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Water-triggered union of multi-component reactions towards the synthesis of a 4*H*-chromene hybrid scaffold†

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An unprecedented union of multi-component reactions to construct pyrazole- and pyranopyrazole-adorned 4*H*-chromene from simple reactants in water at ambient temperature is reported. This innovative tactic has integrated two distinct four-component reactions (4CRs) that occur transiently to form four new heterocycles *via* ten covalent bonds in a single step.

Synthetic organic chemists have reached a level of intricacy, allowing access to any molecule with desired functionalities and stereochemistry. Nevertheless, there is a paucity of transformations for the efficient construction of small biomolecules and their analogs. Multi-component reactions¹ (MCRs) are economical tools for the achievement of this goal, as they inherently involve the formation of several covalent bonds in one operation. MCR proficiency can be further refined by unifying two or more MCRs. In recent decades, the use of higher-order MCRs to construct structurally diverse and complex skeletons has become attractive in organic synthesis and medicinal chemistry.²

The union of multi-component reactions (union of MCRs) is an elegant tactic for performing higher-order MCRs and accessing diverse and complex molecular architectures. This approach was first coined by Ugi.³ The union of MCRs is generally achieved by tandem MCRs⁴ or by installing suitable building blocks with orthogonal functionality.⁵ The focus of union of MCRs is the orthogonal reactivity of any one of the reactants, which can be combined by two different MCRs without functional-group protection. Nurturing MCRs in water⁶ to attain important scaffolds from simple reactants is viewed as a greener approach to populate the chemical space.⁷ Diversity-oriented synthesis⁸ (DOS), a fascinating area of research in organic synthesis with its sub-disciplines of privileged sub-structure-based diversity-oriented synthesis⁹ (pDOS) and biology-oriented synthesis¹⁰ (BIOS), has provided several guiding principles to access biologically relevant small molecules.¹¹ However, unification of the guiding principles of DOS with union of MCRs in water to access biologically relevant complex scaffold remains a challenge. Very few reports on union of MCRs have focused on the eminent Ugi-4-component reaction (U-

4CR) permutation with other MCRs. Indeed, to the best of our knowledge, union of MCRs without the involvement of U-4CRs has not been accomplished so far. The development of new unions of MCR is limited by the compatibility of reactant and reactions in a given solvent.^{4f} Herein, we report an innovative strategy that combines two different known 4CRs, which displays solvent compatibilities and produces multiple functional groups in one pot to achieve higher-order MCRs, leading to 4*H*-chromene scaffolds.

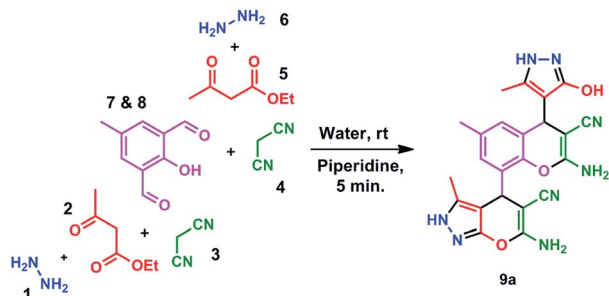
At the outset, we established a pyranopyrazole four-component reaction (PP4CR) in water to access a multi-functionalized pyranopyrazole scaffold.¹² To create skeletal diversity, we installed a single-reactant-replacement¹³ (SRR) strategy into our PP4CR by orthogonal functionality on the oxo component. Consequently, skeletally diverse and medicinally important 4*H*-chromene¹⁴ and 4*H*-thiochromene¹⁵ derivatives were achieved. Encouraged by these results, we planned to combine these two recent 4CRs in water. As a pDOS approach, we rationally employed 2-hydroxy-5-methylisophthalaldehyde as an oxo component into our PP4CR and performed a pseudo-eight-component reaction to unite these two distinct 4CRs to obtain a complex structure with multi-functionality in a single core possessing the pyranopyrazole and 4*H*-chromene skeletons. Thus, we are the first to describe pseudo-eight-component reactions (8CRs) in water, with unification of two disparate 4CRs to access an unprecedented bioactive pyranopyrazole-substituted 4*H*-chromene scaffold (Scheme 1).

