ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 10263–10265

www.rsc.org/chemcomm

COMMUNICATION

$Yb(OTf)_3$ catalyzed new cascade reaction: a facile assembly of fused quinazolinones†

K. Siva Kumar,[ab] P. Mahesh Kumar,[a] M. Appi Reddy,[a] Md. Ferozuddin,[a] M. Sreenivasulu,[a] Ahamed A. Jafar,[b] G. R. Krishna,[c] C. Malla Reddy,[c] D. Rambabu,[d] K. Shiva Kumar,[d] Sarbani Pal[e] and Manojit Pal*[d]

Received 21st June 2011, Accepted 1st August 2011
DOI: 10.1039/c1cc13695j

A one-pot Yb(III)-mediated cascade reaction has been developed leading to small molecules based on a novel structural motif, *i.e.* quinazolin-4-one moiety fused with an isoquinoline ring, for potential inhibition of TNF-α.

Metal catalyzed cascade[1a] and multi-component reactions[1b] (MCRs) have emerged as major strategies in heterocyclic synthesis. Extending these reactions into combinatorial and solid phase syntheses often provides an array of novel heterocyclic frameworks accessible to medicinal/pharmaceutical chemists thereby facilitating identification of new lead structures in the area of drug discovery. While transition metal catalysts are being used extensively for this purpose the use of lanthanides has also been explored.[2] Several lanthanide triflates including $Yb(OTf)_3$ have shown excellent catalytic behavior in various known MCRs such as the Biginelli and Hantzsch reaction.

Dysregulation of TNF-α (Tumor Necrosis Factor-α, a multifunctional cytokine mediator for critical immune functions, including inflammation, infection, and antitumor responses)[3] is implicated in autoinflammatory diseases such as rheumatoid or psoriatic arthritis, and Crohn's disease.[4] A number of synthetic antibodies *e.g.* etanercept, infliximab, and adalimumab have been approved for the treatment of inflammatory diseases. However, due to their potential to cause severe side effects effort has been devoted to identify small molecules as inhibitors of TNF-α.[5] Only few small molecule based inhibitors have been reported till date.[6] Herein we report few small molecules as potential inhibitors of TNF-α synthesized *via* a new three component as well as cascade reaction catalyzed by $Yb(OTf)_3$. In view of promising TNF-α inhibitory properties of 6,6a-dihydroisoindolo-[2,1-*a*]quinazoline-5,11-diones[6b] (**A**, Fig. 1) new chemical entities were designed from **A**. Considering primarily the hydrophobic interactions between **A** and the TNF-α protein as observed in the related docking studies,[6b] the structure **C** was arrived *via* **B** by introducing hydrophobicity into **A** (Fig. 1). Moreover, the substituent R′ was introduced to expand the scope of library generation.

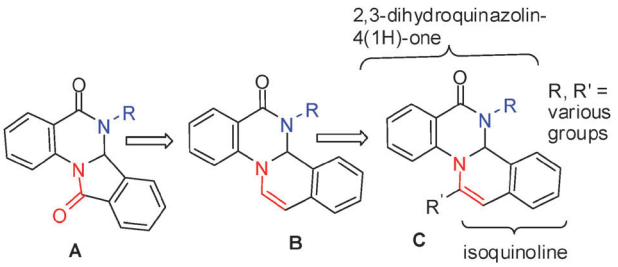


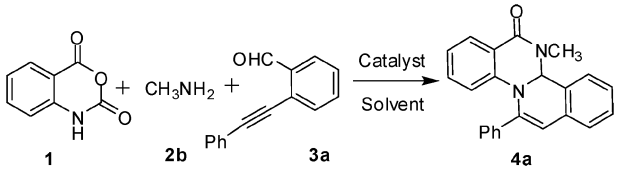
Fig. 1 Design of novel TNF-α inhibitors (**C**) derived from **A**.

