


Cite this: *RSC Adv.*, 2023, **13**, 2680

Received 8th October 2022  
Accepted 18th December 2022

DOI: 10.1039/d2ra06341g  
rsc.li/rsc-advances

## A novel and efficient one-pot strategy for the synthesis of 1,2,4-triazoles: access to synthesis of penipanoid A and its analogues†

A. Satyanarayana Reddy, <sup>a,b</sup> V. Krishna Reddy,<sup>a</sup> G. Nageswara Rao,<sup>b</sup> K. Basavaiah <sup>b</sup> and Kalyan C. Nagulapalli Venkata<sup>c</sup>

We developed a novel one-pot strategy for synthesizing biologically important 1,2,4-triazole motifs from easily accessible 4-hydroxy phenylacetic acid, formamidine hydrochloride and hydrazine derivatives under mild conditions. This strategy enabled us to synthesize the natural penipanoid A and its analogues in one step.

### Introduction

Heterocyclic natural products are important lead molecules in the design of drugs and agricultural products. Synthesis of heterocycles is challenging and arduous; new and efficient methods are needed for their synthesis.<sup>1</sup> The five-membered ring system consisting of three nitrogen hetero atoms defines a fascinating class of compounds known as triazoles. Triazoles are considered a privileged class of heterocycles due to their vast array of biological activities.<sup>2</sup> In recent years the chemistry of triazoles has received considerable attention owing to their application in agrochemicals, fine chemicals, and pharmaceuticals.<sup>3</sup> Triazoles (Fig. 1) exist in two isomeric forms 1,2,3-triazole and 1,2,4-triazoles. 1,2,4-triazoles are present in many drug molecules (Fig. 2). The literature itself proved that 1,2,4-triazoles possess a wide range of physiological activities. The nucleus 1,2,4-triazoles have anti-bacterial, anti-fungal, anti-tubercular, anti-cancer, anti-inflammatory, and anti-viral activities.<sup>4</sup>

Penipanoid A (**4a**) is a 1,2,4-triazole-based natural product isolated from the deep-sea sediment of marine fungus *Penicillium paneum* SD-44 and exhibits cytotoxicity and antimicrobial activity.<sup>5</sup> Given its interesting biological activity we embarked on the synthesis of **4a** and its analogues. Earlier studies in the literature reported the multistep approaches towards the synthesis of **4a**.<sup>6,7</sup> We herein report an efficient one-pot approach to synthesize **4a** and its analogues. To the best of

our knowledge, this is the first example towards synthesis of penipanoid A natural product derivatives. We envision that this method will allow us to quickly study the structural activity relationship of active penipanoid A analogs towards identifying novel antimicrobial agents.

### Results and discussion

We started our investigation by synthesizing acylamidine intermediate (**2a**) using 4-hydroxyphenyl acetic acid and the

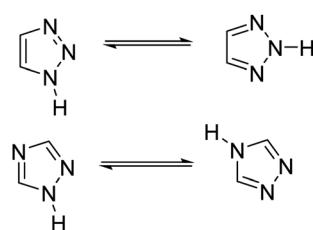


Fig. 1 Structures of 1,2,3-triazoles and 1,2,4-triazoles.

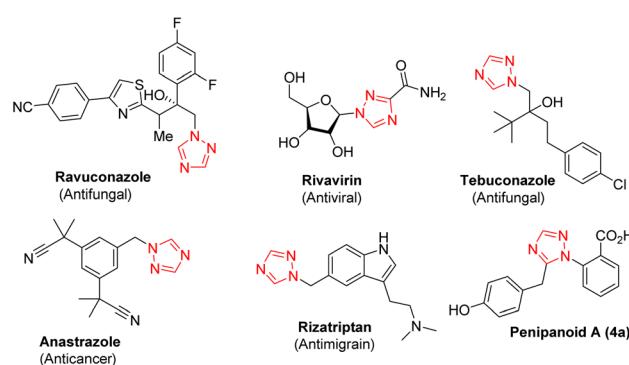


Fig. 2 Structures of some bioactive 1,2,4-triazoles.

<sup>a</sup>Chemistry Services, Aragen Lifesciences Pvt. Ltd., Survey No: 125 (part) & 126, IDA Mallapur, Hyderabad 500 076, Telangana State, India

<sup>b</sup>Department of Inorganic & Analytical Chemistry, Andhra University, Waltair Junction, Visakhapatnam, Andhra Pradesh, 530 003, India

<sup>c</sup>Department of Pharmaceutical and Administrative Sciences, University of Health Sciences and Pharmacy, St. Louis, MO, 63110, USA

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d2ra06341g>



formamidine hydrochloride. We employed peptide coupling reaction conditions for the study.<sup>8</sup> We monitored the reaction by LC-MS and once 4-hydroxyphenyl acetic acid was totally consumed we added 2-hydrazinylbenzoic acid hydrochloride and acetic acid to the reaction vessel to obtain the product. We set out to study the effect of variants on the reaction. Several conditions (coupling reagents, solvents, and bases) were thoroughly studied for the reaction of 4-hydroxyphenyl acetic acid and the formamidine hydrochloride by LC-MS, culminating in the use of HATU as the peptide coupling reagent.<sup>7</sup> Next, we studied the effect of bases, and we investigated both organic and inorganic bases.

