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Facile synthesis of 1,4-benzodiazepine-2,5-diones and quinazolinones from amino acids as anti-tubercular agents†

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A family of 1,4-benzodiazepine-2,5-diones and quinazolinones with diverse substituents at the C-3 position were synthesized *via* a novel, simple and convenient methodology using H_2PtCl_6 as the catalyst. The substitution at the C-3 position was varied using pre-defined amino acids as precursors. The synthesized benzodiazepines were screened for anti-mycobacterial tuberculosis (anti-TB) activity. The results revealed that the 1,4-benzodiazepine-2,5-diones displayed promising activity in comparison with their open chain precursors, which indicates that the diazepine frame is vital for their activity. The compounds **4h** and **4f** were found to be the lead nominees in the series with MIC values of 1.55 and 2.87 μg mL^{-1}, respectively. A docking study was carried out on the enoyl acyl carrier protein to provide a better understanding of the mechanism of action of these compounds. Based on this study, the 1,4-benzodiazepine-2,5-dione framework is a good starting point for the development of new lead drug candidates in the treatment of multi-drug resistant tuberculosis.

Introduction

The 1,4-benzodiazepine-2,5-dione scaffold, a subset of benzodiazepinone, and its derivatives possess diverse therapeutic properties and are ubiquitous in medicinal chemistry. Functionalized benzodiazepinone structures exhibit a diverse array of biological activities and have stimulated substantial interest in the scientific community.[1] Moreover, due to its physicochemical properties, this scaffold is considered a novel non-peptide peptidomimetic and exists as active core structure in many therapeutics.[2] As an illustration of its significance, it is involved in the development of drugs against some of the most deadly diseases in the word, such as HIV, diabetes and obesity, by inhibiting metabolic pathways such as capsid assembly[3] and monoacylglycerol acyltransferase-2.[4] Also, it is present in several natural products and their derivatives are active anticholinesterase agents,[5] histone deacetylase inhibitors,[6] melanocortin agonists,[7] glycoprotein IIb–IIIa antagonism agents,[8] endothelin receptor antagonists,[9] HDM2-p53 interaction antagonists,[10] anxiolytic agents,[11] antileishmanial agents[12] and herbicidal agents.[13]

On the other hand, quinazolinones are fused heterocycles, which are present in many naturally occurring alkaloids.[14] They are extensively explored in both the synthetic and biological fields due to their diverse range of biological properties such as antimicrobial,[15] antimalarial,[16] anticancer,[17] anti-inflammatory,[18] anticonvulsants,[19] antitubercular,[20] antidepressant[21] and antidiabetic.[22] Some important biologically active 1,4-benzodiazepine-2,5-diones and quinazolinones are given in Fig. 1. Besides, amino acid/peptide conjugated heterocyclic compounds are reported to have diverse biological activities.[23] This prompted us to develop a new method involving amino acids for the construction of heterocycles.

The development of efficient and environmentally benign synthetic methodologies for biologically important heterocycles from the same intermediate is one of the major challenges in modern organic synthesis. A literature survey revealed that three major strategies are used for the synthesis of 1,4-benzodiazepine-2,5-dione. The first is the condensation of an anthranilic acid or its derivative with α-amino acid followed by seven-membered ring closure mediated by either acid or base.[24] The second is a versatile Ugi four-component condensation employing a substituted *N*-Boc protected anthranilic acid, aldehyde, isonitrile and amine.[25] The third approach is the base-induced rearrangement of

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† Electronic supplementary information (ESI) available: The detailed experimental procedures and characterization data for all compounds. See DOI: 10.1039/c8nj04936j