Various pharmacological properties and synthesis of 2-aryl-2,3-dihydroquinazolin-4(1*H*)-ones[7] and 2,3-diaryl-1,2-dihydroisoquinolines have been reported.[8] While the synthesis of their combined form *i.e.* 12-aryl-4b*H*-isoquinolino[2,1-*a*]quinazolin-6(5*H*)-one has been disclosed recently[9] corresponding 5-substituted analogues (**C**; R = alkyl or aryl) are not known. Therefore, generation of a compound library based on **C** to evaluate their TNF-α inhibiting property was the major goal whereas development of a suitable methodology leading to the heterocyclic structure **C** was the major challenge. We envisaged that a combination of isatoic anhydride (**1**) and an amine (**2**) could provide the required precursor of the quinazolin-4-one moiety *in situ* and the use of *o*-alkynyl benzaldehyde (**3**) could complete the construction of the fused isoquinoline ring in the presence of a suitable catalyst. Accordingly, the reaction of **1**, methylamine (**2a**) and 2-(phenylethynyl)benzaldehyde (**3a**) was examined under various conditions (Table 1). The initial use of catalyst $Cu(OTf)_2$ (entries 1–3, Table 1) was not successful either at low or elevated temperatures in DCE or acetonitrile as the desired product **4a** was isolated in low or poor yield. Replacing the transition metal catalyst by a lanthanide triflate *i.e.* $Eu(OTf)_3$ improved the product yield

[a] *Custom Pharmaceutical Services, Dr Reddy's Laboratories Limited, Bollaram Road Miyapur, Hyderabad 500 049, India*
[b] *PG and Research Department of Chemistry, Jamal Mohamed College, Tiruchirappalli 620020, Tamil Nadu, India*
[c] *Department of Chemical Sciences, Indian Institute of Science Education and Research, Kolkata, West Bengal 741252, India*
[d] *Institute of Life Sciences, University of Hyderabad Campus, Gachibowli, Hyderabad 500 046, India. E-mail: manojitpal@rediffmail.com*
[e] *Department of Chemistry, MNR Degree and PG College, Kukatpally, Hyderabad, India*

† Electronic supplementary information (ESI) available: Experimental procedures, spectral data for all new compounds, results of docking study. CCDC 828186. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc13695j

Table 1 Effect of reaction conditions on MCR using isatoic anhydride (**1**) with methylamine (**2a**) and 2-(phenylethynyl)benzaldehyde (**3a**)[a]



1 2b 3a 4a

Entry	Catalyst	Solvent	T/°C	Time/h	%Yield[b]
1	$Cu(OTf)_2$	DCE	25–30	48	25
2	$Cu(OTf)_2$	DCE	80–85	24	20
3	$Cu(OTf)_2$	MeCN	80–85	24	10
4	$Eu(OTf)_3$	DCE	25–30	24	40
5	$Eu(OTf)_3$	DCE	80–85	24	20
6	$Yb(OTf)_3$	DCE	25–30	48	70
7	$Yb(OTf)_3$	MeCN	25–30	48	35
8	$Yb(OTf)_3$	DCE	25–30	48	49[c]

[a] All the reactions were carried out using **1** (6.13 mmol), **2a** (6.71 mmol), **3a** (6.74 mmol) and a catalyst (0.61 mmol) in a solvent (10 mL). [b] Isolated yield. [c] 0.30 mmol of $Yb(OTf)_3$ was used. DCE = 1,2-dichloroethane.

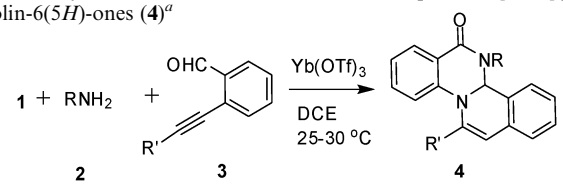
marginally when the reaction was performed at 25–35 °C in DCE (entry 4, Table 1) but not at higher temperatures (entry 5, Table 1). Good yield of **4a** however was obtained when $Yb(OTf)_3$ was used in DCE (entry 6, Table 1) but not in MeCN (entry 7, Table 1). The use of lower quantity of catalyst decreased the product yield (entry 8, Table 1). The MCR did not provide **4a** in the absence of $Yb(OTf)_3$ confirming the key role played by the catalyst.