The pseudo-8CR performed in water using two equivalents of hydrazine hydrate 96% (1), ethyl acetoacetate (2), malononitrile (3), and one equivalent of 2-hydroxy-5-methylisophthalaldehyde (7 and 8) in the presence of piperidine 10% base at ambient temperature resulted in the formation of product **9a** within 5 min. The product was identified by nuclear magnetic resonance (NMR) as a complex heterocyclic hybrid architecture of 4*H*-chromene adorned with a pyrazole and pyranopyrazole substructure. To verify that this

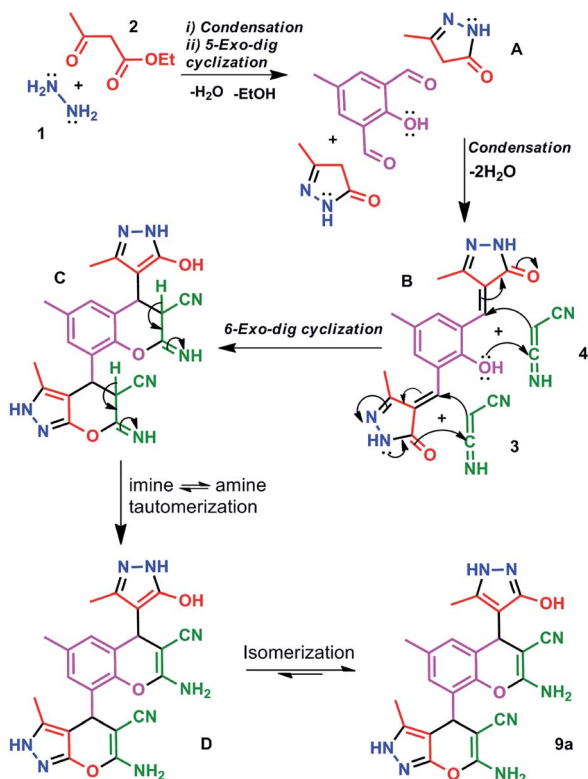
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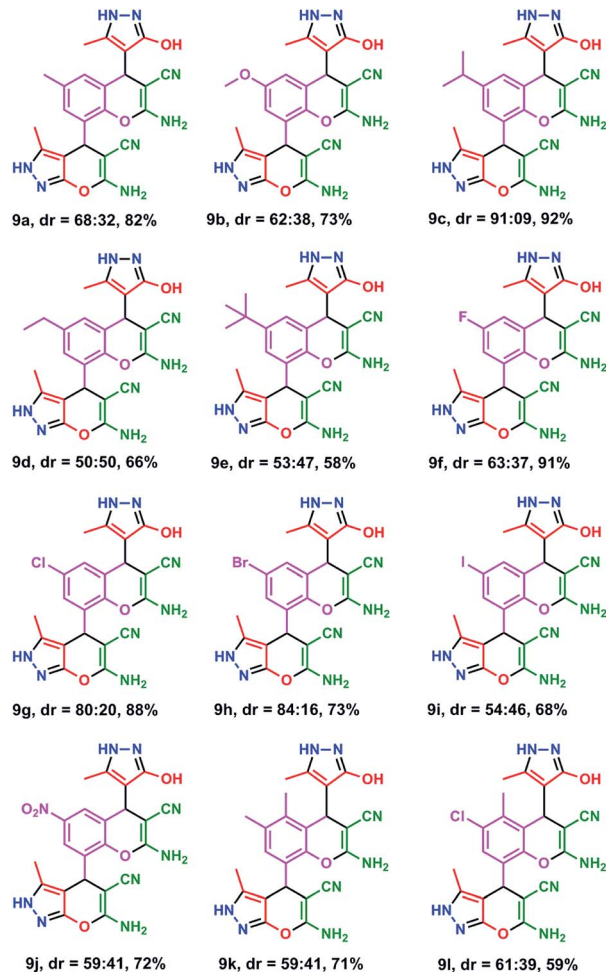
Scheme 1 Pseudo-eight-component reaction in water.



