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ORIGINAL ARTICLE

Synthesis and anti-inflammatory and antimicrobial activities of some novel 2-methylquinazolin-4(3H)-one derivatives bearing urea, thiourea and sulphonamide functionalities

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Abstract A variety of novel 2-methylquinazolin-4(3H)-one derivatives (**1**–**29**) bearing urea, thiourea and sulphonamide functionalities at position 3 of biological interest have been synthesized and screened for their anti-inflammatory (TNF-α and IL-6) and antimicrobial activities (antibacterial and antifungal). "Biological evaluation study revealed that the compounds **3**, **4**, **6**, **9**, **16** and **18** were found to have promising anti-inflammatory activity (up to 62–84% TNF-α and 73–92% IL-6 inhibitory activity) at concentration of 10 μM with reference to standard dexamethasone (75% TNF-α and 84% IL-6 inhibitory activities at 1 μM) and **7**, **10**, **12**, **23**, **25** and **28** have antimicrobial activity at MIC of 10–30 μg/mL against selected pathogenic bacteria and fungi."

1. Introduction

The current interest in the development of new antimicrobial agents can be partially ascribed both to the increasing emergence of bacterial resistance to antibiotic therapy and to newly emerging pathogens (Cohen, 2000; Barrett and Barrett, 2003). Despite a number of antibiotics available for the treatment of bacterial infections, emergence of multi-drug resistant organisms has posed a great challenge to the scientists and it is well known that non-steroidal anti-inflammatory drugs (NSAIDs) are associated with several side effects such as gastrointestinal mucosal damage, bleeding, intolerance and renal toxicity (Bombardier et al., 2000; Silverstien et al., 2000).

Non-steroidal anti-inflammatory drugs (NSAIDs) are therapeutically important in the treatment of rheumatoid arthritis and in various types of inflammatory conditions, but their therapeutic utility has been limited due to their frequently observed gastrointestinal side effects. Thus, there is an urgent need for new targets that are required for the design and development of novel anti-inflammatory agents as an alternative to NSAIDs (Shishoo et al., 1999). Tumour necrosis factor alpha (TNF-α)