The compound **4a** was characterized by the appearance of the C=O signal at 1706 cm^{-1} in IR and 163.2 ppm in ^{13}C NMR spectra. A signal at 5.64δ in the ^{1}H NMR and 74.6 ppm in the ^{13}C NMR spectra confirmed the presence of C–H at the vinylic and C-4b position of the isoquinoline ring respectively.

We examined the scope of the present Yb(III)-catalyzed reaction using the optimized conditions which provided 4b*H*-isoquinolino[2,1-*a*]quinazolin-6(5*H*)-one with a variety of substitution patterns (Table 2). The reaction proceeded well with a variety of aliphatic and aromatic amines (**2**) and *o*-alkynyl benzaldehydes (**3**) to give a range of 5,12-disubstituted derivatives (Table 2). All the compounds synthesized were characterized by spectral and analytical data and this was supported by the molecular structure of **4b** being confirmed by X-ray analysis (Fig. 2).[10]

Mechanistically, the reaction seems to proceed *via* (i) generation of *N*-substituted *o*-aminobenzamide from **1** and **2** *in situ* which on (ii) condensation with **3** provides the corresponding imine. (iii) A subsequent intramolecular and regiospecific nucleophilic attack of the imine nitrogen at the Yb-coordinated alkyne (**E-1**) generates the corresponding (2-(2-carbamoylphenyl)isoquinolinium-4-yl)ytterbium ion (**E-2**, Scheme 1) which (iv) undergoes further nucleophilic attack by the amide nitrogen at C-1 in an intramolecular fashion to give **4** (*via* **E-3**).[11] Alternatively, 2-(*o*-alkynylphenyl)-2,3-dihydroquinazolin-4-one intermediate formed through an intramolecular cyclization of the iminoalkyne–Yb complex undergoes a Yb(III)-assisted regiospecific intramolecular hydroamination reaction leading to the formation of **4**

Table 2 Synthesis of 5,12-disubstituted 4b*H*-isoquinolino[2,1-*a*]quinazolin-6(5*H*)-ones (**4**)[a]



2 3 4

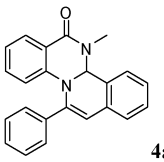
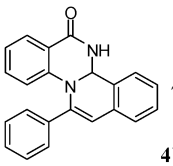
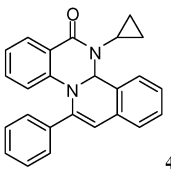
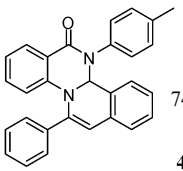
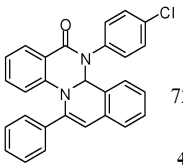
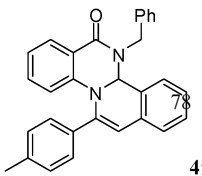
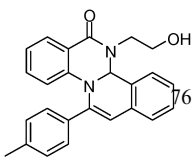
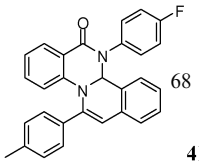
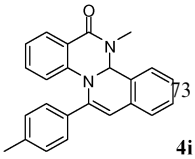
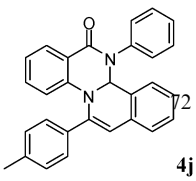
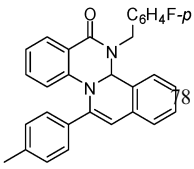
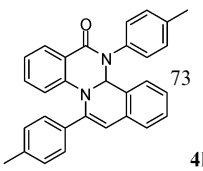
Entry	Amines **2**; R =	Alkynes **3**; R′ =	Products **4**	%Yield[b]
1	**2a**; CH_3	**3a**; C_6H_5	 **4a**	70
2	**2b**[c]	**3a**	 **4b**	72
3	**2c**; c-propyl	**3a**	 **4c**	64
4	**2d**; $C_6H_4CH_3$-*p*	**3a**	 **4d**	74
5	**2e**; C_6H_4Cl-*p*	**3a**	 **4e**	72
6	**2f**; $C_6H_5CH_2$	**3b**; $C_6H_4CH_3$-*p*	 **4f**	78
7	**2g**; CH_2CH_2OH	**3b**	 **4g**	76
8	**2h**; C_6H_4F-*p*	**3b**	 **4h**	68

