A new three-component reaction: Green synthesis of novel isoindolo[2,1-a]quinazoline derivatives as potent inhibitors of TNF-α

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COMMUNICATION

A new three-component reaction: green synthesis of novel isoindolo[2,1-*a*]quinazoline derivatives as potent inhibitors of TNF-α†

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Concurrent construction of five and six membered fused *N*-heretocyclic ring was achieved *via* a conceptually new three-component reaction affording 6,6a-dihydroisoindolo-[2,1-*a*]quinazoline-5,11-diones as novel inhibitors of TNF-α *in vitro*. This represents one of the few examples of direct TNF-α inhibition by small molecules.

Multi-component reactions (MCRs)[1] allow simple and flexible assembly of three or more building blocks in a user-friendly one-pot operations to form a product containing substantial elements of all the reactants. Through the generation of a combinatorial library MCRs often provide convergent, atom-economic, expedient and eco-friendly chemical methods for the discovery of new chemical entities (NCEs) required by pharmaceutical and agrochemical industries.[2] While MCRs like the Strecker, Passerini, Ugi, Pauson–Khand and Biginelli reactions as well as the Mannich condensation have become powerful tool in organic synthesis their usage for the construction of heteroaryl-based structures is not common.[3] Incidentally, most of the drugs currently in the market or in the clinical trials contain heterocyclic structures. Thus development of new MCR leading to novel heteroaryl derivatives is of high interest both in academic and industrial organizations.

TNF-α (Tumor Necrosis Factor-alpha), one of the key cytokine mediators involved in the inflammatory response is used as a marker for many inflammatory disorders.[4a] The biological importance of TNF-α inhibition in the treatment of inflammatory disorders such as rheumatoid arthritis, Crohn's disease, and ulcerative colitis became apparent with the discovery and use of infliximab, a monoclonal antibody directed against TNF-α.[4b] However, inhibition of TNF-α by small molecules is not common in the literature.[4c] In this communication we wish to present our preliminary work on the design, and identification of novel small molecules as inhibitors[4c] of TNF-α synthesis of which was carried out using a conceptually new MCR.

During the last ten years the pharmaceutical industry has focused on the development of novel anti-inflammatory agents that inhibit phosphodiesterase 4 (PDE-4) as well as TNF-α to treat chronic obstructive pulmonary disease (COPD) and asthma.[5] Because of its notable anti-inflammatory and analgesic pharmacological profile the well known PDE-4 inhibitor Nitraquazone (**A**, Fig. 1) or 3-ethyl-1-(3-nitrophenyl)-2,4(1*H*,3*H*)-quinazolinedione[6] (TVX-2706) has been used as a starting template to develop potent inhibitors with improved pharmacological properties.[7] In our effort to develop novel inhibitors of TNF-α we thought that **A** could be an interesting starting point. Thus the possible areas of interaction as hydrogen bond acceptors for **A** were analyzed. Subsequent manipulation of the *N*-aryl amide moiety of **A** without disturbing the possible areas of interactions afforded a new heterocyclic structure *i.e.* 6,6a-dihydroisoindolo[2,1-*a*]-quinazoline-5,11-dione (**C** *via* **B**, Fig. 1) that was explored as a basic scaffold for the discovery of novel TNF-α inhibitors.

While as an individual class of heterocycles 2-aryl-2,3-dihydroquinazolin-4(1*H*)-one[8] and 2-arylisoindolin-1-one[9] are well known in the literature their combined form *i.e.* 6,6a-dihydroisoindolo[2,1-*a*]quinazoline-5,11-diones are rather uncommon. One of the major challenges and aim of the present work was therefore to develop a suitable methodology leading to the heterocyclic structure **C**. We envisaged that the

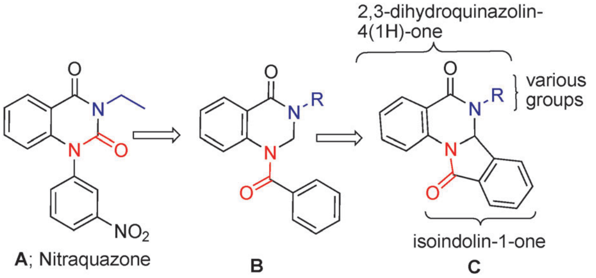

Fig. 1 Design of novel inhibitors of TNF-α/PDE-4B.