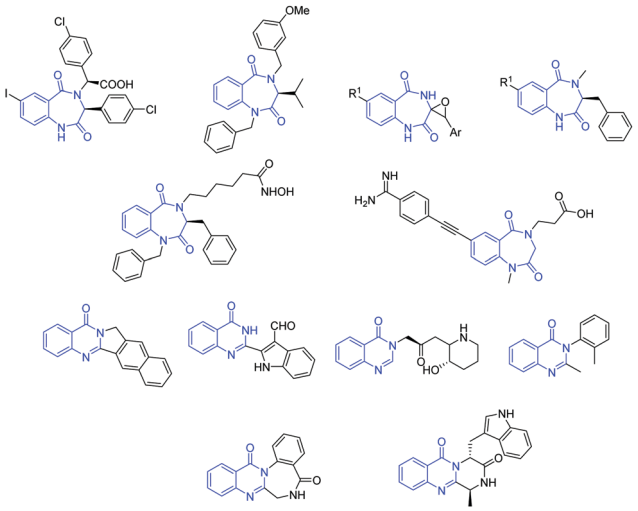
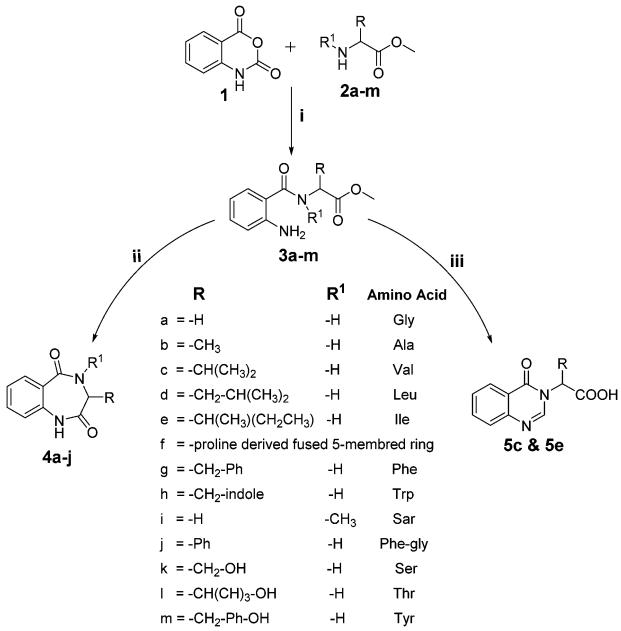


Fig. 1 Selected structures of some biologically active compounds containing 1,4-benzodiazepine-2,5-dione and quinazolinone motifs.



Scheme 1 Reagents and reaction conditions: (i) Na_2CO_3, ACN:H_2O, 4 h, and rt; (ii) 15 mol% H_2PtCl_6, THF, reflux, and 30 min; and (iii) (a) hydrated or anhydrous H_2PtCl_6, DMF, reflux, and 30 min and (b) 1 N NaOH, rt, and 30 min.

3-aminoquinoline-2,4-diones to yield 1,4-benzodiazepine-2,5-dione.[26] The first is less advantageous than the other two methods, which generally uses harsh reaction conditions, long reaction time and results in a low yield of products.

Similarly, there are several methodologies available for the synthesis of quinazolinone. Among them, the most common approach involves amidation followed by base-mediated oxidative cyclization of 2-aminobenzonitrile, 2-aminobenzoic acid or 2-aminobenzamide.[27] Several related approaches are employed through the condensation of 2-aminobenzoic acid derivatives with imidate,[28] polymer-bound isothioureas,[29] guanidine,[30] alkyl or aromatic diamines[31] or aldehydes[32] followed by oxidative ring closure under basic conditions or intramolecular cyclodehydration under acidic conditions. Other methods involve microwave-promoted cyclocondensation[33] or the use of catalysts/reagents such as ionic liquids,[34] T3P®,[35] PEG-4000,[36] $H_3PW_{12}O_{40}{\cdot}13H_2O$,[37] silica-supported Preyssler nanoparticles[38] I_2/KI,[39] $InCl_3$,[40] iron,[41] $Pd_2(dba)_3$/Xantphos[42] and $Pd(OAc)_2/PPh_3$.[43]

Due to the considerable synthetic and biological importance of 1,4-benzodiazepine-2,5-dione and quinazolinone derivatives, it is necessary to discover new strategies for their synthesis. As a part of our interest in exploring the applicability of chloroplatinic acid as a catalyst in organic synthesis,[44] herein, we report a novel approach for the synthesis of C-3 substituted 1,4-benzodiazepine-2,5-diones and quinazolinones from isatoic anhydride and amino acid methyl esters as starting materials in a simple two-step protocol. The anti-TB activity of the synthesized compounds with a docking study correlation is also presented.

