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FULL-LENGTH PAPER

Ultrasound-promoted synthesis and immunosuppressive activity of novel quinazoline derivatives

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Abstract An environmentally friendly and mild Bischler cyclization was developed to access quinazolines with diverse substitution. Based on this method, a library of 53 quinazoline derivatives was prepared and tested in vitro for cytotoxicity and inhibition on T-cell and B-cell proliferation. Compounds **6b**, **7b**, **17b**, **33**, and **35** showed higher inhibitory activity on both T-cell and B-cell proliferations, with IC_{50} values of 6.16, 6.30, 5.43, 2.54, and 9.80 μM on T-cell, respectively. All the tested compounds showed no obvious cytotoxicity at 10 μM concentration. The preliminary structure–activity relationship was concluded revealing that 4-position is the key modification site for potent quinazoline immunosuppressive agent.

Keywords Immunosuppressive activity · Bischler cyclization · Ultrasound irradiation · SAR · Quinazoline

Introduction

Immunosuppressants, e.g., cyclosporine A (CsA), tacrolimus (FK506), sirolimus (rapamycin), and rituximab, are an important class of clinical drugs used in the prevention of transplant rejection (mainly heart, liver, kidney, and lung) and treatment of autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and psoriasis [1,2]. The first three drugs act by inhibiting T lymphocyte proliferation during an immune response [3–5]. Rapamycin suppresses T-cell activation, mainly through inhibition of proliferation induced by growth-promoting lymphokines [2]. Rituximab binds to protein CD20, which is primarily found on the surface of B-cells, and induces apoptosis of B-cell [6]. Despite the efficacy of these immunosuppressive drugs on organ transplantation and treatment of autoimmune diseases in the clinic, their side effects, including liver toxicity, nephrotoxicity, malignancy, infection, cardiovascular toxicity, and others cannot be neglected [7–11]. Therefore, the search for novel immunosuppressants with a comparable efficacy but lower toxicity is an important mission for medicinal chemistry.

We previously reported a series of 5,7-dimethoxyquinoline derivatives with potent inhibitory activity on the proliferation of T-cell [12]. The initial structure–activity investigation revealed that quinoline core, 5,7-dimethoxyl, and *ortho*-substituted benzoate/sulfonate are important moieties for immunosuppressive potential and disclosed 5,7-dimethoxyquinolin-4-yl 2,6-dichlorobenzoate (**Q1**) and 5,7-dimethoxyquinolin-4-yl 4-methylbenzenesulfonate (**Q2**) as promising leads, with 94 and 82 % inhibition of ConA-induced T-cell proliferation at 10 μM, respectively, without obvious cytotoxicity (Fig. 1).

Quinazoline is an important heterocyclic analogue of quinoline (Fig. 1). Quinazoline derivatives exhibit a variety of biological activities, including antimalarial, anti-inflammatory, antifungal, and anticancer [13–17]. However, their effect on immunosuppressive activity has not been studied sufficiently. Considering the structural similarity of

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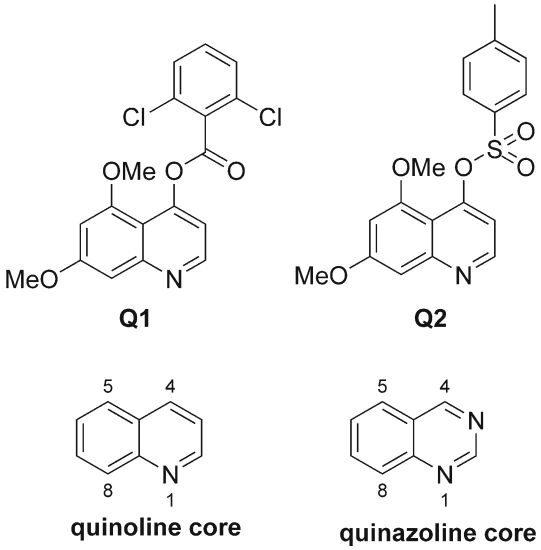
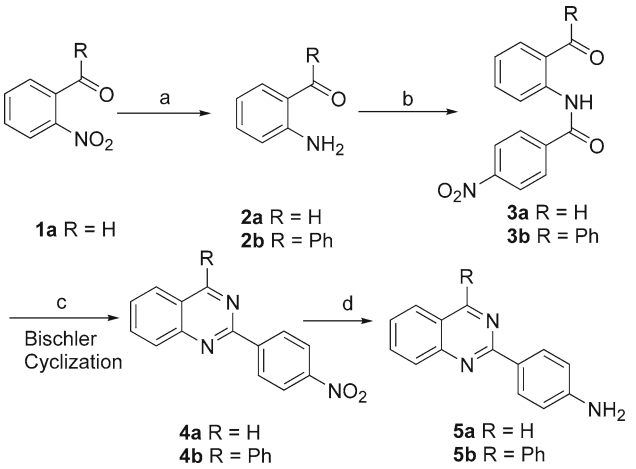


Fig. 1 Structure of quinoline, quinazoline, and potent quinoline derivatives



Scheme 1 Synthetic route of quinazoline core. Reagent and conditions: (*a*) iron powder, catalyst: concentrated HCl, ethanol/water, 50 °C; (*b*) 4-nitrobenzoic acid chloride, TEA, DCM, 0 °C; (*c*) 25 % ammonia water, water, ultrasound 250 W, 80 °C, 3 h; (*d*) iron powder, concentrated HCl as catalyst, ethanol/water, 50 °C

quinoline and quinazoline, we put our interest on quinazoline derivatives to explore new immunosuppressive agents.

As a continuation of our work in the search for new immunosuppressive agent [12,18,19], herein, we report a synthesis of novel quinazoline derivatives using a modified green Bischler cyclization reaction as a key step with the assistant of ultrasound irradiation. The immunosuppressive activity of the synthesized compounds was evaluated with T/B-cell functional assays and their cytotoxicity was tested. The preliminary structure–activity relationship (SAR) is also discussed.

Results and discussion

Chemistry

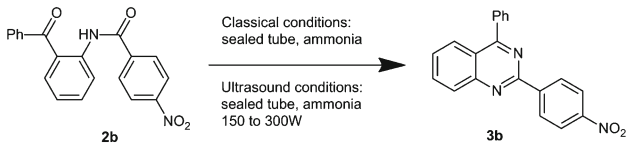
The construction of the quinazoline ring has been extensively described in the literature [20]. The Bischler cyclization is the oldest synthetic strategies for quinazoline derivatives [21–23], which needs high temperature (higher than 120 °C) and pressure in saturated alcoholic ammonia at least for 5 h. A variant of this method involves the passage of ammonia through a fused mixture of amides and sodium acetate at temperatures higher than 160 °C [24]. These harsh conditions and tedious work-ups restrict its usage for high functionalized quinazoline derivatives. However, it is a convenient route to prepare 2,4-disubstituted quinazolines avoiding the use of toxic chemicals such as phosphorous oxychloride, thionyl chloride [25–27]. The growing importance of quinazoline derivatives in therapeutics as well as the development of green synthetic protocol encourages the search for environmentally benign synthetic methods for their preparations.