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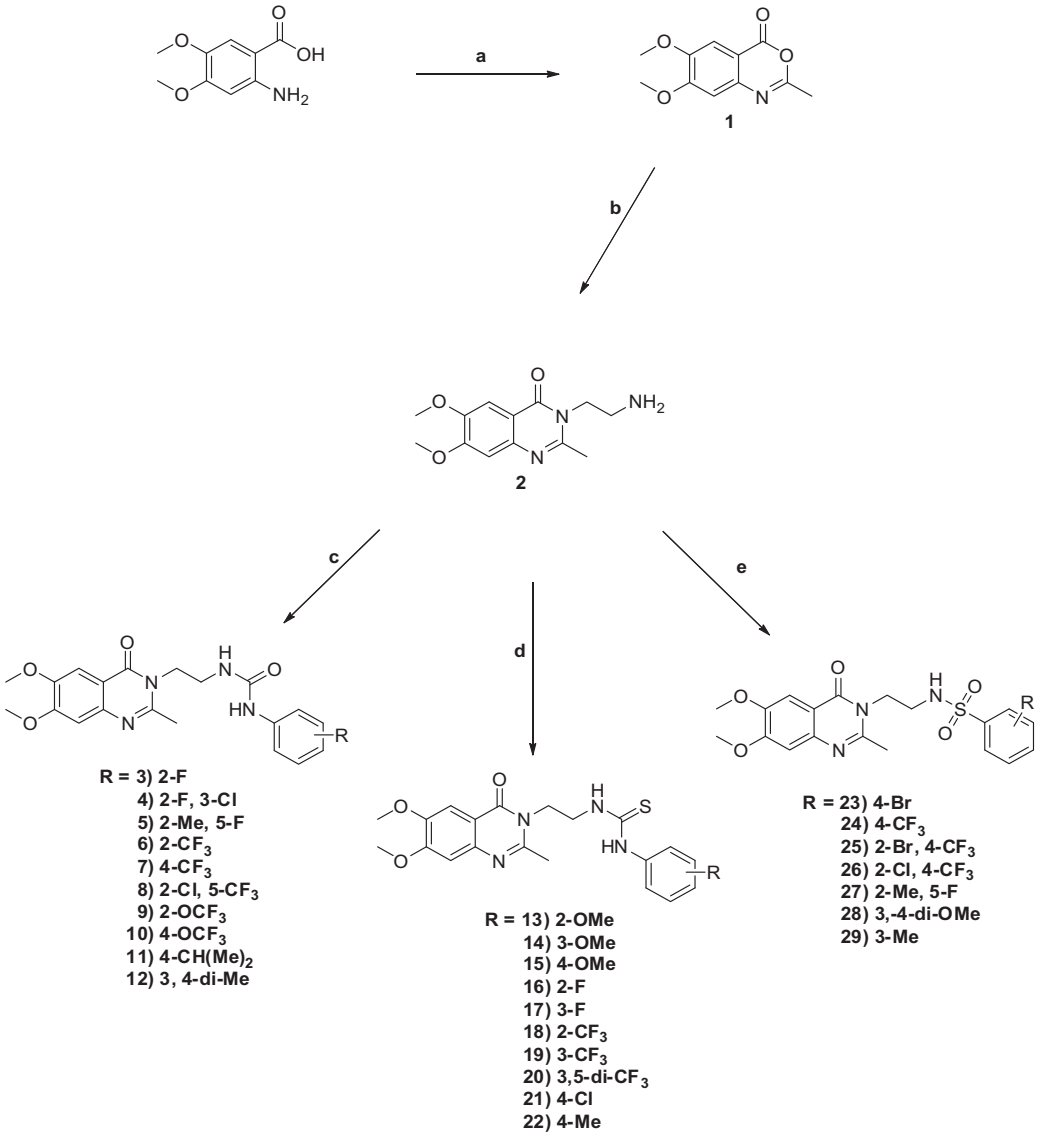
and interleukin-6 (IL-6) are the two important multifunctional pro-inflammatory cytokines involved in the pathogenesis of autoimmune, inflammatory, cardiovascular, neurodegenerative and cancer diseases through a series of cytokine signalling pathways (Papadakis and Targan, 2000; Krishnamoorthy and Honn, 2006). IL-6 contributes to the initiation and extension of the inflammatory process and considered as a central mediator in a range of inflammatory diseases but it has not received the desired attention in drug discovery (Dominic and Raj, 2009). TNF-α and IL-6 are thus pharmaceutically important molecular targets for the treatment of the above-mentioned diseases. So there appears to be a need for the development of new, safer and more active NSAIDs and antimicrobial drugs with improved efficacy and better toxicity profile (Cohen, 1992).

In medicinal chemistry quinazolin-4(3H)-one is a basic unit found in various naturally occurring bioactive alkaloids such as febrifugine, isofebrifugine, vasicinone, echinozolinone, etc. (Mhaske and Argade, 2006) and also the literature survey revealed that the presence of substitution at position 2 as well as at position 3 in it has been reported to be associated with the diverse range of pharmacological activities like antimicrobial (Grover and Kini, 2006; Nanda et al., 2007; Panneerselvam et al., 2009; Mohamed et al., 2010), analgesic/anti-inflammatory (Maggio et al., 2001; Kumar et al., 2003; Alagarsamy et al., 2003a,b; Chao et al., 1999), CNS depressant/anticonvulsant (Srivastava and Kumar, 2002, 2004), anti-cancer (Kamal et al., 2010) and anti-HIV, anti-viral/Cytotoxic (Dinakaran et al., 2003).



Scheme 1 Synthesis of novel 3-(2-aminoethyl)-2-methylquinazolin-4(3H)-one derivatives bearing urea, thiourea and sulphonamide functionalities (**1**–**29**).

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In addition the importance of functionalities like urea, thiourea and sulphonamide in medicinal chemistry is well recognized in the literature and the presence of which is often a major importance to activity. Quinazolinone bearing urea functionality have sedative-hypnotic/anticonvulsant/cytotoxicity/anti-HIV-1/antimicrobial/CNS depressant activities (Kashaw et al., 2008, 2009, 2011) and thiourea functionality have analgesic/anti-inflammatory/antibacterial (Alagarsamy et al., 2003a,b, 2005) and anticonvulsant /analgesic/cytotoxic/ antimicrobial activities (Suresha et al., 2011) while quinazolinone bearing sulphonamide functionality have anti inflammatory and antimicrobial activities (Venkataraman et al., 2010; Patel and Patel, 2010). Moreover, the potential of 2-methylquinazolin-4(3H)-one derivatives bearing urea, thiourea and sulphonamide functionalities as to their anti-inflammatory activity hitherto remained untested.