Results and discussion

Chemistry

Various functionalized precursors, 2-aminobenzamido methyl ester (**3a–m**), required for this study were synthesized from commercially available isatoic anhydride **1** and L-amino acid methyl ester hydrochlorides (**2a–m**) in 61–68% yield (Scheme 1). To optimize the reaction conditions for the synthesis of 3-methyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (**4b**), initially we conducted several screening experiments using different solvents with compound **3b** as a model substrate with 10 mol% H_2PtCl_6 as the catalyst. Amongst the solvents used, THF was found to be the best solvent at its reflux temperature with respect to reaction time and yield (30 min, 71%, Table 1a, entry 6). However, other solvents including methanol,

Table 1 Optimization of solvent, catalyst loading and catalyst screening

(a) Solvent optimization with 10 mol% of H_2PtCl_6 catalyst and **3b** as the model substrate

S. no.	Solvent	Temperature	Yield in %
1	Methanol	Reflux	62
2	Acetonitrile	Reflux	34
3	Acetone	Reflux	48
4	Toluene	Reflux	53
5	Diethyl ether	Reflux	29
6	THF	Reflux	71
7	THF	rt	18

(b) Optimization of catalyst loading with **3b** as the model substrate in THF at reflux temperature

S. no.	Catalyst load in mol%	Yield in %
1	5	68
2	10	71
3	15	86
4	20	83

(c) Catalyst screening with **3b** as the model substrate in THF at reflux temperature

S. no.	Catalyst	Catalyst load in mol%	Yield in %
1	Pt metal powder (Pt)	15	13
2	PtO_2	15	39

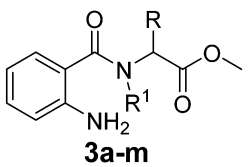
acetonitrile, acetone, toluene and diethyl ether failed to give the product in satisfactory yields (Table 1a, entries 1–5). It is reasonable to assume that the chloroplatinic acid catalyst assisted the ring closure. Further, reaction in THF at rt gave **4b** in a lower yield (Table 1a, entry 7). Thus, we selected THF as the reaction medium to explore the effect of catalyst concentration on the product yield and reaction time. It was found that an increase in catalyst concentration from 5 mol% to 20 mol% resulted in an increase in product yield and decrease in reaction time (Table 1b). Thus, yield (86%) and reaction time (30 min, Table 1) were saturated at 15 mol% of H_2PtCl_6 (Table 1b, entry 3). A further increase in the amount of catalyst had no effect on the reaction yield and time.

Later, we screened the above reaction using 15 mol% of PtO_2 and platinum metal powder (Pt) with compound **3b** as a model substrate in refluxing THF, which gave the product in 56% and 36% yield, respectively (Table 1c). It appeared that the efficiency of this cyclization depends on the acidic character of the catalyst; thus, H_2PtCl_6 was the best.

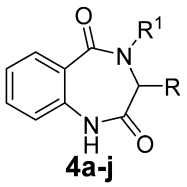
The optimized reaction conditions (15 mol% H_2PtCl_6 in refluxing THF) were used for the synthesis of **4a–j** in varying yields (59–86%). The *N*-unsubstituted substrates (R^1 = H), required 15 mol% of catalyst for efficient cyclization; whereas, the substituted precursor **4i** (R^1 = Me) required only 5 mol% for efficient cyclization. The intermediates **3k–m** failed to give the respective products, which may be due to suppression of the catalytic activity of chloroplatinic acid by the –OH group of the substrates. In contrast, the reactions with moist H_2PtCl_6 were too slow and/or resulted in unacceptable low conversions for practical application for preparative purposes.