Unfortunately, in our reaction conditions, metal carbonates and metal bicarbonates ( $M_2CO_3$  and  $MHCO_3$ ) gave us 2-(4-hydroxyphenyl) acetamide as major side product. Interestingly organic bases such as NMM, DIPEA,  $Et_3N$  gave us desired acylamidine intermediate 2, albeit in varying yields (Table 1, entries 1–3). We found that DIPEA was a superior base and we used it for our future synthetic efforts. Subsequently, we focussed our attention towards identifying suitable solvent. We used DMF, THF and ACN as solvents (Table 1, entries 16–22), we found that best results were seen with DMF (Table 1, entry 2) we hypothesize that DMF's ability to dissolve the coupling agents might enable it to form acylamidine intermediate efficiently.

Table 1 Optimization of conditions<sup>a</sup>

Entry	Coupling agent	Solvent base	Yield (%)
1	HATU	DMF $Et_3N$	55
2	HATU	DMF DIPEA	74
3	HATU	DMF NMM	51
4	HATU	DMF $Cs_2CO_3$	55
5	HATU	DMF $K_2CO_3$	50
6	HATU	DMF $Na_2CO_3$	44
7	HATU	DMF $NaHCO_3$	30
8	EDC.HCl	DMF DIPEA	36
9	PyBOP	DMF DIPEA	N. R.
10	CD	DMF DIPEA	N. R.
11	HATU	THF DIPEA	30
12	HATU	ACN DIPEA	12

<sup>a</sup> Conditions: 1 (1.33 mmol), base (3.99 mmol), in solvent (5 mL) and 2 (1.97 mmol) at room temperature for 18 h.; then added 3 (1.97 mmol) and AcOH (13.14 mmol) at room temperature and heated the mixture 80 °C for 3 h.; NMM (*N*-methyl morpholine); DIPEA (diisopropylethylamine);  $Et_3N$  (Triethylamine); DMF (dimethylformamide); THF (tetrahydrofuran); CAN (acetonitrile); HATU (Hexafluorophosphate azabenzotriazole tetramethyl uronium); EDC.HCl (*N*'-ethyldiisopropylcarbodiimide hydrochloride); PyBOP (benzotriazol-1-yl-oxytritypyrrolidinophosphonium hexafluorophosphate); CD (1,1'-carbonyldiimidazole).

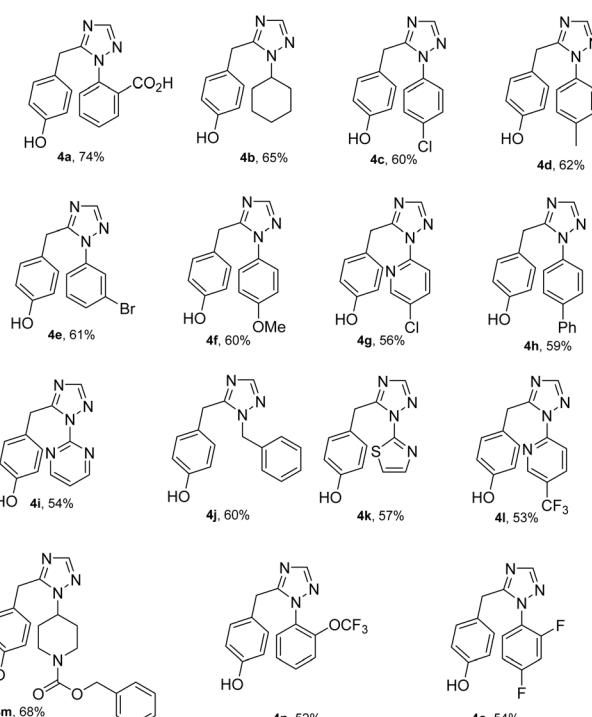


Fig. 3 Synthesis of penipanoid A and its derivatives 4a–o.

The desired protocol proved useful to study the next step towards the formation of our desired final product 1,2,4-triazole. We have applied the similar reaction conditions for the second step which was reported previously.<sup>6</sup> Gratifyingly, the cyclization reaction gave us penipanoid A (4a) in good yield (74%) (Fig. 3).

With the established reaction conditions in hand, we studied the substrate scope using various substituted and unsubstituted hydrazine derivatives to generate penipanoid A analogues. Pleasingly, the reaction is very versatile as we were able to use various substituted hydrazinyl benzoic acid derivatives to generate penipanoid A analogues with ortho, meta and para substitutions and could obtain electron donating and electron withdrawing groups. Additionally, the reaction conditions could tolerate heterocyclic groups (4g, 4i, 4k, 4l) with satisfactory yields (Fig. 4).