In order to construct the quinazoline core, we designed a four-step synthetic route as shown in Scheme 1 referring to the Bischler cyclization as the key step. The first step involves the preparation of *o*-aminobenzoaldehyde (**2a**) from *o*-nitrobenzoaldehyde (**1a**) with iron powder as a reductant in a co-solvent (ethanol and water, V/V, 5:1) catalyzed by hydrochloric acid. Furthermore, **2a** or **2b** (1 equiv) was treated with 4-nitrobenzoyl chloride (1 equiv) and triethylamine (1.2 equiv) in DCM at room temperature (RT). The reaction completed within 2 h according to TLC monitoring (hexane/ethyl acetate, V/V, 5:1) affording amide **3** with quantitative yields, which was then used directly in the next step without further purification.

Concerning the Bischler cyclization step, we first investigated the reaction conditions for the Bischler cyclization by considering the impact of temperature, reaction time, solvent, and additives (acid or base catalysis). When amide **3b** reacts with ammonia (20 equiv) in isopropanol in a sealed tube at 80 °C for 12 h (Table 1, entry 4) the best conversion was 72 % based on 1H NMR analysis. Potentially, higher temperatures (>120 °C) and pressure, as in a classical Bischler reaction, might afford complete conversion. However, the mildness and ease of the reaction conditions led us to explore other alternatives.

Encouraged by our previous experiments and reported results using ultrasound irradiation as an assist in organic syntheses [28–30], we attempted to improve quinazoline formation step via exposure to ultrasound irradiation. Fortunately, after an optimization of reaction conditions (solvent, ultrasound output power), in diluted ammonia water at 80 °C with a 250 W ultrasound output power for 3 h (Table 1, entry 6), the quinazoline **4b** was furnished in high yield (93 %). It should

Table 1 Optimization of the Bischler cyclization reaction condition



Entry	N source (equiv)	Solvent	Temp. (°C)	Time (h)	US (W)[a]	Conversion (%)[b]
1	NH_4OH (20)	H_2O	60	12	0 (W)	25.0
2	NH_4OH (20)	H_2O	80	12	0 (W)	38.5
3	NH_4OH (20)	H_2O	100	12	0 (W)	43.8
4	NH_4OH (20)	Isopropanol	80	12	0 (W)	72.2
5	NH_4OH (20)	H_2O	80	6	150 (W)	80.2
6	**NH_4OH (20)**	**H_2O**	**80**	**3**	**250 (W)**	**100 (93.3)**[c]
7	NH_4OH (20)	H_2O	60	5	250 (W)	98.1 (91.6)[c]
8	NH_4OH (10)	H_2O	80	6	250 (W)	100 (93.6)[c]
9	Urea (20)	H_2O	100	24	300 (W)	NR[d]
10	NH_4Ac (20)	H_2O	100	24	300 (W)	NR[d]

Reaction condition: **2b** (1.5 mmol), 25% ammonia water (2 mL), and water (4 mL) heated to indicated temperature in a sealed tube with or without ultrasound irradiation

[a] Ultrasound irradiation (output power Watt)

[b] Determined by ^{1}H NMR

[c] The isolated yield is shown in parentheses

[d] Only starting material was recovered

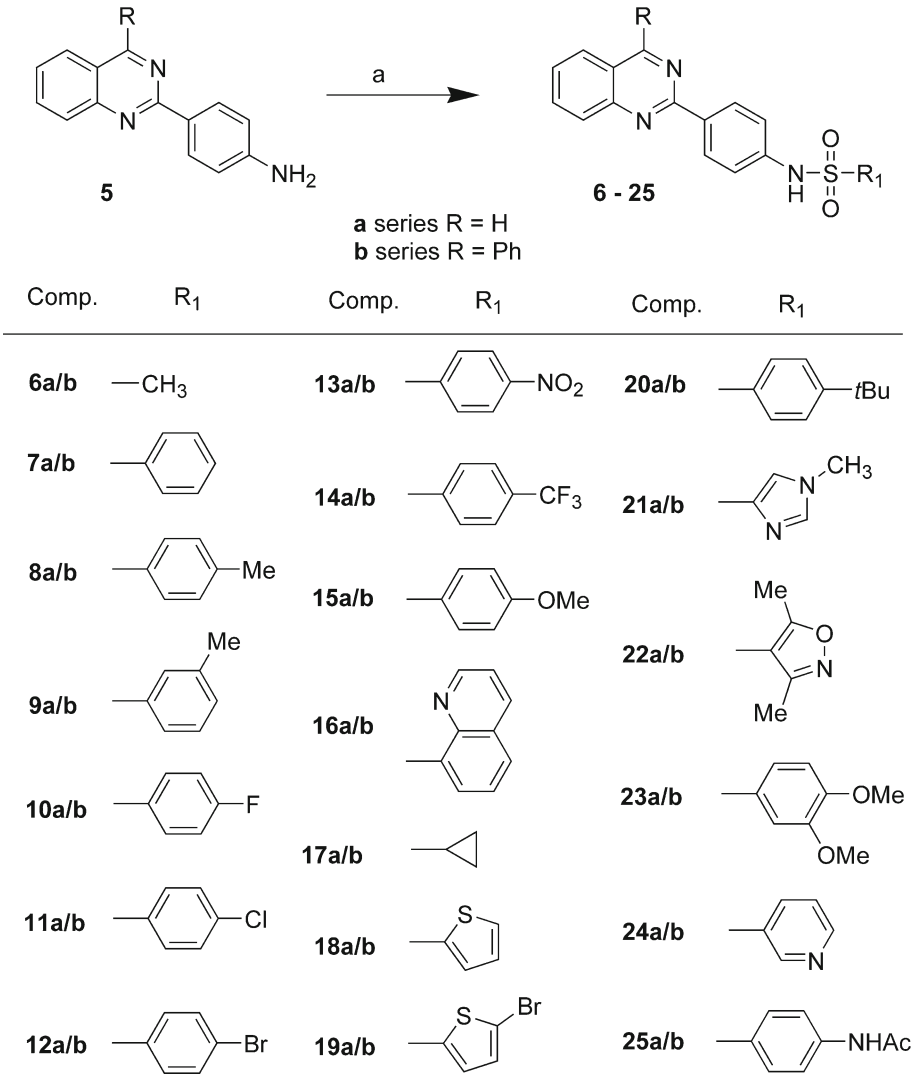
be noted that **4b** can be obtained by simple filtration without the need for further purification making this procedure easily scalable for industrial applications with the added advantage of this being a green protocol as water is used as solvent. The above results revealed that the ultrasound-assisted Bischler cyclization is more efficient and milder than traditional protocol. As shown in Scheme 1, reduction of nitro group of **4** with iron afforded the pivotal amino intermediate **5** in a good yield.