We thought an increase in reaction temperature using a high boiling point solvent would enhance the product yield. Consequently, when DMF was used as the solvent, unexpectedly, quinazolinones **5c** and **5e** were obtained as products in 72% and 78% yield, respectively (Scheme 1). The chemical compositions of all the compounds under investigation were well-characterized and confirmed using standard spectroscopic and analytical methods. The detailed experimental procedures and spectroscopic data of the synthesized compounds are provided in the supplementary material, which is in accordance with the assigned structures of the compounds.

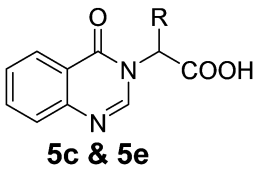
Table 2 *In vitro* anti-TB and docking studies of the compounds **3**, **4** and **5**



3a-m



4a-j



5c & 5e

Compound	R	R^1	Anti-Mtb activity MIC[a] (μg mL^{-1})	Docking score (kcal mol^{-1})	H-Bond interactions with AA[b] residue	π–π stacking interaction
3a	–H	–H	50	−6.508	Tyr-158	NF
3b	–CH_3	–H	100	−6.696	Tyr-158	NF
3c	–$CH(CH_3)_2$	–H	25	−7.631	Tyr-158	NF
3d	–CH_2–$CH(CH_3)_2$	–H	25	−8.279	Tyr-158	NF
3e	–$CH(CH_3)$–CH_2–CH_3	–H	25	−8.437	Tyr-158	NF
3f	Proline derived		12.5	−8.53	Tyr-158	NF
3g[c]	**–CH_2–Ph**	**–H**	**6.08 ± 0.81**	**−10.51**	**Tyr-158**	**Phe-149**
3h[c]	**–CH_2–Indole**	**–H**	**5.75 ± 0.43**	**−11.1**	**Tyr-158**	**Phe-149**
3i	–H	–CH_3	50	−7.636	Tyr-158	Tyr-158
3j	–Ph	–H	25	−9.0206	NF	NF
3k	–CH_2–OH	–H	25	−8.16	Tyr-158	Phe-149
3l	–$CH(OH)$–CH_3	–H	25	−8.105	Tyr-158	NF
3m	–CH_2–Ph–OH	–H	25	−10.08	Tyr-158	Phe-149
4a	–H	–H	100	−6.003	NF	Tyr-158
4b	–CH_3	–H	25	−6.522	NF	Tyr-158
4c[c]	**–$CH(CH_3)_2$**	**–H**	**5.75 ± 0.43**	**−7.972**	**Tyr-158**	**NF**
4d	–CH_2–$CH(CH_3)_2$	–H	12.5	−8.706	Tyr-158	Tyr-158
4e	–$CH(CH_3)$–CH_2–CH_3	–H	12.5	−8.667	Tyr-158	NF
4f[c]	**Proline derived**		**2.87 ± 0.21**	**−7.908**	**NF**	**Tyr-158**
4g[c]	**–CH_2–Ph**	**–H**	**6.08 ± 0.81**	**−8.855**	**NF**	**NF**
4h[c]	**–CH_2–Indole**	**–H**	**1.55 ± 0.05**	**−9.221**	**NF**	**Tyr-158**
4i	–H	–CH_3	50	−7.248	Tyr-158	NF
4j	–Ph	–H	50	−8.26	Tyr-158	NF
5c	–$CH(CH_3)_2$	–H	12.5	−9.317	Tyr-158	NF
5e	–$CH(CH_3)$–CH_2–CH_3	–H	12.5	−8.863	Tyr-158	NF
Pyrazinamide	—	—	3.12	−4.233	Tyr-158	NF
Ciprofloxacin	—	—	3.12	−7.279	NF	Phe-149
Streptomycin	—	—	6.25	−9.63	Tyr-158	NF

[a] MIC is defined as the minimum concentration of compound required to inhibit bacterial growth completely (0% growth). [b] Amino acid. [c] The values are the means of three determinations; and NF: not formed.

