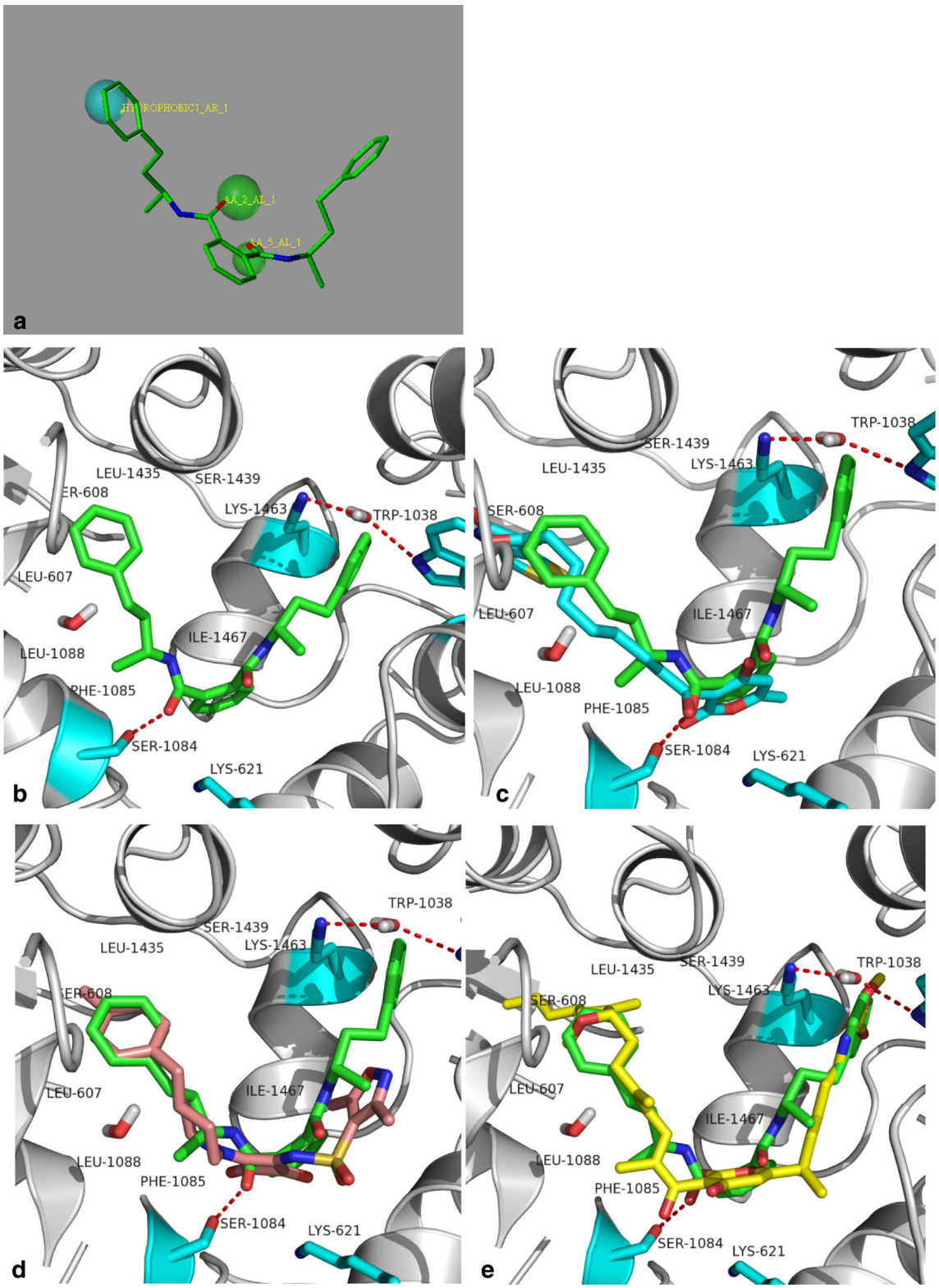


Fig. 8 Interaction between ZINC16225971 and Switch Region. **a** ZINC16225971 superposed to model; **b** binding model between ZINC16225971 and pocket residues; **c** comparison between ZINC16225971 and Hyd-bird agents; **d** ZINC16225971 and squaramides-1; **e** ZINC16225971 and corallopyronin