It has reported that quinazoline-4-sulfonamides have behaved as inverse agonists at the human histamine H_4 receptor (H_4R) which is considered a potential drug target for the treatment of autoimmune diseases such as asthma, allergic rhinitis, and pruritus [31,32]. For exploratory purposes, we synthesized a series of quinazoline-2-sulfonamides derivatives. The amino group of **5** was further modified by sulfonyl chlorides, aiming to get new quinazoline-4-sulfonamides derivatives. Synthesis of quinazoline sulfonamides **6**–**25** was outlined in Scheme 2. In order to obtain a robust SAR, 20 sulfonamides of amino compounds 4-unsubstituted quinazoline **5a** and 4-phenylquinazoline **5b** were prepared. Sulfonyl chlorides were selected to contain electron-donating, electron-withdrawing, aromatic, aliphatic, heterocyclic, hydrogen bond donor, and hydrogen bond acceptor groups. Compound **5** was treated with corresponding sulfonyl chlorides (1.1 equiv) slowly in the presence of triethylamine (TEA, 1.5 equiv) in dichloromethane or without TEA in pyridine at RT. Because the electronic-withdrawing effect of quinazoline ring reduces the nucleophilicity of the amino group of **5**, the reactions were performed in pyridine, heated to 50 °C and completed within 5 h. Sulfonamides **6** –**25** were afforded in good to excellent yields.

It has been reported that the urea moiety could enhance bioactivity by multitude hydrogen bond donors and acceptors [33,34]. For exploratory purposes, we synthesized a series of 2-urea-containing quinazoline derivatives by reacting aminoquinazoline **5b** with isocyanates (Scheme 3). **5b** was treated with corresponding isocyanates (1.1 equiv) in toluene at 70 °C for 7 h where the precipitated solids were filtered and washed with ethyl ether to afford pure products **26** –**34** as white solids. Amide **35**, lack of a NH group as a hydrogen bond donor compared to that of ureas (**26**–**34**), was prepared for SAR study, via **5b** reacted with furan-2-carbonyl chloride in DCM.

Our previous study revealed that 5,7-dimethoxylquinoline as a promising core for inhibition activity on a ConA-induced T-cell proliferation assay [12]. The methylated-hydroxyl groups of 5,7-dimethoxylquinoline (**Q1** and **Q2**) are essential for the enhanced inhibitory activity as the remove of the methyl groups resulted in a decrease of inhibition rate. Based on this observation, we designed a

Scheme 2 Synthesis of paralleled quinazoline sulfonamide derivatives (**6**–**25**). Reagents and conditions: (*a*) sulfonyl chloride, pyridine, RT to 50 °C, 5 h



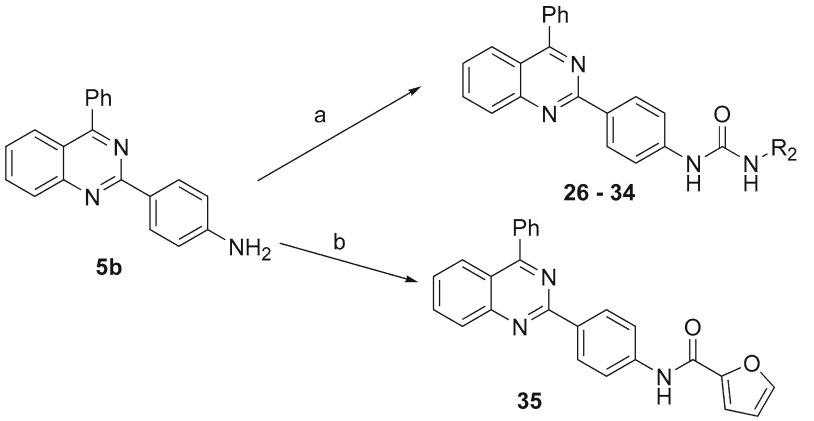
similar 5,7-dimethoxylquinazoline core from compound **36** (Scheme 4), a key intermediate for 5,7-dimethoxylquinoline as well. Compound **36**, which was prepared from commercial available 3,5-dimethoxyaniline in two steps as we previously described [12], was further subjected to ultrasound-promoted Bischler cyclization conditions providing quinazoline **37** as a white solid. The electronic properties of **37** make the 4-methyl group more electron deficient over the 2-methyl group [20,35], which favored the regio-specific condensation of the 4-methyl group with aldehydes. Reaction of **37** with *o*-nitrobenzoaldehyde in glacial acetic acid under reflux afforded 4-styrylquinazoline **38**. To further confirm the chemical property of 4-methyl group, we used 2-methyl-4-phenyl and 2-phenyl-4-methyl quinazolines as quinazolines as substrates and found that while the former quinazoline did not react with *o*-nitrobenzoaldehyde, the latter did. Pd/C catalyzed hydrogenation of **38** afforded a C=C double bond and nitro group both reduced product **39** that was further functionalized to amide **40**.

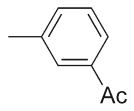
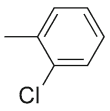
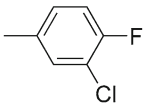
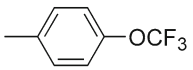
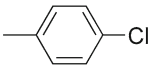
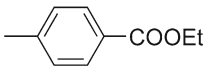
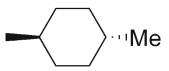
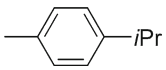
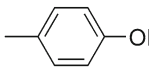
Bioassay

First, the inhibitory activity on ConA-induced T-cell proliferation of all the synthesized compounds was tested at 10 μM concentration and their cytotoxicity on murine spleen cells without adding ConA was evaluated with methyl thiazolyl tetrazolium assay (MTT assay) at the same concentration. The IC_{50} values were obtained for those compounds exhibiting potent activity and low cytotoxicity. The results are summarized in Table 2.