Scheme 2 Plausible mechanism.

union of MCRs occurred either in tandem or in a one-pot manner, we performed an MCR using equimolar hydrazine hydrate 96% (1), ethyl acetoacetate (2), malononitrile (3), and 2-hydroxy-5-methylisophthalaldehyde (7 and 8) in water. The reaction yielded 9a only, which was confirmed by ^1H NMR. The result suggests that both 4CRs might occur simultaneously. Thus, the reaction could not be controlled to obtain either a 4*H*-chromene or pyranopyrazole scaffold of a single 4CR while retaining the aldehyde functionality, which can be exploited in other MCRs. This reaction represents an unprecedented example of the true union of MCRs. The reaction occurred according to the mechanism shown in Scheme 2.

Initially, component 1 and 2 are involved in the condensation followed by 5-*exo*-dig azacyclization to yield 3-methyl pyrazolin-5-one (A) instantly. A undergoes a Knoevenagel condensation

Fig. 1 Library of pyrazole- and pyranopyrazole-adorned 4*H*-chromene scaffolds.

reaction with 2-hydroxy-5-methylisophthalaldehyde to form the intermediate B. The malononitrile (3) exists in nitrile-ketenimine tautomerism¹⁶ in water medium. The intermediate B is involved 6-*exo*-dig-oxocyclization with component 3. Cumulatively, four heterocycles are formed by 10 covalent bonds, such as C-C, C-N, and C-O. At the final stage, isomerization occurs to obtain the 1*H*-isomer of the pyrazole ring. A deshielding for H'_4 and consequent shielding for C'_4 of pyranopyrazole were observed in comparison with the corresponding H_4 and C_4 chemical shifts of chromene, indicating the proximity of H'_4 to the oxygen of the chromene moiety. The chromene derivatives are adorned with diverse carbo- and heterocyclic motifs, which are ubiquitous in natural products as well as synthetic bioactive molecules, and exhibit vital biological and pharmacological activities.¹⁷

The reaction showed similar selectivity with good-to-excellent yield when different 2-hydroxyisophthalaldehydes were used as oxo building blocks. The products were created in the course of reactions having two chiral centers. Only two diastereomers of the four possible stereoisomers were distinguishable in ^1H and ^{13}C NMR, and were inseparable by column chromatography. The diastereomer ratio was calculated from ^1H NMR (Fig. 1).

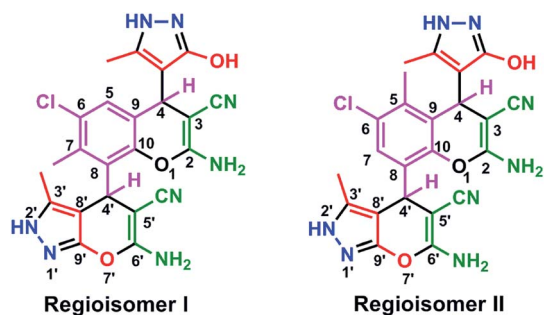


Fig. 2 Possible regio isomers of pyranopyrazole-adorned 4*H*-chromen (9I).

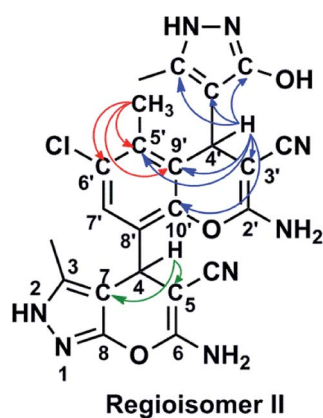


Fig. 3 HMBC correlations of compound 9I.