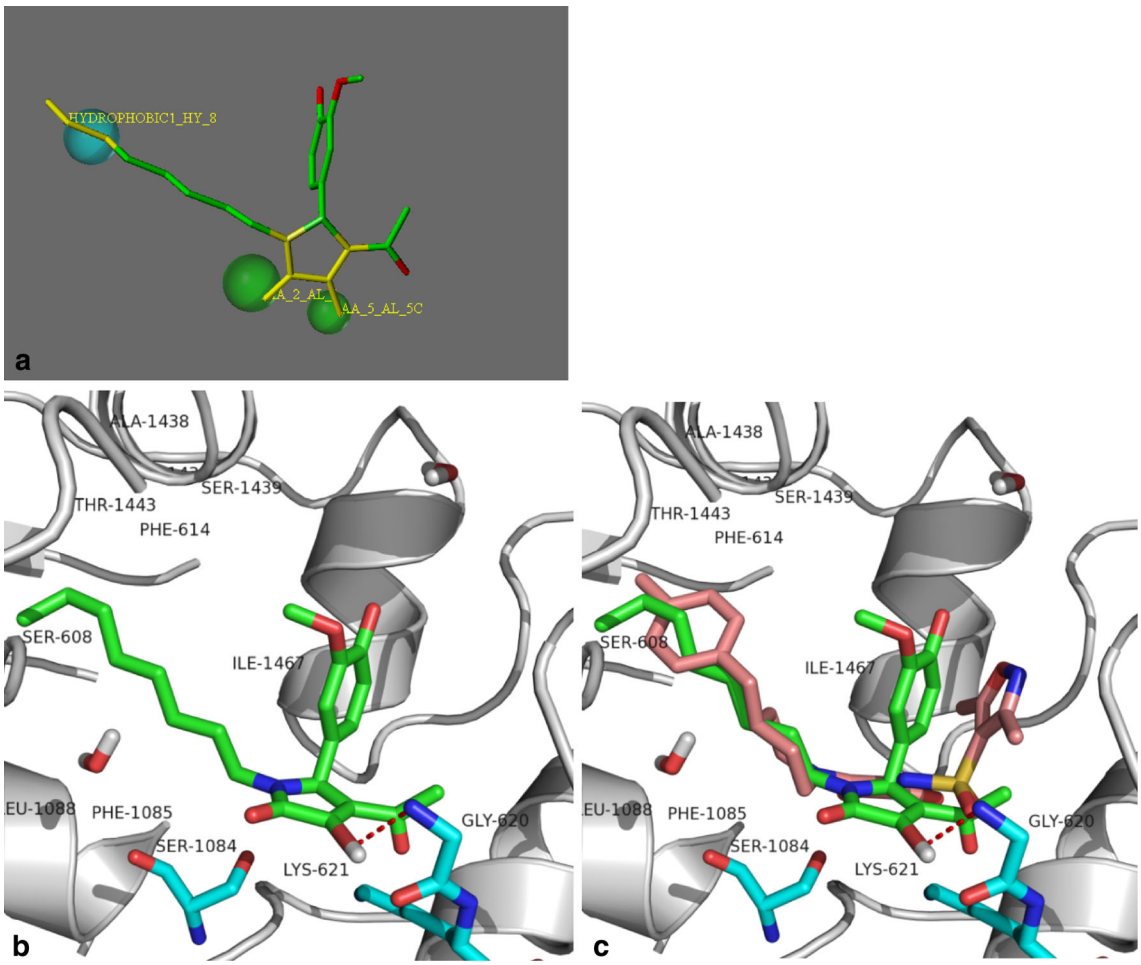


Fig. 9 Interaction between ZINC03848730 and Switch Region. **a** ZINC03848730 superposed to model; **b** binding model between ZINC03848730 and pocket residues; **c** ZINC03848730 and Squaramides-1

and hybrid type = 45.39). After two screening steps, these hits were calculated by docking program. Herein, two compounds were exampled and exhibited in features matching as well as ligand–protein contact (Fig. 8). Regarding to ZINC16225971, each of ketonic oxygen aligns acceptor atoms and terminal naphthenic moiety contains a center processing hydrophobic activity (Fig. 8a). As depicted in Fig. 8b, ZINC16225971 unwinds fully in whole SR pocket, and a hydrogen bond is formed between ketonic oxygen and SER-1084. Moreover, naphthenic in hydrophobic sub-pocket cooperates with surrounding hydrophobic surface (LEU-1435, SER-608, LEU-607, LEU-1088, PHE-1085, SER-1439, LYS-1463, and ILE-1467). Alignment with hybrid-type agent, squaramides in whole pocket are shown in Fig. 8c, d. ZINC16225971 mimic both of them in a plane excellently. In hydrogen bond sub-pocket, another naphthenic moiety shows no ability of interaction compared to corallopyronin (Fig. 8e) and myxopyronin (not shown).

ZINC08438730, structurally unrelated to ZINC16225971, satisfies all the features perfectly (Fig. 9a). In Fig. 9b, eight carbonic chains are encircled by surrounding hydrophobic residues and match favorable hydrophobic contact, a hydrogen bond occurs from GLY-620 instead of LYS-621. Compared to squaramides-1, this compound shares same binding location and limited by hydrogen sub-pocket moiety (Fig. 9c).

From above examples, it is suggested that ten structurally unrelated candidates not only have same bind mode to Switch Region significantly but also provide a new chance to explore de novo antibiotics. Moreover, three sub-pockets from binding site shed lights on de novo drug design.

Conclusion

Pharmacophore modeling based on recently discovered inhibitors is fully applied in initial modeling phase. Binding affinities from docking not only offers fundamental and valuable information about important features present in ligand–protein complex, but it also provides significant geometric comparison in each sub-pockets. In this study,

multiple template inhibitors offer a pharmacophore query, which retains the important inhibitor—''Switch Region''—interaction features and has been submitted to database for screening. The hits have been further investigated through a similarity research procedure.

The main characteristic of the present study is the integration of pharmacophore model inserting newly founded Switch Region inhibitors and multi-template similarity research to identify potential binders. In addition, present study is more comprehensive study for modeling and screening of inhibitors for the RNAP ''Switch Region''. Furthermore, we believe that the selected potential inhibitors may represent a new starting point to brand new antibiotics.

Acknowledgments This work was supported by the Science and Technology Bureau of Chengdu (No.12DXYB112JH-002, Study of novel antibiotic agents based on bacterial "Switch Region" target).

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