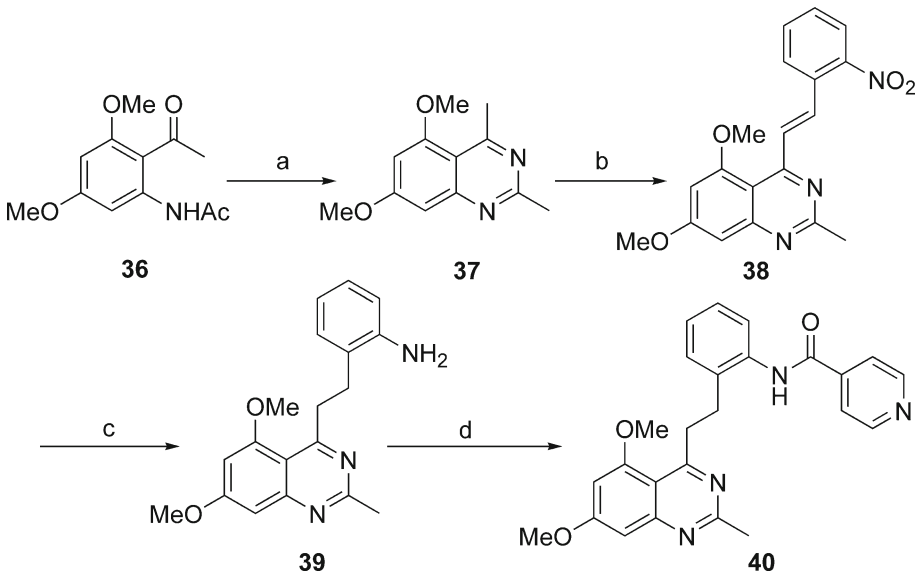
As it can been seen from Table 2, all the sulfonamide derivatives in ***b*** series showed stronger inhibitory activity on ConA-induced T-cell proliferation at 10 μM than those of ***a*** series (**6a**–**25a** vs **6b**–**25b**). Some compounds, such as **7b**–**10b** and **18b** displayed more than three times improved activity compared with the corresponding ones in ***a*** series (**7a**–**10a** and **18a**). It was noted that compounds **11a**, **19a**, **20a**, **24a**, **25a** were inactive at 10 μM, while their corresponding compounds **11b**, **19b**, **20b**, **24b**, and **25b**

Scheme 3 Synthesis of 4-phenylquinazoline urea and amide derivatives (**26**–**35**). Reagents and conditions: (*a*) isocyanate, toluene, 70 °C, 7 h; (*b*) furan-2-carbonyl chloride, TEA, DCM, 0 °C to RT, 3 h



Comp.	R_2	Comp.	R_2	Comp.	R_2
26		**29**		**32**	
27		**30**		**33**	
28		**31**		**34**	

Scheme 4 Synthesis of 4-alkyl-5,7-dimethoxylquinazoline derivatives (**38**–**40**). Reagents and conditions: (*a*) 25 % ammonia water, water, ultrasound 250 W, 80 °C, 3 h; (*b*) 2-nitrobenzoadehyde, glacial acid, reflux, overnight; (*c*) 10 % Pd/C, H_2 1 atm, MeOH, RT, 5 h; (d) isonicotinoyl chloride, TEA, DCM, RT, 3 h



were active. Furthermore, 4-alkenyl (**38**)- and 4-alkyl (**39**)-substituted compounds also exhibited stronger inhibitory activity. These results unambiguously demonstrated that 4-position should be a key modification site of quinazoline for a potent inhibitory activity on ConA-induced T-cell proliferation, and the inhibitory activity of compounds modified at 4-position was increased in the following order: 4-unsubstituted < 4-phenyl.

Interestingly, all the heterocyclic sulfonamide moieties, such as quinoline (**16**), thiophene (**18**, **19**), imidazole (**21**), isoxazole (**22**), and pyridine (**24**) seemed inefficient on improving activity. Meanwhile, aliphatic sulfonamides (**6b** and **17b**) showed better results than those of aromatics. Sulfonamides with electron-donating groups (**15b**, 40.2 %; **25b**, 48.4 %) exhibited a better potency than those bearing electron-withdrawing groups (**13b**, 15.7 %; **14b**, 18.2 %).

Table 2 Effect of quinazoline derivatives on murine T-cell proliferation induced by ConA (5 μg/mL)

Comp.	Inhibition rate (%)	Cytotoxicity (%)	IC_{50} (μM)
6a	23.8 ± 4.6**	1.7 ± 9.1	nd
6b	60.4 ± 1.3**	16.2 ± 6.4**	6.16
7a	20.2 ± 3.7**	9.6 ± 6.6	nd
7b	74.8 ± 12.7**	14.8 ± 8.8**	6.30
8a	10.0 ± 3.8**	11.3 ± 15.6	nd
8b	47.9 ± 9.6**	0.1 ± 5.6	nd
9a	9.3 ± 2.6*	8.1 ± 5.8	nd
9b	30.7 ± 2.1**	1.0 ± 2.2	nd
10a	10.2 ± 3.4*	2.4 ± 5.5	nd
10b	49.7 ± 1.8**	3.6 ± 7.5	nd
11a	−6.7 ± 11.6	0 ± 3.7	nd
11b	29.7 ± 3.9**	−13.3 ± 8.2*	nd
12a	1.7 ± 14.2	−0.9 ± 3.1	nd
12b	25.7 ± 8.6*	−10.9 ± 10.9	nd
13a	−10.7 ± 8.8	1.7 ± 6.4	nd
13b	15.7 ± 8.6**	−2.9 ± 10.7	nd
14a	−13.4 ± 6.9*	0.1 ± 9.7	nd
14b	18.2 ± 2.6*	2.8 ± 12.6	nd
15a	−0.5 ± 8.7	9.3 ± 12.1	nd
15b	40.2 ± 1.4**	10.2 ± 10.7	nd
16a	15.8 ± 5.4*	32.2 ± 18.1	nd
16b	36.7 ± 7.0**	28.2 ± 3.3**	nd
17a	25.7 ± 1.0*	5.6 ± 14.0	nd
17b	66.3 ± 6.9**	15.5 ± 3.4**	5.43
18a	9.9 ± 4.6**	3.3 ± 10.8	nd
18b	40.9 ± 8.2**	2.7 ± 5.1	nd
19a	−14.6 ± 3.7*	−2.8 ± 7.0	nd
19b	26.1 ± 2.4**	0.8 ± 6.8	nd
20a	−12.0 ± 3.7*	−10.1 ± 5.9	nd
20b	25.4 ± 7.7**	−13.9 ± 15.1*	nd
21a	4.7 ± 5.5	1.7 ± 9.1	nd
21b	37.9 ± 7.8**	23.4 ± 4.9**	nd
22a	27.4 ± 4.2**	23.2 ± 9.5*	nd
22b	55.1 ± 1.2**	16.4 ± 2.3**	nd
23a	−6.5 ± 5.9	24.3 ± 13.3	nd
23b	24.3 ± 5.8**	3.5 ± 11.1	nd
24a	−7.4 ± 12.0	4.7 ± 6.5	nd
24b	30.5 ± 7.4**	12.9 ± 5.4	nd
25a	−10.9 ± 7.3**	8.0 ± 6.3*	nd
25b	48.4 ± 5.3**	4.8 ± 6.1	nd
26	48.9 ± 3.7**	−3.6 ± 4.2	nd
27	46.6 ± 5.8**	−16.7 ± 10.1*	nd
28	14.7 ± 8.2**	−8.1 ± 6.5	nd
29	39.4 ± 4.0**	−22.7 ± 5.1*	nd
30	38.1 ± 3.9**	−1.6 ± 8.8	nd
31	52.8 ± 11.3**	−12.1 ± 14.5**	nd
32	28.8 ± 6.2**	−11.2 ± 3.4**	nd
33	89.1 ± 7.7**	20.3 ± 9.1**	2.54
34	9.3 ± 3.5*	−16.1 ± 11.5**	nd
35	73.7 ± 1.0*	26.8 ± 5.6**	9.80
38	64.4 ± 5.8**	37.5 ± 12.7**	nd
39	35.0 ± 8.8**	35.1 ± 3.2*	nd
40	27.2 ± 10.0**	8.5 ± 8.2	nd
CsA	76.4 ± 5.5**	14.5 ± 10.8*	nd