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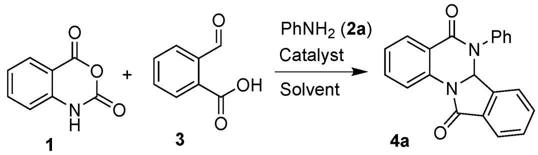
† Electronic supplementary information (ESI) available: Experimental procedures, spectral data for all new compounds, results of docking study. CCDC 807140–807141. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc10715a

Table 1 Effect of reaction conditions on MCR using isatoic anhydride (**1**) with aniline (**2a**) and 2-formylbenzoic acid[a] (**3**)



Entry	Solvent	$T/°C$	Time (h)	% Yield[b]
1	EtOH	80–85	15	72
2	*i*-PrOH	80–85	15	70
3	Methanol	60–65	24	40
4	Methanol	25	24	50[c]
5	1,4-Dioxane	100	8	60
6	DCM	40	24	—
7	EtOH	80–85	15	75[d] (70)[e]

[a] All the reactions were carried out using isatoic anhydride **1** (6.13 mmol), aniline **2a** (6.7 mmol) and 2-formylbenzoic acid **3** (6.74 mmol) and anhydrous CSA (0.31 mmol) in a solvent (10 mL). [b] Isolated yield. [c] Yield of 2-amino-*N*-phenylbenzamide. [d] Montmorillonite K10 (5% w/w) was used in place of CSA. [e] Recovered Montmorillonite K10 was used.

one-pot three-component synthesis of 2,3-dihydroquinazolin-4(1*H*)-one from isatoic anhydride, ammonium acetate and an aldehyde could be handy in the present case. Thus to maintain the "R" group of **C** the ammonium acetate was replaced by appropriate amines and 2-formylbenzoic acid was chosen as a third component that would eventually allow the construction of the fused isoindolin-1-one ring. To this end we have observed that treatment of isatoic anhydride (**1**) with aniline (**2a**) and 2-formylbenzoic acid (**3**) in the presence of commercially available anhydrous (+)-camphor-10-sulfonic acid (CSA) in ethanol at 80–85 °C produced 6-phenyl-6,6a-dihydroisoindolo-[2,1-*a*]quinazoline-5,11-dione (**4a**) as the only product (entry 1, Table 1). Among the other solvents examined *i*-PrOH was found to be equally effective (entry 2, Table 1) whereas MeOH provided **4a** in low yield (entry 3, Table 1). Notably, 2-amino-*N*-phenylbenzamide was obtained at 25 °C in MeOH indicating the intermediacy of this compound in the present MCR. The use of 1,4-dioxane and CH_2Cl_2 was found to be either less or not effective (entry 5 & 6, Table 1). The MCR did not proceed in the absence of CSA, indicating the vital role played by the catalyst. The MCR was sluggish when *p*-TSA was used in place of CSA. To develop an environmentally friendly process we examined the use of montmorillonite K10 as a catalyst and observed that MCR proceeds well (entry 7, Table 1). To test the recyclability of the catalyst, montmorillonite K10 recovered by simple filtration was reused and the MCR afforded **4a** without affecting the yield significantly (entry 7, Table 1). The compound **4a** was characterized by the appearance of two C=O signals at 1723 & 1686 cm^{-1} in IR and 164.7 & 163.4 ppm in ^{13}C NMR spectra. A signal at 6.60 δ in the ^1H NMR and 71.5 ppm in the ^{13}C NMR spectra confirmed the presence of C–H group at 6a-position of **4a**.[10a]