We subsequently investigated the use of unsymmetrical disubstituted isophthalaldehydes as an oxo component to this pseudo-8CR. The reaction occurred regioselectively, and the possible regio isomers of **9I** are shown in Fig. 2.

The regio-isomer of **9I** was characterized by heteronuclear multiple bond correlation spectroscopy (HMBC) (Fig. 3). In the ^1H NMR of **9I**, the signals at (4.59 + 4.58) and (5.19 + 5.18) ppm were assignable C_4 and C'_4 protons, respectively. These proton signals were considered as starting points for analyzing the HMBC correlation spectrum to identify the isomer formed in this reaction.

In HMBC, the C'_4 proton correlates with only two carbon (C'_8 and C'_5) signals at (97.06 + 96.85) and 55.24 ppm. The C_4 proton correlates to four carbon signals at the chromene moiety and three carbon signals at the pyrazole ring C_3 (56.15 + 55.15), C_5 (132.59 + 132.44), C_9 123.57, C_{10} 159.22, C_3'' (135.59 + 135.53), C_4'' (103.87 + 103.59), and C_5'' 145.46 ppm, respectively. The signals at (2.11 + 2.07) ppm, which are assignable to methyl protons attached to aromatic ring, correlate with three carbon signals assignable to the *ipso* carbon C_5 (132.59 + 132.44), two ortho carbons C_6 (128.66), and C_9 (123.57 ppm) of the aromatic ring. The common correlations for C_4 and aromatic methyl protons confirm that the methyl group is adjacent to C_4 . The structure of the regio-isomer **II** was assigned unambiguously by HMBC experiments. On cross-matching, the C_4 proton correlates with the aromatic methyl protons correlations two carbon signals at (132.59 + 132.44) and 123.57 ppm are common in both correlations.

Gratifyingly, our union of MCRs is an ideal platform for the rapid construction of privileged scaffolds, introducing both diversity and complexity in a single-step manner with orthogonal functionality.

Conclusions

We have developed a true union of MCRs from simple reactants in water *via* a single step at ambient temperature. This elegant strategy involves the spontaneous formation of ten covalent bonds to access complex and diverse drug-like molecules. The products of union of MCRs also bear orthogonal functionality that may be selectively exploited to create novel compounds having been identified in leads and drugs. Further studies of synthesized scaffolds are in progress in our laboratory.

Experimental

To a stirred aqueous (25 mL) mixture of hydrazine hydrate 96% **1** (107 mg, 2 mmol), ethyl acetoacetate **2** (260 mg, 2 mmol), and malononitrile **3** (132 mg, 2 mmol), 2-hydroxyisophthalaldehyde **4** (1 mmol) and 5 mol% of piperidine catalyst were added successively at room temperature under an open atmosphere with vigorous stirring for 5–10 min. The solid produced from the reaction mixture was filtered, and washed with water and then with ethyl acetate and/or cold ethanol. The products obtained were pure on thin layer chromatography (TLC) and NMR spectra.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- (a) R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown and T. A. Keating, Multiple-Component Condensation Strategies for Combinatorial Library Synthesis, *Acc. Chem. Res.*, 1996, **29**, 123–132; (b) M. A. Mironov, Design of Multi-Component Reactions: From Libraries of Compounds to Libraries of Reactions, *QSAR Comb. Sci.*, 2006, **25**, 423–431; (c) W. Zhu, M. Mena, N. Sun, E. Jnoff, P. Pasau and L. Ghosez, Multicomponent Reactions for the Synthesis of Complex Piperidine Scaffolds, *Angew. Chem., Int. Ed.*, 2009, **48**, 1–5; (d) G. R. Boyce and J. S. Johnson, Three-Component Coupling Reactions of Silyl Glyoxylates, Vinyl Grignard Reagent, and Nitroalkenes: An Efficient, Highly Diastereoselective Approach to Nitrocyclopentanols,