Pharmacology

The preliminary anti-TB screening of all compounds (**3**, **4** and **5**) was performed against *Mycobacterium tuberculosis* (Vaccine strain, $MtbH_{37}Rv$ (ATCC-27294)) using the microplate alamarBlue assay (MABA), as reported by Maria *et al.*[45] The minimum inhibitory concentration (MIC) of the compounds against the $MtbH_{37}Rv$ strain and its correlation with the docking studies are presented in Table 2. The *in vitro* studies indicated that six compounds (**3g**, **3h**, **4c**, **4f**, **4g** and **4h**) have moderate to good activity, while the rest showed lower inhibition against *Mycobacterium tuberculosis* (Mtb) in comparison with the standards. The MIC values of the non-peptide peptidomimetics 1,4-benzodiazepine-2,5-diones (**4**) were found to be better than their acyclic precursors (**3**), signifying that the diazepine ring is vital for the Mtb inhibition. The molecules **3g** and **3h** with phenyl and indole side chains were the most active among the acyclic intermediates (**3**), showing inhibitory concentrations of 6.08 and 5.75 μg mL^{-1} respectively. It was observed from structural activity relationship studies that substitution at the C-3 position enhances activity due to the increase in hydrophobicity in the molecule. The 1,4-benzodiazepine-2,5-dione **4c** with an isopropyl group at the C-3 position had a high docking score of −7.631 kcal mol^{-1} with an MIC value of 5.75 μg mL^{-1}, which is comparable with that of the standards. The 1,4-benzodiazepine-2,5-dione **4f** derived from proline having three fused rings, structurally resembles the naturally occurring aszonalenin. This compound showed a high docking score of −7.908 kcal mol^{-1} and *in vitro* activity at 2.87 μg mL^{-1} against Mtb, which is comparable with that of the standards. The molecule **4g** with phenyl substitution at C-3, with much more hydrophobicity, showed equal activity against Mtb (6.08 μg mL^{-1}) as its acyclic precursor **3g**, leaving no explanation for this deviation. The molecule of **4h** tethered with an indole side chain derived from tryptophan was found to be the most active among the series examined, exhibiting a superior docking score of −9.221 kcal mol^{-1} and lowest MIC value of 1.55 μg mL^{-1}, which is much lower than that of the standards. Notably, the 4-*N*-methylated benzo[1,4]diazepine-2,5-dione **4i** derived from the amino acid sarcosine showed decreased biological activity, which may be due the presence of *N*-substitution, indicating the need for an unconstrained –CO–NH- bond in the 1,4-benzodiazepine-2,5-dione ring for better receptor interaction. The 1,4-benzodiazepine-2,5-diones derived from tryptophan (**4h**) and proline (**4f**) were found to be the most efficient in the series. Thus, the presence of active indole or fused pyrrolidine moieties on the 1,4-benzodiazepine-2,5-dione may have added a key-boost for their activity. These molecules can open a new door for the development of active anti-TB drug candidates in the future.

Docking study

A molecular docking study was performed to support the mode of action, interaction and preferred binding sites of the targeted compounds with the active sites of the bacterial protein. The enoyl acyl carrier reductase (InhA, PDB ID-2NSD) of Mtb was chosen as the bacterial protein-bearing active site. InhA is a key enzyme involving the type II fatty acid biosynthesis pathway of Mtb and has been identified as a high-confidence drug target.[46] Thus, we focused and docked the target compounds using the GLIDE module of Schrodinger. The docking scores of all the targeted compounds are listed in Table 2. The docking studies showed that docking scores over the range of −6.003 to −11.1, which are comparable to the standard drug pyrazinamide and ciprofloxacin with docking scores of −4.233 and −7.279, respectively. The higher negative docking value of the targeted candidates is marked as efficient binding for the ligand. The result showed that the compounds **3g**, **3h**, **4c**, **4f**, **4g** and **4h** exhibited better receptor interaction with superior docking-score values of −10.51, −11.1, −7.972, −7.908, −8.855 and −9.221, respectively, which is in agreement with our observed *in vitro* anti-TB result. The lead compounds (**4c**, **4f**, **4g** and **4h**) representing the 2D and 3D dock pictures are shown in Fig. 2. Among them, compound **4h** had the highest docking score due to having one π–π staking interaction with the amino acid residues of the protein.

