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Research paper

Design, synthesis and biological evaluation of chalconyl blended triazole allied organosilatranes as giardicidal and trichomonacidal agents

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ABSTRACT

A series of chalconyl blended triazole allied silatranes (**7a**–**g**/**8a**–**g**/**9a**–**g**) were synthesized in good yields using a simple, economical and biocompatible synthetic route. The blend of three different pharmacologically active moieties into a single scaffold resulted into synergistic effect in their bioactivity. Various substitutions were tried to study the structure activity relationship (SAR) of the synthesized compounds on the basis of biological results. All the newly synthesized compounds were well characterized by IR, ^{1}H and ^{13}C NMR, low resolution mass spectroscopy and elemental analysis. The structures of **7a** and **7c** were authenticated by single crystal X-ray crystallography. These compounds were screened by using Molinspiration software for their physicochemical properties and all the compounds showed good oral bioavailability. The antiparasitic activity of the newly synthesized compounds was evaluated against unicellular parasites (*Giardia lamblia* and *Trichomonas vaginalis*) in comparison to standard drug (metronidazole) by 3-(4,5-dimethylthiazol-yl)-diphenyl tetrazolium bromide (MTT) assay. All the compounds displayed significant activity against *G. lamblia* and *T. vaginalis* with IC_{50} values ranging from 19.58–131.2 μM to 18.24–101.26 μM respectively. The entire library of compounds was found to be more active than metronidazole except **9a**, **9f** and **9g**. Notably, **9e** and **7e** were found to be most significant against *G. lamblia* and *T. vaginalis* respectively.

1. Introduction

Parasitic diseases are an important public health problem in developing countries [1]. Among the diarrhoea causing agents, giardiasis is an important parasitic cause, commonly treated with metronidazole [2]. Apart from causing diarrhoea, it can lead to wide range of clinical manifestations such as abdominal pain, nausea, dehydration, vomiting, and malabsorption syndrome producing adverse effect on growth and development [3–6]. Around 280 million people, especially children, are infected around the world [7–9].

Trichomoniasis is another parasitic disease caused by a single-celled protozoan parasite *Trichomonas vaginalis*. It is a sexually transmitted disease leading to clinical manifestations such as malodorous vaginal discharge, dysuria, lower abdominal pain and damage of vaginal epithelium, increasing the risk to HIV infection and cervical neoplasia [10–13]. Most commonly used drugs for the treatment of giardiasis and trichomoniasis are metronidazole **1** (Fig. 1), tinidazole, furazolidone, paramomycin or nitazoxanide **2** (Fig. 1) [14,15].

Metronidazole affects electron transport and it is metabolized to produce a reactive reduced form which is cytotoxic for parasites [16]. A recently reported broad spectrum antiparasitic agent, nitroheterocycle nitazoxanide (NTZ) has got few unpleasant effects

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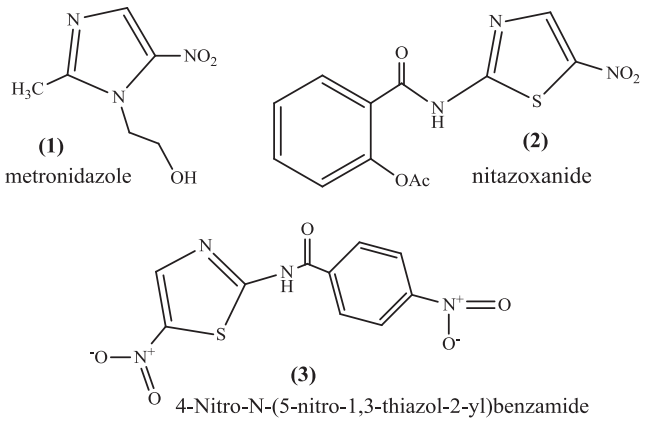

Fig. 1. Commonly used drugs for giardiasis and trichomoniasis.

such as nausea and vomiting [17]. Mendez et al. have latterly reported a new analogue of NTZ **3** (Fig. 1) and tested their antigiardial activities [18]. These chemotherapeutic antiparasitic agents are usually associated with several side effects such as treatment failures, activity against normal intestinal flora, parasite resistance and possible carcinogenicity [5,19–22]. These issues lead to an imperative quest for more effective, selective and less toxic drugs to treat both these diseases.

In the development of new drugs, it is convenient to have a range of diverse chemical structures with the desired pharmacological activity [12]. "Molecular hybridization" is one of the many strategies, which has been successfully applied for the design, and development of new and efficient hybrids [23–25]. It involves the combination of two or more chemical entities to form new hybrid moieties exhibiting additive pharmacological activities [26]. Considering this, the design of our synthesis is based on the individual activities of the selected moieties with the anticipation of their higher activity in the hybrid molecules. Chalcones, 1,2,3-triazoles and silatranes have been investigated as important fragments possessing wide range of biological activities.