- Angew. Chem., Int. Ed.*, 2010, **49**, 1–5; (e) *Multicomponent Reactions: Concepts and Applications for design and Synthesis*, ed. R. P. Herrera and E. Marqués López, John Wiley & Sons, Inc., 2015; (f) T. Zarganes-Tzitzikas, A. L. Chandgude and A. Dömling, Multicomponent Reactions, Union of MCRs and Beyond, *Chem. Rec.*, 2015, **15**, 981–996.
- 2 (a) M. E. Welsch, S. A. Snyder and B. R. Stockwell, Privileged Scaffolds for Library Design and Drug Discovery, *Curr. Opin. Chem. Biol.*, 2010, **14**, 347–361; (b) I. Monfardini, J. W. Huang, B. Beck, J. F. Cellitti, M. Pellicchia and A. Dömling, Screening Multicomponent Reactions for X-Linked Inhibitor of Apoptosis-Baculoviral Inhibitor of Apoptosis Protein Repeats Domain Binder, *J. Med. Chem.*, 2011, **54**, 890–900; (c) D. M. Beal and L. H. Jones, Molecular Scaffolds Using Multiple Orthogonal Conjugations: Applications in Chemical Biology and Drug Discovery, *Angew. Chem., Int. Ed.*, 2012, **51**, 6320–6326.
- 3 (a) A. Dömling and I. Ugi, The Seven-Component Reaction, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 563–564; (b) A. Dömling, E. Herdtweck and I. Ugi, MCR V.¹ Seven-Component Reaction, *Acta Chem. Scand.*, 1998, **52**, 107–113.
- 4 (a) I. Ugi, A. Demharter, W. Hörl and T. Schmid, Ugi Reactions with trifunctional α -Amino Acids, Aldehydes, Isocyanides and Alcohols, *Tetrahedron*, 1996, **52**, 11657–11664; (b) F. Constabel and I. Ugi, Repetitive Ugi Reactions, *Tetrahedron*, 2001, **57**, 5785–5789; (c) I. K. Ugi, B. Ebert and W. Hörl, Formation of 1,10-iminodicarboxylic acid derivatives, 2,6-diketo-piperazine and dibenzodiazocine-2,6-dione by variations of multicomponent reactions, *Chemosphere*, 2001, **43**, 75–81; (d) D. E. Portlock, R. Ostaszewski, D. Naskar and L. West, A tandem Petasis–Ugi multi component condensation reaction: solution phase synthesis of six dimensional libraries, *Tetrahedron Lett.*, 2003, **59**, 603–605; (e) D. E. Portlock, D. Naskar, L. West, R. Ostaszewski and J. J. Chen, Solid-phase synthesis of five-dimensional libraries via a tandem Petasis–Ugi multi-component condensation reaction, *Tetrahedron Lett.*, 2003, **44**, 5121–5124; (f) D. Naskar, A. Roy, W. L. Seibel, L. West and D. E. Portlock, The synthesis of aza- β -lactams via tandem Petasis–Ugi multi-component condensation and 1,3-diisopropylcarbodiimide (DIC) condensation reaction, *Tetrahedron Lett.*, 2003, **44**, 6297–6300; (g) M. Paravidino, R. Scheffelaar, R. F. Schmitz, F. J. J. de Kanter, M. B. Groen, E. Ruijter and R. V. A. Orru, A Flexible Six-Component Reaction To Access Constrained Depsipeptides Based on a Dihydropyridinone Core, *J. Org. Chem.*, 2007, **72**, 10239–10242; (h) N. Elders, D. van der Born, L. J. D. Hendrickx, B. J. J. Timmer, A. Krause, E. Janssen, F. J. J. de Kanter, E. Ruijter and R. V. A. Orru, The Efficient One-Pot Reaction of up to Eight Components by the Union of Multicomponent Reactions, *Angew. Chem., Int. Ed.*, 2009, **48**, 5856–5859; (i) T. H. Al-Tel, R. A. Al-Qawasmeh and W. Voelter, Rapid Assembly of Polyfunctional Structures Using a One-Pot Five- and Six-Component Sequential Groebke–Blackburn/Ugi/Passerini Process, *Eur. J. Org. Chem.*, 2010, 5586–5593; (j) T. Niu, L. Gu, W. Yi and C. Cai, Copper-free Route to Triazole-Modified Peptidomimetic by the Combination of Two Multicomponent Reactions in One Pot, *ACS Comb. Sci.*, 2012, **14**, 309–315.