Table 2 (*continued*)

Entry	Amines **2**; R =	Alkynes **3**; R′ =	Products **4**	%Yield[b]
9	**2a**	**3b**	 **4i**	73
10	**2i**; C_6H_5	**3b**	 **4j**	72
11	**2j**; $CH_2C_6H_4F$-*p*	**3b**	 **4k**	78
12	**2d**	**3b**	 **4l**	73

[a] All the reactions were carried out using **1** (6.13 mmol), **2** (6.71 mmol), **3** (6.74 mmol) and $Yb(OTf)_3$ (0.61 mmol) in DCE (10 mL) at 25–30 °C for 48 h. [b] Isolated yield. [c] $(NH_4)_2CO_3$ was used in place of RNH_2.

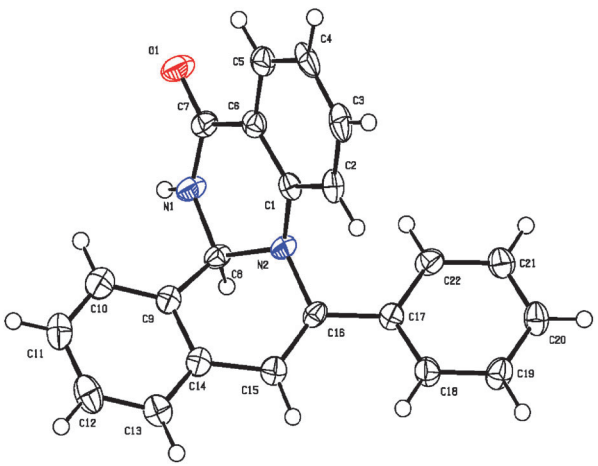
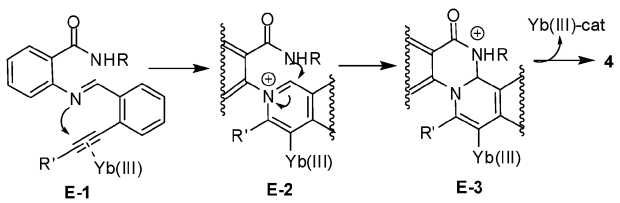
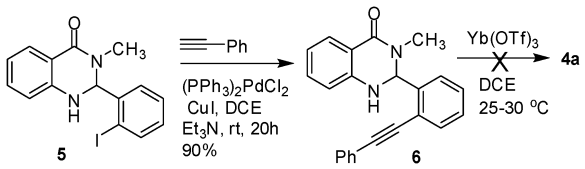


Fig. 2 X-Ray crystal structure of **4b** (ORTEP diagram). Thermal ellipsoids are drawn at 50% probability level.



Scheme 1 Proposed reaction mechanism.



Scheme 2 Preparation of alkyne **6** and its reaction with $Yb(OTf)_3$.

(see ESI†). To gain further evidence, the alkyne **6** prepared from the iodide **5** (obtained *via* a known method[11]) was treated with $Yb(OTf)_3$ at 25–35 °C in DCE (Scheme 2). However, formation of **4a** was not observed even after 24 h indicating that the present cascade reaction does not follow the alternative path as proposed.