The concentration of all the tested compounds was 10 μM at both inhibitory rate and cytotoxicity measurements. The concentration of CsA was 1 μM. For cytotoxicity measurement, only the tested compounds were added in the cells. The sign of "−" indicated enhancement effect on the cell proliferation

Data are expressed as mean ± SD, $n = 3$. Significant differences compared with control group (0.0 %)

nd not determined

* $p < 0.05$, ** $p < 0.01$

Halogen-substituted sulfonamides displayed an inhibitory order in: F>Cl>Br which was reversed to our previous reported quinoline derivatives [12].

Urea compound **33**, with a *p*-ester group, showed the most potent inhibitory activity among all the compounds, with an inhibitory rate of 89.1 % at 10 μM and an IC_{50} value 2.54 μM. Electron-donating groups, such as, ethoxy (**34**, 9.3 %), gave poor results on inhibition. Moreover, fluoro-containing derivatives were ineffective. Amide compound **35** was most potent than most of the urea derivatives.

Unfortunately, 5,7-dimethoxylquinazoline derivatives (**38**, **39**, and **40**) did not display ideal improvements of the inhibitory activity as our previously described quinoline derivatives. However, some useful structure–activity information still could be drawn: reduction of double bond and nitro group lowered the activity; acylation amino group further reduced the activity.

It should be mentioned that there was no obvious cytotoxicity of the synthesized compounds observed at 10 μM. The most toxic compounds **16a**, **38**, and **39** show growth inhibitory rate of 32.2, 37.5, and 35.1 % at 10 μM, respectively. However, the three compounds exhibit only 15.8, 64.4, and 35.0 % inhibitory activity on ConA-induced T-cell proliferation at 10 μM, respectively. These results indicated that the inhibitory activity on ConA-induced T-cell proliferation did not come from the cytotoxicity of the compounds.

B-cells, as one of the main types of lymphatic cells, play a key roles in the immune system, and as a target for the treatment of RA the B-cell has attracted many interests over the last decade [36–38]. Therefore, all the compounds were

Table 3 Effect of selected quinazoline derivatives on murine B-cell proliferation induced by LPS (10 μg/mL)

Comp.	Inhibition rate (%)
6b	47.5 ± 16.3**
7b	50.3 ± 4.8**
17b	61.7 ± 12.1**
CsA	41.8 ± 11.1**
33	86.9 ± 7.2**
35	65.7 ± 4.7**
27	82.8 ± 5.8**

Data are expressed as mean±SD, n=3. The concentration of CsA was 1 μM. Significant differences compared with control group (0.0 %)
** $p < 0.01$

further assayed for their inhibitory activity on LPS-induced B-cell proliferation by MTT method. Only the active compounds are listed in Table 3. Interestingly, compounds **6b**, **7b**, **17b**, **33**, and **35** not only showed the potent inhibitory activity on T-cell proliferation but also suppressed the B-cell proliferation effectively. It is noteworthy that compound **27** suppresses T-cell in moderate rate (46.6 %), while it significantly inhibits B-cell proliferation (82.8 %), which might be aroused from the unique property of trifluoromethyl moiety.

On the basis of the above results, a preliminary SAR could be concluded as follows: (1) 4-position of quinazoline is a crucial modification site, 4-substituted quinazolines is potent than 4-unsubstituted ones, the order was in 4-unsubstituted < 4-phenyl, (2) aliphatic sulfonamides showed a much better activity compared to aromatics on T-cell proliferation, (3) urea-containing ester quinazoline derivative is active on inhibiting T-cell proliferation, while trifluoromethyl-containing urea derivative is potent on B-cell proliferation.

Conclusion

An efficient and mild synthesis of quinazoline core was developed via a green Bischler cyclization as a key step in water under ultrasound irradiation. With this method, a series of novel quinazoline derivatives were prepared and their inhibitory activity on ConA-induced T-cell and LPS-induced B-cell proliferations together with cytotoxicity were tested in vitro. Among the derivatives, compounds **6b**, **7b**, **17b**, **33**, and **35** not only showed a potent inhibitory activity on T-cell proliferation but also effectively suppressed B-cell proliferation at 10 μM. The devised SAR indicated that 4-position is a key modification site for potent quinazoline immunosuppressive agent. The ester and trifluoromethyl groups are key structural moieties for urea-containing quinazoline derivatives exhibiting good inhibitory activity on T- and B-cell proliferations. The current results would pave the way for the design and development of quinazoline derivatives as immunosuppressant in the future, and the detailed bioactivity evaluation is undergoing.

Experimental

Synthesis

General

All reagents and solvents were used as supplied without further purification. Melting points were measured with an X-4 melting point apparatus (Bei Jing Taike Co., Ltd.) and were uncorrected. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ or DMSO-d_6 or TFA-d_4 on a Brucker 300 spectrometer at RT, respectively, and tetramethylsilane (TMS) served as an internal standard. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m (multiplet) as well as b (broad). Coupling constants (J) are given in hertz. ESI-MS and high-resolution MS (HRMS) were carried out on a LTQ Orbitrap XL (The Thermo Scientific, USA). Sonication was performed in a KQ-300DE ultrasonic cleaner (Kunshan ultrasonic instrument Co., Ltd.) at a frequency of 40 kHz and an output power 120–300 W. All experiments were monitored by thin layer chromatography (TLC). TLC was performed on pre-coated silica gel plates (Qingdao Haiyang Chemical Co., Ltd). Amine **2b** was purchased from Accela ChemBio Co., Ltd.