- 5 (a) H. Bienaymé, Reagent Explosion: an Efficient Method to Increase Library Size and Diversity, *Tetrahedron Lett.*, 1998, **39**, 4255–4258; (b) A. Dömling, The discovery of new isocyanide-based multi-component reactions, *Curr. Opin. Chem. Biol.*, 2000, **4**, 318–323; (c) S. Brauch, L. Gabriel and B. Westermann, Seven-component reactions by sequential chemoselective Ugi–Mumm/Ugi–Smiles reactions, *Chem. Commun.*, 2010, **46**, 3387–3389.
- 6 (a) C. J. Li and L. Chen, Organic chemistry in water, *Chem. Soc. Rev.*, 2006, **35**, 68–82; (b) K. Kumaravel and G. Vasuki, Multi-Component Reactions in Water, *Curr. Org. Chem.*, 2009, **13**, 1820–1841.
- 7 (a) H. Waldmann, *et. al.*, Bioactivity-guided mapping and navigation of chemical space, *Nat. Chem. Biol.*, 2009, **5**, 585–592; (b) R. S. Bon and H. Waldmann, Bioactivity-Guided Navigation of Chemical Space, *Acc. Chem. Res.*, 2010, **43**, 1103–1114; (c) M. E. Welsch, S. A. Snyder and B. R. Stockwell, Privileged scaffolds for library design and drug discovery, *Curr. Opin. Chem. Biol.*, 2010, **14**, 347–361; (d) H. Lachance, S. Wetzel, K. Kumar and H. Waldmann, Charting, Navigating, and Populating Natural Product Chemical Space for Drug Discovery, *J. Med. Chem.*, 2012, **55**, 5989–6001.
- 8 (a) M. D. Burke and S. L. Schreiber, A Planning Strategy for Diversity-Oriented Synthesis, *Angew. Chem., Int. Ed.*, 2004, **43**, 46–58; (b) R. J. Spandl, A. Bender and D. R. Spring, Diversity-oriented synthesis; a spectrum of approaches and results, *Org. Biomol. Chem.*, 2008, **6**, 1149–1158; (c) S. L. Schreiber, Organic chemistry: Molecular diversity by design, *Nature*, 2009, **457**, 153–154; (d) E. Ruijter, R. Scheffelaar and R. V. A. Orru, Multicomponent reaction design in the quest for molecular complexity and diversity, *Angew. Chem., Int. Ed.*, 2011, **50**, 6234–6246; (e) W. R. J. D. Galloway and D. R. Spring, Better leads come from diversity, *Nature*, 2011, **470**, 43.
- 9 S. Oh and S. B. Park, A design strategy for drug-like polyheterocycles with privileged substructures for discovery of specific small-molecule modulators, *Chem. Commun.*, 2011, **47**, 12754–12761.
- 10 (a) M. Koch, A. Schuffenhauer, M. Scheck, S. Wetzel, M. Casaulta, A. Odermatt, P. Ertl and H. Waldmann, Charting biologically relevant chemical space: A structural classification of natural products (SCONP), *Proc. Natl. Acad. Sci. U.S.A.*, 2005, **102**, 17272–17277; (b) R. S. Bon and H. Waldmann, Bioactivity-Guided Navigation of Chemical Space, *Acc. Chem. Res.*, 2010, **43**, 1103–1114; (c) S. Wetzel, R. S. Bon, K. Kumar and H. Waldmann, Biology-Oriented Synthesis, *Angew. Chem., Int. Ed.*, 2011, **50**, 10800–10826.
- 11 (a) B. R. Stockwell and S. L. Schreiber, Probing the role of homomeric and heteromeric receptor interactions in TGF- β signaling using small molecule dimerizers, *Curr. Biol.*, 1998, **8**, 761–773; (b) S. L. Schreiber, Target-Oriented and Diversity-Oriented Organic Synthesis in Drug Discovery,