In conclusion, a new cascade reaction catalyzed by $Yb(OTf)_3$ has been developed that allowed concurrent construction of two six membered fused *N*-heterocyclic rings thereby rapid access to a library of small molecules based on a novel structural motif. Two of these compounds showed inhibition of TNF-α *in vitro*[12] and may have potential for therapeutic applications.

KSK thanks Dr Vilas Dahanukar and the analytical group of DRL. MP thanks Prof. J. Iqbal for support.

Notes and references

1 (*a*) For a scholarly review, see: K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed.*, 2006, **45**, 7134; (*b*) For an in-depth review, see: D. M. D'Souza and T. J. J. Müller, *Chem. Soc. Rev.*, 2007, **36**, 1095.

2 P. J. Tambade, Y. P. Patil and B. M. Bhanage, *Curr. Org. Chem.*, 2009, **13**, 1805.

3 H. Wajant, K. Pfizenmaier and P. Scheurich, *Cell Death Differ.*, 2003, **10**, 45.

4 B. B. Aggarwal, *Nat. Rev. Immunol.*, 2003, **3**, 745.

5 M. A. Palladino, F. R. Bahjat, E. A. Theodorakis and L. L. Moldawer, *Nat. Rev. Drug Discovery*, 2003, **2**, 736 and references cited therein.

6 For leading references, see: (*a*) D. Shiu-Hin Chan, H.-M. Lee, F. Yang, C.-M. Che, C. C. L. Wong, R. Abagyan, C.-H. Leung and D.-L. Ma, *Angew. Chem., Int. Ed.*, 2010, **49**, 2860; (*b*) K. S. Kumar, P. M. Kumar, K. A. Kumar, M. Sreenivasulu, A. A. Jafar, D. Rambabu, G. R. Krishna, C. M. Reddy, R. Kapavarapu, K. Shivakumar, K. K. Priya, K. V. L. Parsa and M. Pal, *Chem. Commun.*, 2011, **47**, 5010.

7 M. Dabiri, P. Salehi, S. Otokesh, M. Baghbanzadeh, G. Kozehgary and A. A. Mohammadi, *Tetrahedron Lett.*, 2005, **46**, 6123 and references cited therein.

8 M. Kihara, M. Ikeuchi and Y. Nagao, *Drug Des. Discovery*, 1995, **12**, 259 and references cited therein.

9 N. T. Patil, A. K. Mutyala, P. G. V. V. Lakshmi, P. V. K. Raju and B. Sridhar, *Eur. J. Org. Chem.*, 2010, 1999.

10 Crystal data of **4b**: molecular formula = $C_{22}H_{16}N_2O$, formula weight = 324.37, crystal system = monoclinic, space group = $P2_1/n$, a = 9.388(6) Å, b = 11.595(8) Å, c = 15.005(10) Å, V = 1627.3(19) Å^3, T = 100(2) K, Z = 4, D_c = 1.324 Mg m^{-3}, μ(Mo-Kα) = 0.08 mm^{-1}, 6728 reflections measured, 3152 independent reflections, 1525 observed reflections [$I > 2.0\sigma(I)$], R_1_obs = 0.079, goodness of fit = 0.765. CCDC 828186†.

11 M. Baghbanzadeh, P. Salehi, M. Dabiri and G. Kozehgary, *Synthesis*, 2006, 344.

12 Some of the compounds synthesized were tested for their TNF-α inhibitory potential *in vitro*.[6b] Compounds **4h** and **4i** showed 29% and 47% inhibition of TNF-α at 10 μM. The docking results of **4i** with TNF-α protein (see ESI†) showed good interactions with the hydrophobic binding site (binding energy −5.6 kcal mol^{-1}) consisting primarily of H-bonding interaction of the C=O group of **4i** with the –NH group of W118 (tryptophan) residue of the TNF-α protein.