*2-Aminobenzaldehyde (***2a***)*

A 1-L round-bottomed flask was charged with 2-nitrobenzaldehyde (**1a**, 15.1 g, 100 mmol), ethanol (370 mL), water (80 mL), and iron powder (44.8 g, 800 mmol), and heated to 50 °C. While stirring concentrated hydrochloric acid (1 mL) was added as catalyst. The progress of the reaction was monitored by TLC (hexane/ethyl acetate, V/V, 5:1). Upon completion, the reaction mixture was allowed to cool, filtered under suction, and washed with ethanol. The filtrate was evaporated to dryness under reduced pressure, ethyl acetate (400 mL) was added, and the solution was washed with brine, dried over Na_2SO_4. Ethyl acetate was removed under reduced pressure to afford **2a** as pale yellow oil, 11.3 g, Yield: 93 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.87 (s, 1H), 7.48 (dd, J = 7.8, 1.4 Hz, 1H), 7.36–7.27 (m, 1H), 6.75 (t, J = 7.4 Hz, 1H), 6.65 (d, J = 8.3 Hz, 1H), 6.12 (brs, 2H); MS (ESI): 122.10 $[M+H]^+$.

General procedure for compounds **3**

To a solution of **2** (70 mmol) and triethlyamine (11.7 mL, 84 mmol, 1.2 equiv) in dichloromethane (DCM) (200 mL)

cooled in an ice-water bath 4-nitrobenzoic acid chloride (13.0 g, 70 mmol, 1.0 equiv) was added in portions. The progress of the reaction was monitored by TLC (hexane/ethyl acetate, V/V, 5:1). Upon completion, the solvent was removed under reduced pressure. To the residue, water (500 mL) was added and the mixture exposed to ultrasound irradiation for 15 min and filtered. The filter cake was washed with water and dried under reduced pressure to give desired amide **3**.

*N-(2-Formylphenyl)-4-nitrobenzamide (**3a**)*

Pale yellow solid; Yield: 92.4 %; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.26 (s, 1H), 10.02 (s, 1H), 8.93 (d, J = 8.4 Hz, 1H), 8.51–8.33 (m, 2H), 8.29–8.14 (m, 2H), 7.86–7.67 (m, 2H), 7.46–7.29 (m, 1H); MS (ESI): 270.95 $[M+H]^+$.

*N-(2-Benzoylphenyl)-4-nitrobenzamide (**3b**)*

Pale yellow solid; Yield: 95.8 %; ^{1}H NMR (300 MHz, $CDCl_3$ δ = 12.21 (s, 1H), 8.87 (dd, J = 8.8, 1.0 Hz, 1H), 8.42–8.31 (m, 2H), 8.28–8.18 (m, 2H), 7.81–7.59 (m, 5H), 7.52 (t, J = 7.4 Hz, 2H), 7.24–7.11 (m, 1H); MS (ESI): 347.00 $[M+H]^+$.

General procedure for quinazoline cores **4** and **37**

A 250-mL sealed tube was charged with amides **3** or **36** (18 mmol), 25 % ammonia water (24 mL, 360 mmol), and water (150 mL). The tube was located in the maximum energy area in the ultrasonic generator at 80 °C and exposed for 3 h. The resulting mixture was cooled to RT and filtered. The filter cake was washed with water and dried under reduced pressure to furnish the desired products **4** and **37**.

*2-(4-Nitrophenyl)quinazoline (**4a**)*

Pale yellow solid; Yield: 89.5 %; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.52 (s, 1H), 8.82 (d, J = 9.0 Hz, 2H), 8.38 (d, J = 9.0 Hz, 2H), 8.14 (d, J = 8.9 Hz, 1H), 7.98 (t, J = 7.7 Hz, 2H), 7.78–7.63 (m, 1H); ^{13}C NMR (75 MHz, TFA-d_4) δ = 152.8, 150.7, 146.3, 142.30, 134.9, 132.5, 129.9, 129.8, 124.4, 124.3, 122.5; MS (ESI): 252.00 $[M+H]^+$.

*2-(4-Nitrophenyl)-4-phenylquinazoline (**4b**)*

White solid; Yield: 93.3 %; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.89 (d, J = 9.0 Hz, 2H), 8.36 (d, J = 9.0 Hz, 2H), 8.19 (dd, J = 7.7, 6.3 Hz, 2H), 8.02–7.81 (m, 3H), 7.70–7.54 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.2, 162.4, 156.4 153.7, 148.6, 141.8, 138.6, 134.8, 134.7, 134.0, 133.9, 133.3, 132.7, 131.7, 128.2, 126.5; MS (ESI): 327.95 $[M+H]^+$.

*5,7-Dimethoxy-2,4-dimethylquinazoline (**37**)*

White solid; Yield: 95.2 %; Mp = 106–108 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 6.79 (d, J = 2.3 Hz, 1H), 6.59 (d, J = 2.3 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 2.82 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.9, 163.9, 163.4, 158.5, 154.0, 110.6, 99.1, 98.8, 56.3, 55.9, 27.3, 25.9; MS (ESI): 219.00 $[M+H]^+$; HRMS (ESI): calcd for $C_{12}H_{14}N_2O_2$ $[M+H]^+$ 219.1134, found 219.1130.

General procedure for amino quinazoline cores **5**

A 250-mL round-bottomed flask was charged with nitroquinazoline **4** (20 mmol), ethanol (150 mL), water (30 mL), and iron powder (9 g, 160 mmol), heated to 50 °C, and concentrated hydrochloric acid (0.5 mL) was added as catalyst. The progress of the reaction was monitored by TLC (hexane/ethyl acetate, V/V, 5:1). Upon completion, the reaction mixture was cooled to RT, filtered under suction, and washed with ethanol. The filtrate was evaporated to dryness under reduced pressure, DCM (200 mL) was added, and the solution was washed with brine, and dried over Na_2SO_4. DCM was removed under reduced pressure to afford **5**.

*4-(Quinazolin-2-yl)aniline (**5a**)*

Pale yellow solid; Yield: 88.1 %; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.39 (d, J = 0.6 Hz, 1H), 8.55–8.37 (m, 2H), 8.03 (d, J = 9.0 Hz, 1H), 7.91–7.80 (m, 2H), 7.54 (td, J = 7.3, 1.1 Hz, 1H), 6.90–6.69 (m, 2H), 3.91 (s, 2H); MS (ESI): 222.10 $[M+H]^+$.

