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Structure-guided discovery of 1,3,5-triazine–pyrazole conjugates as antibacterial and antibiofilm agent against pathogens causing human diseases with favorable metabolic fate ☆

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ABSTRACT

Impressed by the exceptional antibacterial activity exhibited by our earlier designed molecules originating from 1,3,5-triazine, the present study was undertaken to synthesize a novel series of 1,3,5-triazine–pyrazole conjugates to bring diversity around the core skeleton. The target analogues showed potent antibacterial activity against tested Gram-positive and Gram-negative microorganisms. The toxicity and metabolic site prediction studies were also held out to set an effective lead candidate for the future antibacterial drug discovery initiatives.

The overwhelming phenomenon of resistance towards the currently available antibiotics creates a significant lacuna in the health care for humankind. Alas, it can be ascribed to the widely misuse of these miracle drugs throughout the past 70 years and could weaken the major advances achieved in the treatment of infections.[1] Antimicrobial resistance (AMR) is now deemed as a global public health crisis which accounts for the death of 25 000 people and related costs of over €1.5 billion in healthcare expenses alone in European continent.[2] Paradoxically, in recent years, as the problems associated with the emergence of resistance to existing drug's increases, there has been gradually decline in the discovery of newer antimicrobial agents and drugs in the clinical pipeline.[3] The prevention of pharmaceutical industries on the investment of new projects related with discovery of antibiotics due to far too low incentives than lifestyle medication have made present situation catastrophic.[4] However, in part, technical difficulties associated with the identification of suitable novel compounds for development as candidate antibacterial make this situation complex. Regarding the fact, in 2010, Infectious Diseases Society of America (IDSA) outlines its '10 × '20' initiative, calling for a worldwide effort to acquire ten new antibiotics by 2020.[5]

The innovation of new antibacterial entity with low economic inputs has always a prolific option to cope with this state of affairs. Analogues derived from 1,3,5-triazine accommodated well with the above aim owing to its simple work-up and potent antibacterial activity. In our ongoing task to develop newer antimicrobial entity from 1,3,5-triazine, earlier, we had developed various hybrid analogues of 1,3,5-traizine clubbed with thiazole.[6] It was found that substitution of thiazole on pendant location makes the compound potent in comparison to non-substituent. In advancement of this observation and to optimize the pendant position, until now we have reported the various hybrid conjugates of 1,3,5-triazine with 1,3-thiazine,[7] piperazine,[8] and 1,3,4-thiadiazole,[9] 4-aminoquioline[10,11] and thiazolidin-4-one[12] Figure 1.

Our previous study has suggested that, the structure–activity relationship (SAR) could be exemplified on the nature of pendant substituent (i.e., pharmacophore), covalent bridge used to connect 1,3,5-triazine with pendant substituent, variety of fragment attached to the other two wings of 1,3,5-triazine and the nature of the substituent on the wings above. In our recent communication, inhibition of bacterial translation was disclosed as the mechanism of action of these 1,3,5-triazine conjugates.[7]

Present paper deals with the synthesis, antibacterial activity, antibiofilm, in silico toxicity, and metabolic site prediction of conjugates derived from 1,3,5-triazine and pyrazole. Moreover, this