We were pleased to find that the present green MCR provided 6,6a-dihydroisoindolo[2,1-a]quinazoline-5,11-diones with a variety of substitution patterns (Table 2). The reaction proceeded well with a variety of aliphatic and aromatic amines to give a range of 6-substituted derivatives (Table 2). All the

Table 2 Green synthesis of 6-substituted-6,6a-dihydroisoindolo-[2,1-*a*]quinazoline-5,11-diones[a]

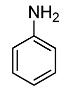
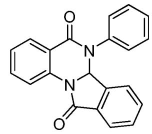
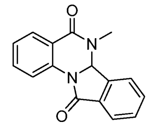
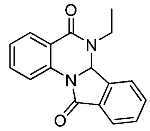
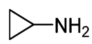
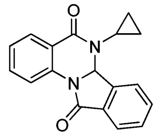
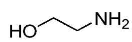
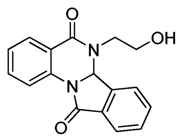
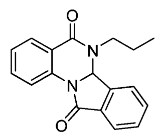
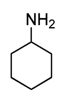
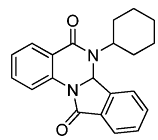
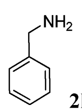
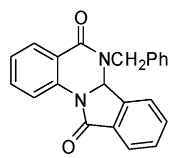
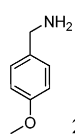
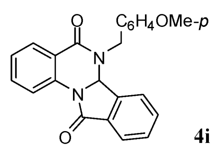
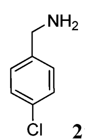
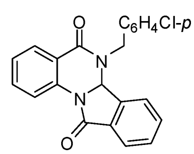
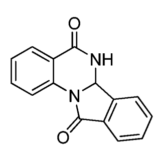
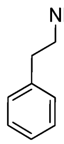
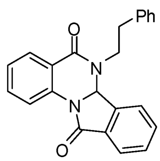
Entry	Amines (**2**)	Products (**4**)	Time (h)	Yield[b] (%)
1	 **2a**	 **4a**	15	72
2	$MeNH_2$ **2b**	 **4b**	12	93
3	$EtNH_2$ **2c**	 **4c**	15	85
4	 **2d**	 **4d**	12	80
5	 **2e**	 **4e**	8	95
6	*n*-$PrNH_2$ **2f**	 **4f**	15	92
7	 **2g**	 **4g**	12	75
8	 **2h**	 **4h**	7	85
9	 **2i**	 **4i**	7	84
10	 **2j**	 **4j**	8	82
11	$(NH_4)_2CO_3$ **2k**	 **4k**	10	92

Table 2 (*continued*)

Entry	Amines (2)	Products (4)	Time (h)	Yield[b] (%)
12	 2l	 4l	12	78

[a] All the reactions were carried out using isatoic anhydride **1** (6.13 mmol), amine **2** (6.7 mmol) and 2-formylbenzoic acid **3** (6.74 mmol) and Montmorillonite K10 (5% w/w) in EtOH (10 mL) at 80–85 °C. [b] Isolated yield.

compounds synthesized were characterized by spectral and analytical data and this was supported by the molecular structure of **4j** being confirmed by X-ray analysis (Fig. 2).[10b] Some of the compounds synthesized were tested for their TNF-α inhibitory potential *in vitro*.[11] Compounds **4h–4k** showed significant inhibition of TNF-α at 10 μM whereas the compound **4k** showed dose-depended inhibition with an IC_{50} value 9.33 μM (Fig. 3). This was supported by the docking results of **4k** with TNF-α protein (see ESI†) which showed strong interactions with the hydrophobic binding site (binding energy −8.57 Kcal/mol) consisting primarily of glycine, leucine and tyrosine residues. The binding interaction therefore not unexpectedly contributed mainly by hydrophobic and van der Waals type interactions. Since the low potency, poor selectivity and adverse side effects are associated with some of the small molecules based inhibitors[12] the development of new inhibitors remained a highly desirable goal. Thus, compounds **4h–k** may have medicinal value with potential therapeutic applications.