*4-(4-Phenylquinazolin-2-yl)aniline (**5b**)*

Pale yellow solid; Yield: 92.3%; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.54 (d, J = 8.6 Hz, 2H), 8.08 (t, J = 7.8 Hz, 2H), 7.96–7.75 (m, 3H), 7.67–7.51 (m, 3H), 7.47 (t, J = 7.5 Hz, 1H), 6.79 (d, J = 8.5 Hz, 2H), 3.98 (s, 2H); MS (ESI): 298.00 $[M+H]^+$.

General procedure for paralleled sulfonamide derivatives (**6**–**25**)

To a solution of **5b** (1 mmol) in pyridine (8 mL) was added sulfonyl chloride (1.1 mmol, 1.1 equiv) in portions, at RT, followed, stirred at 50 °C for 5 h. Pyridine was removed under reduced pressure, ethyl acetate (50 mL) was added, and the solution was washed with saturated $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4. Ethyl acetate was removed under reduced pressure. The residue was washed with ethyl ether, and furnished target compounds (**6**–**25**). For characterizations of **7**–**25** see Supporting Information.

*N-(4-(Quinazolin-2-yl)phenyl)methanesulfonamide (**6a**)*

Brown solid; Yield: 83.1 %; Mp = 193–195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.47 (s, 1H), 8.64 (d, *J* = 8.6 Hz, 2H), 8.12 (d, *J* = 8.3 Hz, 1H), 8.02–7.88 (m, 2H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 2H), 6.71 (s, 1H), 3.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 160.5, 150.6, 138.9, 134.7, 134.2, 130.1, 128.4, 127.3, 127.1, 123.5, 119.47, 39.50; MS (ESI): 297.95 $[M+H]^+$; HRMS (ESI): calcd for $C_15H_14N_3O_2S$ $[M+H]^+$ 300.0807, found 300.0793.

*N-(4-(4-Phenylquinazolin-2-yl)phenyl)methanesul fonamide (**6b**)*

Pale yellow solid; Yield: 85.4 %; Mp = 224–226 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.69 (d, *J* = 8.5 Hz, 2H), 8.14 (t, *J* = 7.5 Hz, 2H), 7.97–7.79 (m, 3H), 7.68–7.49 (m, 4H), 7.36 (d, *J* = 8.6 Hz, 2H), 6.81 (s, 1H), 3.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.4, 159.2, 151.8, 138.8, 137.4, 135.0, 133.6, 130.2, 130.1, 123.0, 128.9, 128.5, 127.0, 121.6, 119.5, 39.4; MS (ESI): 370.00 $[M+H]^+$; HRMS (ESI): calcd for $C_21H_18N_3O_2S$ $[M+H]^+$ 376.1120, found 376.1100.

General procedure for urea derivatives (**26**–**34**)

To a solution of **5b** (1 mmol) in toluene (8 mL) was added isocyanate (1.1 mmol, 1.1 equiv) in portions, at RT, followed, stirred at 70 °C for 7 h. Toluene was removed under reduced pressure, ethyl ether (15 mL) was added, the mixture was filtered and washed with ethyl ether to furnished target compounds (**26**–**34**). For characterizations of **27**–**34** see Supporting Information.

*1-(3-Acetylphenyl)-3-(4-(4-phenylquinazolin-2-yl)phenyl) urea (**26**)*

White solid; Yield: 86.5 %; Mp = 254–256 °C; ^{1}H NMR (300 MHz, DMSO) δ = 9.05 (s, 1H), 8.98 (s, 1H), 8.53 (d, *J* = 8.7 Hz, 2H), 8.18–7.93 (m, 4H), 7.93–7.81 (m, 2H), 7.74–7.55 (m, 8H), 7.45 (d, *J* = 7.9 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ = 198.1, 168.3, 159.3, 152.7, 151.7, 142.5, 140.3, 137.8, 137.4, 134.7, 131.4, 130.4, 130.3, 129.6, 129.5, 129.0, 128.9, 127.8, 127.2, 123.3, 122.5, 121.2, 118.3, 117.9, 27.1; MS (ESI): 459.00 $[M+H]^+$; HRMS (ESI): calcd for $C_29H_23N_4O_2$ $[M+H]^+$ 459.1821, found 459.1804.

*Synthesis of amide (**35**)*

To a solution of **5b** (1 mmol) and TEA (0.2 mL, 1.5 mmol) in DCM (8 mL) was added furan-2-carbonyl chloride (1.1 mmol, 1.1 equiv) dropwise, at RT, followed, stirred at RT for 3 h. DCM was removed under reduced pressure, ethyl acetate (50 mL) was added, and the solution was washed with saturated $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4. Ethyl acetate was removed under reduced pressure. The residue was subjected to silica gel column chromatography (2.5 % MeOH/DCM), and furnished target compounds (**35**). White solid; Yield: 61.6 %; Mp = 199–201 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.74 (d, *J* = 7.7 Hz, 2H), 8.34–8.03 (m, 3H), 8.00–7.74 (m, 4H), 7.67–7.44 (m, 5H), 7.32–7.21 (m, 2H), 6.58 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.3, 159.5, 155.9, 151.8, 147.7, 144.2, 139.5, 137.6, 134.1, 133.5, 130.1, 129.9, 129.6, 128.9, 128.4, 127.0, 126.8, 121.5, 119.4, 115.4, 112.6; MS (ESI): 392.10 $[M+H]^+$; HRMS (ESI): calcd for $C_25H_18N_3O_2$ $[M+H]^+$ 392.1399, found 392.1379.

*Synthesis of 4-alkly-5,7-dimethoxylquinazoline derivatives (**38**–**40**)*

*(E)-5, 7-dimethoxy- 2-methyl-4- (2-nitrostyryl)quinazoline (**38**)* A mixture of **37** (2.28 g, 10 mmol), 2-nitrobenzoadehyde (1.8 g, 12 mmol, 1.2 equiv), and glacial acid (50 mL) was refluxed overnight. The solvent was removed under reduced pressure, and the residue was subjected to silica gel column chromatography (40 % EA/PE) afforded **38** as yellow solid, 2.8 g, Yield: 79.8 %. Mp = 231–233 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.41 (d, *J* = 15.6 Hz, 1H), 8.33 (d, *J* = 15.6 Hz, 1H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 7.5 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 6.97 (s, 1H), 6.52 (d, *J* = 2.0 Hz, 1H), 3.99 (s, 3H), 3.95 (s, 3H), 2.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 175.1, 164.1, 160.2, 158.0, 155.3, 148.6, 132.9, 132.6, 132.5, 132.2, 129.0, 128.9, 124.6, 109.7, 99.5, 98.8, 55.9, 55.7, 25.9; MS (ESI): 352.10 $[M+H]^+$; HRMS (ESI): calcd for $C_19H_18N_3O_4$ $[M+H]^+$ 352.1297, found 352.1277.