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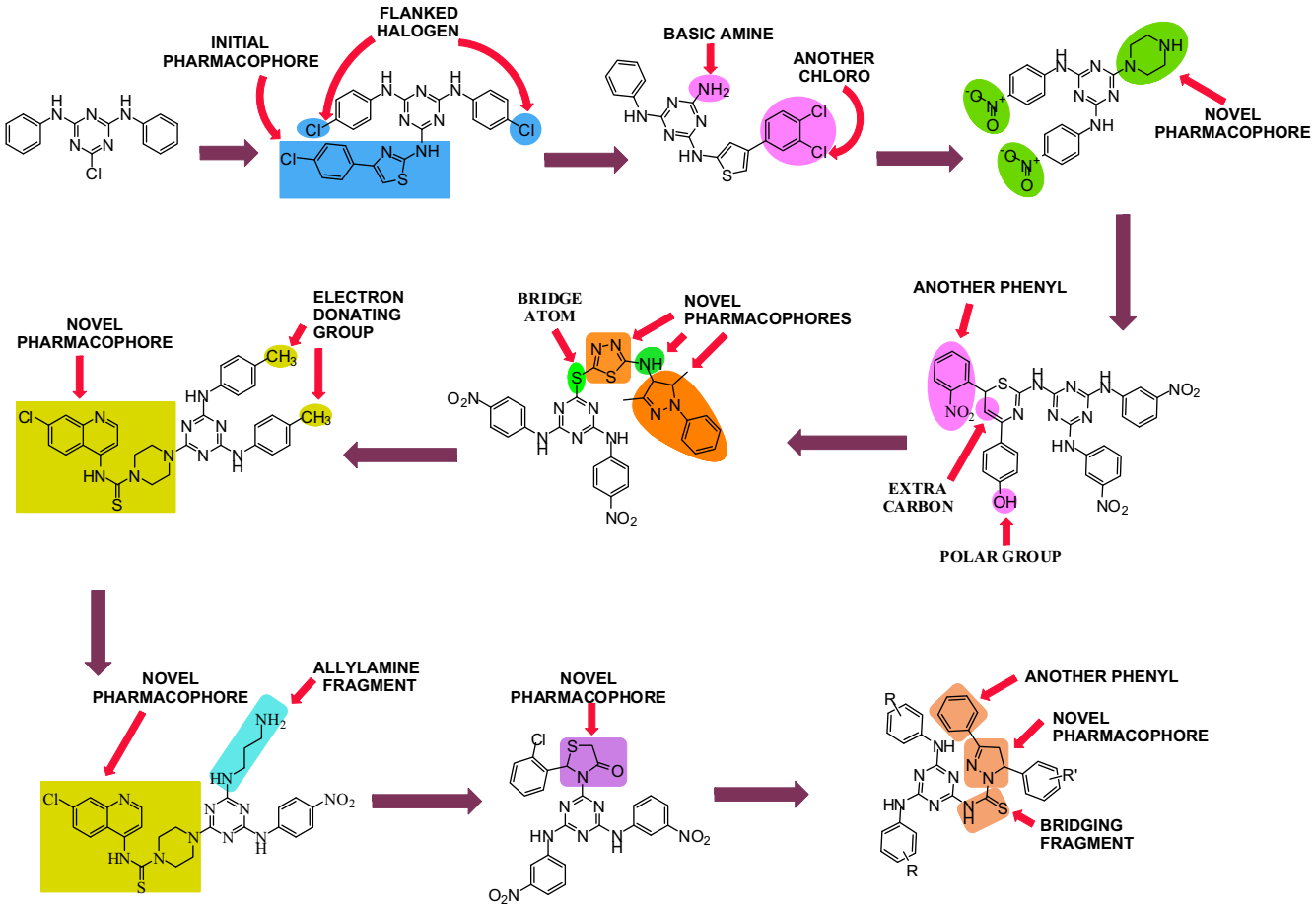
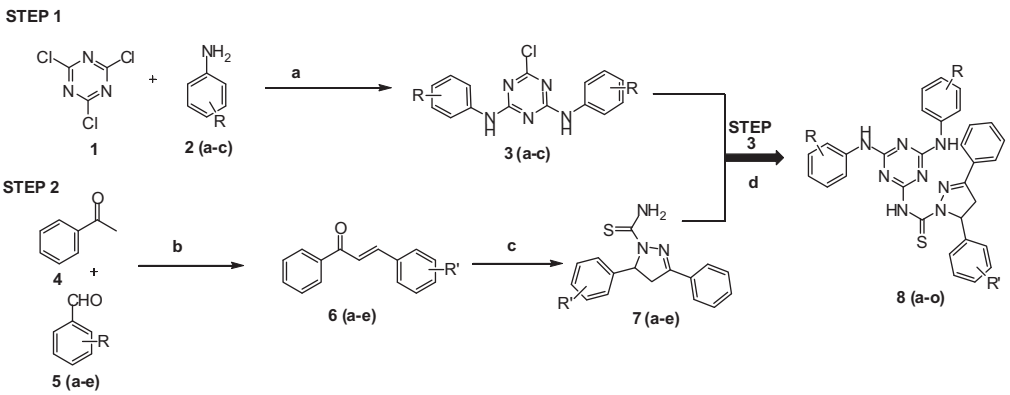


Figure 1. Structure-guided design of target 1,3,5-triazine–pyrazole conjugate.

study also provides the fresh insight and advancement about the SAR of hybrid 1,3,5-triazine conjugates.

The synthesis of title conjugates **8** (**a**–**o**) were accomplished via multi-step reaction as outlined in Scheme 1. The commercially available 2,4,6-trichloro-1,3,5-triazine (**1**) was treated with two equivalents of distinguished amines **2** (**a**–**c**) in the presence of $NaHCO_3$ followed by stirring and reflux at 40–45 °C to furnish di-substituted phenyl amines **3** (**a**–**c**) with the yield ranging from 71–89%, Step 1. The substituted chalcones **6** (**a**–**e**) was conveniently and efficiently obtained in 81–90% by crossed aldol condensation reaction between enolisable acetophenone (**4**) and substituted aldehydes **5** (**a**–**e**). Further, these substituted chalcones **6** (**a**–**e**) was then allowed to undergo Cyclo-condensation reaction in the presence of thiosemicarbazide to afford the next reaction intermediate in good yields (62–81%), 5-(substituted-phenyl)-3-phenyl-4,5-dihydro-pyrazole-1-carbothioic acid amide, **7** (**a**–**e**), Step 2. Finally, the target hybrid conjugates of 1,3,5-triazine–pyrazole **8** (**a**–**o**) was obtained through clubbing of mono chloro 1,3,5-triazine-2,4-diamine **3** (**a**–**c**) and 4,5-dihydro-pyrazole-1-carbothioic acid amide **7** (**a**–**e**) fragments in the presence of K_2CO_3 as activating base under vigorous condition. These analogues were synthesized in excellent to good yields (62–84%).



Code	R	R'
8a	4-Cl	H
8b	4-Cl	2-NO_2
8c	4-Cl	4-NO_2
8d	4-Cl	2-Cl
8e	4-Cl	4-Cl
8f	3-NO_2	H
8g	3-NO_2	2-NO_2
8h	3-NO_2	4-NO_2
8i	3-NO_2	2-Cl
8j	3-NO_2	4-Cl
8k	4-F	H
8l	4-F	2-NO_2
8m	4-F	4-NO_2
8n	4-F	2-Cl
8o	4-F	4-Cl

Scheme 1. Reagents and conditions: (a) $NaHCO_3$, 40–45 °C; (b) NaOH, stirring for 24 h; (c) thiosemicarbazide, ethanol, aq NaOH, reflux for 8 h; (d) 120–135 °C K_2CO_3, reflux.