This π–π staking interaction occurred from the aromatic ring of the diazepine-2,5-dione (**4h**) to the Tyr-158 of the bacterial

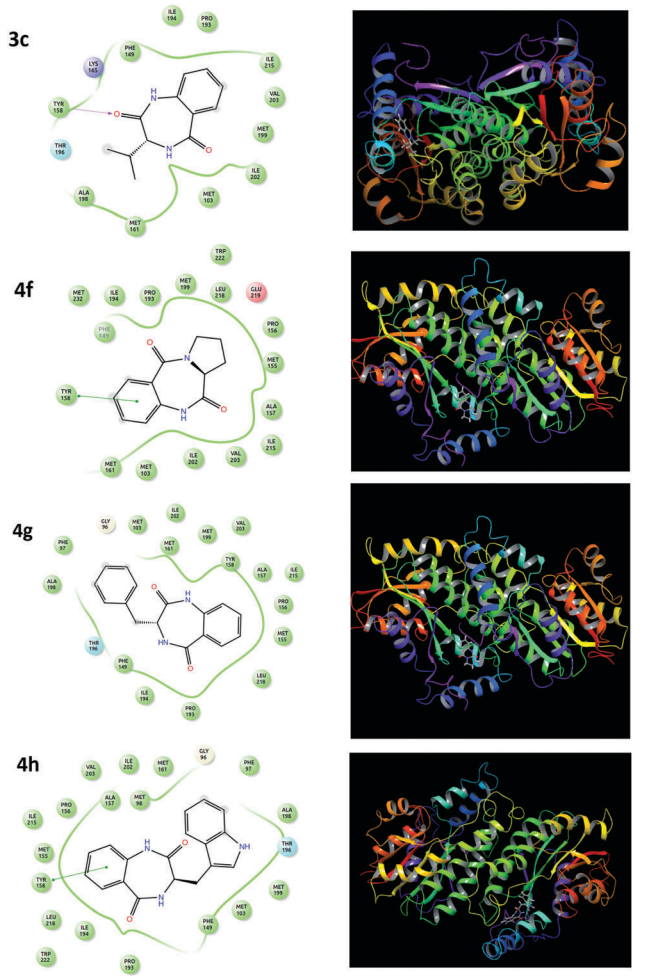


Fig. 2 2D and 3D representations of the **4c**, **4f**, **4g** and **4h** molecular docking studies with the InhA protein.

protein (InhA). Similarly, the benzodiazepinediones derived from valine (**4c**), proline (**4f**) and phenylalanine (**4g**) also exhibited hydrogen bonding interaction/π–π staking interaction with the amino acid residues of the protein, which are depicted in Fig. 2.

Conclusions

In conclusion, a novel approach to 1,4-benzodiazepine-2,5-dione and quinazolinone scaffolds from the same precursor, 2-amino-benzamido methyl ester (**3**), using chloroplatinic acid under mild reaction conditions was reported. The structure of 1,4-diazepine-2,5-dione was varied using various L-amino acid methyl ester hydrochlorides. Furthermore, we studied the anti-mycobacterial activity and docking correlations of the synthesized compounds. All the compounds were found to be active against Mtb, and among them **4f** and **4h** derived from proline and tryptophan, respectively, showed better activity compared to traditional anti-TB drugs. The 1,4-diazepine-2,5-dione derived from the tryptophan **4h** was found to be the most active in terms of *in vitro* screening, which had an MIC value of 1.55 μg mL^{-1} with a docking score of −10.58 kcal mol^{-1}. These amino acid-derived, biocompatible, non-peptide peptidomimetics open a new door in anti-TB drug design perspective by providing an entire range of highly specific and non-toxic boost candidates.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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