- Science*, 2000, **287**, 1964–1969; (c) B. R. Stockwell, Exploring biology with small organic molecules, *Nature*, 2004, **432**, 846–856; (d) S. L. Schreiber, *et. al.*, Towards patient-based cancer therapeutics, *Nat. Biotechnol.*, 2010, **28**, 904–906; (e) S. Murrison, S. K. Maurya, C. Einzinger, B. McKeever-Abbas, S. Warriner and A. Nelson, Synthesis of Skeletally Diverse Alkaloid-Like Small Molecules, *Eur. J. Org. Chem.*, 2011, **12**, 2354–2359; (f) P. J. Hajduk, Small molecules, great potential, *Nature*, 2011, **470**, 42; (g) S. L. Schreiber, *et. al.*, An Interactive Resource to Identify Cancer Genetic and Lineage Dependencies Targeted by Small Molecules, *Cell*, 2013, **154**, 1151–1161.
- 12 G. Vasuki and K. Kumaravel, Rapid four-component reactions in water: synthesis of pyranopyrazoles, *Tetrahedron Lett.*, 2008, **49**, 5636–5638.
- 13 B. Ganem, Strategies for Innovation in Multicomponent Reaction Design, *Acc. Chem. Res.*, 2009, **42**, 463–472.
- 14 K. Kumaravel and G. Vasuki, Four-component catalyst-free reaction in water: Combinatorial library synthesis of novel 2-amino-4-(5-hydroxy-3-methyl-1H-pyrazol-4-yl)-4H-chromene-3-carbonitrile derivatives, *Green Chem.*, 2009, **11**, 1945–1947.
- 15 K. Kumaravel and G. Vasuki, Unpublished result.
- 16 (a) T. R. Kasturi, B. N. Mylari, A. Balasubramanyam and C. N. R. Rao, Spectroscopic studies of keto-enol equilibria, *Can. J. Chem.*, 1962, **40**, 2272–2277; (b) T. R. Kasturi, V. K. Sharma, A. Srinivasan and G. Subrahmanyam, Nitrile-ketenimine tautomerism in substituted alkylidene malononitriles and alkylidene cyanoacetates, *Tetrahedron*, 1973, **29**, 4103–4109.
- 17 (a) J.-L. Wang, D. Liu, Z.-J. Zhang, S. Shan, X. Han, S. M. Srinivasula, C. M. Croce, E. S. Alnemri and Z. Huang, Structure-based discovery of an organic compound that binds Bcl-2 protein and induces apoptosis of tumor cells, *Proc. Natl. Acad. Sci. U.S.A.*, 2000, **97**, 7124–7129; (b) M. J. Gorczynski, R. M. Leal, S. L. Mooberry, J. H. Bushweller and M. L. Brown, Synthesis and evaluation of substituted 4-aryloxy- and 4-arylsulfanyl-phenyl-2-aminothiazoles as inhibitors of human breast cancer cell proliferation, *Bioorg. Med. Chem.*, 2004, **12**, 1029–1036; (c) M. Vosooghi, S. Rajabalian, M. Sorkhi, M. Badinloo, M. Nakhjiri and A. S. Negahbani, *et. al.*, Synthesis and cytotoxic activity of some 2-amino-4-aryl-3-cyano-7-(dimethylamino)-4H-chromenes, *Res. Pharm. Sci.*, 2010, **5**, 9–14; (d) A. M. Shestopalov, Y. M. Litvinov, L. A. Rodinovskaya, O. R. Malyshev, M. N. Semenova and V. V. Semenov, Polyalkoxy Substituted 4H-Chromenes: Synthesis by Domino Reaction and Anticancer Activity, *ACS Comb. Sci.*, 2012, **14**, 484–490.