Intrigued by these findings, we decided to replace the 4-hydroxyphenyl acetic acid with substituted and unsubstituted phenyl acetic derivatives. Interestingly, we generated novel 1,2,4-triazoles with the phenyl ring (5a–c). Interestingly, we

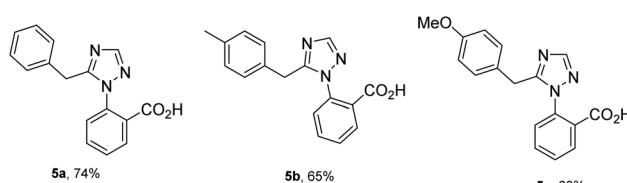


Fig. 4 Synthesis of penipanoid A analogues 5a–c.



generated novel 1,2,4-triazoles without the hydroxyl group on phenyl ring (5a–c).

## Conclusions

In summary, we developed a novel and efficient method for the synthesis of penipanoid A and its analogues. The reaction conditions were optimized and the scope of the reaction with respect to hydrazines and phenyl acetic acids were examined. The optimized protocol allowed the creation of structurally diverse penipanoid A libraries for biological screening. All synthesized compounds are currently being tested for antimicrobial activity, and results will be communicated in due course.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

ASNR, VKR, GNR, KB conceived and designed the project; KCNR contributed to writing the manuscript. Authors thank Dr Aravind Seema department of chemistry, Osmania University, Hyderabad, and Dr Joseph Sambabu Madhirala, senior director in GVK bio. Aragen Science Pvt Ltd, India for constant encouragement and support. Authors are grateful to GVK bio. Aragen sciences Pvt Ltd for its facilities and finally we would like to thank the Centre for Clinical Pharmacology, UHSP, St. Louis, MO 63110, USA.

## Notes and references

1 C. Prandi and E. G. Occhiato, From synthetic control to natural products: a focus on N-heterocycles, *Pest Manage. Sci.*, 2019, **75**(9), 2385.

- 2 For a review, see: A. Al-Masoudi, Y. A. Al-Soud, N. J. Al-Salihi and N. A. Al-Masoudi, *Chem. Heterocycl. Compd.*, 2006, **42**, 1377.
- 3 For a recent one-pot method, see: (a) M. J. Stocks, D. R. Cheshire and R. Reynolds, *Org. Lett.*, 2004, **6**, 2969 For a comprehensive review, see: (b) A. Moulin, M. Bibian, A.-L. Blayo, S. E. Habnouni, J. Martinez and J.-A. Fehrentz, *Chem. Rev.*, 2010, **110**, 1809; (c) C. Temple Jr, *The Chemistry of Heterocyclic Compounds*, ed. J. A. Montgomery, Wiley-Interscience: New York, 1981, Vol. 37, pp. 62–95; (d) K. T. Potts, *Chem. Rev.*, 1961, **61**, 87; (e) J. E. Francis, L. A. Gorczyca, G. C. Mazzeuga and H. Meckler, *Tetrahedron Lett.*, 1987, **28**, 5133; (f) K. Funabiki, N. Noma, G. Kuzuya, M. Matsui and K. Shibata, *J. Chem. Res., Synop.*, 1999, 300; (g) A. R. Katritzky, N. M. Khashab, N. Kirichenko and A. Singh, *J. Org. Chem.*, 2006, **71**, 9051.
- 4 (a) M. Strzelecka and P. Świątek, *Pharmaceuticals*, 2021, **14**(3), 224; (b) R. Aggarwal and G. Sumran, *Eur. J. Med. Chem.*, 2020, **205**(1), 112652.
- 5 C. S. Li, A. Chun-Yan, X. M. Li, S. S. Gao, C. M. Cui, S. Hao-Fen and W. Bin-Gui, *J. Nat. Prod.*, 2011, **74**(5), 1331.
- 6 (a) A. S. Reddy, G. V. K. Reddy, G. N. Rao and K. Basavaiah, *Tetrahedron Lett.*, 2022, **90**, 153612; (b) M. G. Castanedo, P. S. Seng, B. Nicole, T. Sean and S. T. Staben, *J. Org. Chem.*, 2011, **76**(4), 1177; (c) B. Vergani, G. Caprini, G. Fossati, M. Lattanzio, M. Marchini, G. Pavich, M. Pezzuto, C. Ripamonti, G. Sandrone, C. Steinkuhler and A. Stevenazzi, Patent number: WO2018189340A1, PCT/EP2018/059468, 2018.
- 7 (a) L. A. Carpino, *J. Am. Chem. Soc.*, 1993, **115**(10), 4397; (b) L. A. Carpino, H. Imazumi and A. El-Faham, *Angew. Chem., Int. Ed.*, 2002, **41**(3), 441; (c) L. A. Carpino, H. Imazumi and B. M. Foxman, *Org. Lett.*, 2000, **2**(15), 2253.
- 8 C. A. G. N. Montalbetti and V. Falque, *Tetrahedron*, 2005, **61**, 10827.