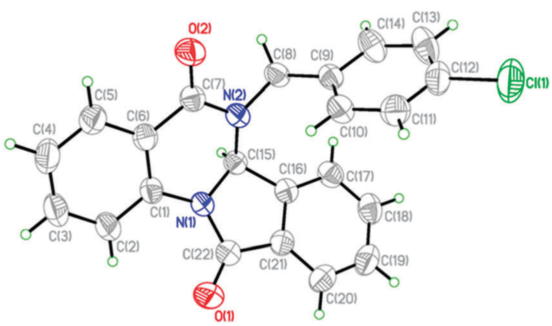


Fig. 2 X-ray crystal structure of **4j** (ORTEP diagram). Thermal ellipsoids are drawn at 50% probability level.

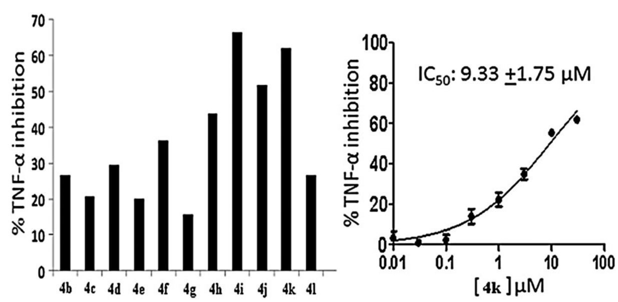


Fig. 3 *In vitro* TNF-α inhibition of compounds **4** and IC_{50} of **4k**.

In conclusion, a green and general synthesis of novel 6,6a-dihydroisoindolo[2,1-*a*]quinazoline-5,11-diones has been accomplished *via* a new three component reaction involving concurrent construction of a five and six membered fused *N*-heterocyclic ring.[13] This research has led to the identification of a small molecule-based potent inhibitor of TNF-α.

KSK thanks Dr Vilas Dahanukar and the analytical group of DRL.

Notes and references

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10 (*a*) Since our attempt to prepare a single crystal of **4a** for X-ray analysis was failed hence 6-(3-chlorophenyl)-6,6a-dihydroisoindolo-[2,1-a]quinazoline-5,11-dione was prepared (by using **1**, **3** and 3-chloroaniline) the structure of which was confirmed by X-ray analysis (see ESI†); (*b*) Crystal data of **4j**: Molecular formula = $C_{22}H_{15}ClN_2O_2$, Formula weight = 374.1, Crystal system = Monoclinic, space group = $P2_1/c$, a = 11.6223(6) Å, b = 7.8255(4) Å, c = 19.9457(10) Å, V = 1772.91(16) Å^3, T = 296 K, Z = 4, D_c = 1.404 Mg m^{-3}, μ(Mo-Kα) = 0.71073 mm^{-1}, 27 323 reflections measured, 3833 independent reflections, 3311 observed reflections [$I > 2.0\sigma(I)$], R_1_obs = 0.047, Goodness of fit = 1.030. Crystallographic data (excluding structure factors) for **4j** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 807140.

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12 (*a*) R. P. McGeary, A. J. Bennett, Q. B. Tran, K. L. Cosgrove and B. P. Ross, *Mini-Rev. Med. Chem.*, 2008, **8**, 1384; (*b*) H. Sun and G. S. Yost, *Chem. Res. Toxicol.*, 2008, **21**, 374; (*c*) The TNF-α inhibitors based on synthetic antibodies *e.g.* etanercept, infliximab, and adalimumab have been approved for the treatment of inflammatory diseases. But their uses cause serious side effects such as eliciting an autoimmune anti-antibody response or the weakening of the body's immune defenses.

13 Mechanistically, the reactionseemsto proceed *via* 2-amino-*N*-arylbenzamide intermediate generated *in situ* from the reaction of **1** with amine **2**. The reaction of this intermediate with 2-formylbenzoic acid **3** provides the second intermediate the azomethine moiety of which subsequently participates in an intramolecular concurrent cyclization involving the carboxylic acid and amide group to give the desired product **4**.