Chalcones (1,3-diarylprop-2-en-1-one) are well known for their diverse activities such as antileishmanial [27], antibacterial [28], antifungal [29], antitumour [30], antimalarial [31,32], antiviral [33], antitubercular [34], antiinvasive [35], anticancer [36], antioxidant [37], antihyperglycemic [38], antiinflammatory [39], analgesic [40], antiplatelet [41], antiulcerative [42] and a large list yet to be mentioned. Moreover, they can be readily synthesized by simple and inexpensive Claisen–Schmidt reaction [43] and various modifications can be made by introducing different substituents on the aromatic rings of chalcones to give a large number of analogues showing immense activities [44–46].

1,2,3-Triazoles are an important class of heterocyclic compounds that received significant attention for the past few decades because of the broad spectrum of their applications in biochemical, pharmaceutical, and material sciences [47–60]. These are attractive connecting units, since they are stable to metabolic degradation, oxidative/reductive conditions and actively participate in dipole–dipole interactions and hydrogen bonding [61]. So, these moieties can be shaped into powerful pharmacophores that can play an important role in bio-conjugation. The copper (I) catalyzed synthesis of 1,2,3-triazoles [62] from azides and terminal alkynes is an increasingly common method for rapid synthesis of organic and bioorganic compounds in high yields and purity [63]. Therefore, the well recognized click route [64] is followed to generate 1,2,3-triazole derivatives.

Silatranes are intracomplex silicon triethanolamine esters of general formula XSi $(OCH_2CH_2)_3N$. The unique structure, specific physicochemical properties, biological activity and prospects of applications as drugs [65–70] have necessitated the search for novel effective methods for synthesizing the new compounds of this type. The unusual trigonal bipyramidal structure of silatranes leads to their high dipole moment and high electronegativity which favours the chemisorption of these molecules on the surface of proteins and lipid layer of cellular membranes either by forming hydrogen bonds with equatorial oxygens or by dipole–dipole interactions. Silatranes also form sorptive layer over cellular membranes to avoid penetration of peroxy radicals and toxins. Their ability to donate silicon that acts as an essential microelement for all living organisms and form triethanolamine as the hydrolysis product which is also biologically active makes them even more fascinating [71].

In light of above findings, we are presenting an efficient way for the molecular stitching of different pharmacophoric elements of silatranes, triazole and chalcones in a single chemical framework resulting into a library of chalcones and further investigation of *in vitro* antiparasitic activity of these compounds on intestinal unicellular parasite (*Giardia lamblia*) and a urogenital tract parasite (*T. vaginalis*).

2. Results and discussion

2.1. Drug design

We have designed the compounds **7a–g**/**8a–g**/**9a–g** on the basis of individual activities of three different biologically potent moieties. In order to coalesce the activity of these groups, molecular nailing was done in an efficient and productive way so that the active group of the three moieties appear together in the final product showing some kind of synergistic effect. Our approach is to substitute ring A of the chalcone moiety with the triazole substituted silatrane. The drug design was also based on the computer aided prediction of the physicochemical properties of the molecules like polar surface area, number of rotational bonds, hydrogen bond donating or accepting ability and lipophilicity values that play an important role in predicting the drug bioavailability [72,73]. The aim of computational analysis is to filter the compounds considered unsuitable for screening purposes. Polar surface area illustrates drug absorption thus predicting that the molecules with PSA >140 have low oral bioavailability. The number of rotational bonds in a molecule is the measure of molecule's flexibility and is found to be a very good descriptor of drug's permeability. The hydrogen bonding capacity is based on the presence of oxygen and nitrogen atoms in the molecule and somehow affects drug's permeation rate. The lipophilic character can be predicted from clog P values and the values $\leq$5 are considered ideal for orally active drugs. These parameters were calculated using Molinspiration software [74] and the results demonstrate that almost all the compounds meet the above mentioned criteria making their important place in drug development.

The jointure of combinatorial chemistry and high throughput screening instigated us to develop such molecules that can be further exploited for their pharmacological activities. Further, different substitutions are trialled to study the structure activity relationship (SAR) of the chalconyl blended triazole encapped silatranes.

2.2. Chemistry

Variously substituted acetylenic chalcones have been synthesized by the most widely used base catalyzed Claisen–Schmidt reaction. Commercially available o/m/p-hydroxyacetophenones are