*2-(2-(5,7-Dimethoxy-2-methylquinazolin-4-yl)ethyl)aniline (**39**)*

Compound **38** (350 mg, 1 mmol) was dissolved in methanol and 10 % Pd/C (35 mg) was added. After removing the system's air and purging with hydrogen two times, the mixture was kept under hydrogen at 1 atm for 5 h at RT. The resulting mixture was filtered, and the filtrate was evaporated to dryness under reduced pressure to furnished **39** as pale yellow solid. 281 mg, Yield: 86.7 %. Mp = 153–155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.15 (dd, *J* = 7.4, 1.0 Hz, 1H), 7.06 (td, *J* = 7.7, 1.6 Hz, 1H), 6.88 (d, *J* = 2.3 Hz, 1H), 6.75 (dd, *J* = 7.4, 1.1 Hz, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 6.50 (d, *J* = 2.2 Hz, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 3.64 (t, *J* = 9.0 Hz, 1H), 2.94 (t, *J* = 9.0 Hz, 1H), 2.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.3, 163.8, 158.1, 154.5, 144.5, 129.5, 127.0, 126.1,

118.3, 115.4, 110.5, 99.2, 99.1, 98.9, 55.8, 55.6, 38.6, 30.9, 26.0; MS (ESI): 324.10 $[M+H]^+$; HRMS (ESI): calcd for $C_19H_22N_3O_2$ $[M+H]^+$ 324.1712, found 324.1693.

*N-(2-(2-(5,7-dimethoxy-2-methylquinazolin-4-yl)ethyl)phenyl)isonicotinamide (**40**)*

To a solution of **39** (160 mg, 0.5 mmol) and TEA (0.1 mL, 0.75 mmol, 1.5 equiv) in DCM (8 mL) was added isonicotinoyl chloride (77 mg, 0.55 mmol, 1.1 equiv), at RT, followed, stirred at RT for 3 h. DCM was removed under reduced pressure, ethyl acetate (50 mL) was added and the solution was washed with saturated $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4. Ethyl acetate was removed under reduced pressure. The residue was subjected to silica gel column chromatography (5 % MeOH/DCM), and furnished **40** as white solid. 312 mg, Yield: 73.0 %. Mp = 196–198 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.85 (s, 1H), 8.82 (d, J = 5.6 Hz, 2H), 7.98 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 4.8 Hz, 2H), 7.32 (d, J = 7.8 Hz, 1H), 7.16 (t, J = 7.4 Hz, 1H), 6.81 (d, J = 2.3 Hz, 1H), 6.49 (d, J = 2.2 Hz, 1H), 3.98 (s, 3H), 3.91 (s, 3H), 3.88 (t, J = 7.0 Hz, 2H), 3.22 (t, J = 6.9 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.3, 164.2, 164.0, 163.1, 158.3, 154.2, 150.5, 142.4, 134.8, 134.0, 129.4, 126.7, 125.8, 124.6, 121.4, 110.6, 99.2, 99.1, 55.9, 55.7, 39.61 (s), 28.4, 25.6; MS (ESI): 429.15 $[M+H]^+$; HRMS (ESI): calcd for $C_25H_25N_4O_3$ $[M+H]^+$ 429.1927, found 429.1900.

Biological assays

Materials

Stock solutions of compounds were prepared with dimethylsulfoxide (DMSO, Sigma) and diluted with RPMI-1640 medium containing 10 % fetal bovine serum (FBS). MTT (3-(4, 5-dimethylthylthiazol-2-yl)-2, 5-diphenyl-tetrazolium bromide), Concanavalin A (ConA) was purchased from Sigma (St Louis, MO). Cyclosporin A (CsA) was obtained from Sandoz Ltd (Basel, Switzerland).

Animals

Female BALB/c mice (6–8 weeks old, 18–22 g) were supplied by the Laboratory Animal Center of Yangzhou University (Jiangsu, China). They were maintained with free access to pellet food and water in plastic cages at 21±2 °C and kept on a 12 h light–dark cycle. Animal welfare and experimental procedures were carried out strictly in accordance with the 'Guide for the Care and Use of Laboratory Animals' (National Research Council, 1996) and the related ethical regulations of our university. All efforts were made to minimize the animals' suffering and to reduce the number of animals used.

MTT assay [12]

Fresh spleen cells were obtained from BALB/c mice (male, 6–8 weeks old). 5×10^5 spleen cells were cultured in triplicate in 96-well flat plates with 200 μL RPMI-1640 media containing 10 % FBS, 100 U/mL penicillin, and 100 U/mL streptomycin in a humidified, 37 °C, 5 % CO_2-containing incubator for 48 h in the presence or absence of various concentrations of compounds. The cells with media alone were used as control. 20 μL MTT (5 mg/mL) reagent was added 4 h before the end of culture. Removed supernatant after centrifuge and DMSO (200 μL) was added. Shaking to make a clear solution and the absorbance value at 570 nm was collected by microplate reader. The percentage of cell growth inhibition was determined using the following formula:

$$\text{Cytotoxicity (\%)} = (1 - [\text{Compounds } (OD_{570}) - \text{Background } (OD_{570})]/[\text{Control } (OD_{570}) - \text{Background } (OD_{570})]) \times 100$$

The compounds were dissolved in dimethylsulfoxide (DMSO) followed by dilution with culture medium to desired concentrations, and DMSO final concentration was 0.1 %. DMSO at 0.1 % was added into control group and showed no effects on cells.

ConA-induced T-cell and LPS-induced B-cell proliferation assay [12]

Fresh spleen cells were obtained from BALB/c mice (male, 6–8 weeks). 5×10^5 Spleen cells were cultured at the same conditions as those mentioned above. The cultures were unstimulated or stimulated with 5 mg/mL ConA or 10 mg/mL of lipopolysaccharide (LPS) to induce T- or B-cell proliferative response, respectively. The compounds were added to cultures with desired concentrations to test their bioactivities. The cells stimulated with ConA or LPS were used as control and CsA as positive control. Proliferation was assessed by MTT assay as above.

Statistics

All experiments were repeated 3–5 times with the similar outcome. The p values between two experimental groups were tested by two-tailed Student's t test, and p values of 0.05 or less were considered to be statistically significant.

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