Motivated by the aforementioned literature and in persistence of our earlier work on different heterocyclic derivatives bearing urea, thiourea and sulphonamide functionalities (Keche et al., 2012a,b; Tale et al., 2011a,b), we envisioned our approach towards design and synthesis of novel structurally diverse series of 2-methylquinazolin-4(3H)-one having urea, thiourea and sulphonamide functionalities at position 3, for their anti-inflammatory and antimicrobial activity. Therefore, a single molecule containing more than one pharmacophore, each with different mode of action could be beneficial for the treatment of inflammation and microbial diseases.

2. Results and discussion

2.1. Chemistry

Our synthetic strategy for a novel series of 2-methylquinazolin-4(3H)-one derivatives (**1**–**29**) bearing urea, thiourea and sulphonamide functionalities is illustrated in Scheme 1. The key intermediate 6,7-dimethoxy-2-methyl-4H-benzo[d] [1,3] oxazin-4-one **1** was synthesized by the reaction of 3,4-dimethoxyanthranilic acid with acetic anhydride in 78% yield. The reaction of **1** with 1,2-ethylenediamine at reflux temperature for 2 h afforded 3-(2-aminoethyl)-6,7-dimethoxy-2-methylquinazolin-4(3H)-one (**2**) in 55% yield.

Having secured parent 3-(2-aminoethyl)-6,7-dimethoxy-2-methylquinazolin-4(3H)-one (**2**) in good yield, next, the desired 3-(2-aminoethyl)-2-methylquinazolin-4(3H)-one derivatives bearing urea (**3**–**12**), thiourea (**13**–**22**) and sulphonamide (**23**–**29**) functionalities were synthesized in good to high yields by reacting **2** with appropriate arylisocyanates, arylisothiocyanates and sulphonyl chloride respectively at room temperature under mild conditions. The purity of the compounds was checked by TLC and HPLC. Spectral data ^{1}H NMR, IR and MS of the newly synthesized compounds **1**–**29** were in full agreement with their proposed structures.

2.2. Biology

The synthesized compounds **1**–**29** were evaluated for in vitro anti-inflammatory activity against the pro-inflammatory cytokines (TNF-α and IL-6) by TNF-α and IL-6 inhibition assay (Hwang et al., 1993) and antimicrobial activity against various Gram-positive, Gram-negative bacteria and fungal strains by using the agar well diffusion method with little modifications (Sridhar et al., 2004). Anti-inflammatory, antibacterial and antifungal activities of 2-methylquinazolin-4(3H)-one derivatives have been presented in Tables 1–3 and some interesting trend was observed as the lipophilicity as well as nature of the substituent presents on benzene ring of ureido, thioureido and sulphonamide terminus affecting the biological activity of the synthesized analogues.

Table 1 Anti-inflammatory activity of novel 3-(2-aminoethyl)-2-methylquinazolin-4(3H)-one derivatives containing urea, thiourea and sulphonamide functionalities.

Compounds	% Inhibition at 10 μM	
	TNF-α	IL-6
1	0	0
2	0	0
3	84	92
4	62	73
5	8	11
6	70	81
7	17	25
8	20	42
9	65	75
10	22	31
11	31	45
12	0	16
13	52	67
14	20	35
15	28	42
16	78	89
17	0	11
18	72	83
19	0	14
20	50	62
21	16	32
22	0	0
23	0	0
24	25	38
25	8	17
26	52	66
27	18	25
28	0	10
29	0	0
Dexamethasone (1 μg/ml)	75	84

2.2.1. Anti-inflammatory activity

As can be seen from Table 1, compounds **3** and **16** exhibited the higher TNF-α (84% and 78%) as well as IL-6 (92% and 89%) inhibitory activity as compared to the standard dexamethasone but at higher concentration (10 μM) and found to be potent anti-inflammatory agents while compounds **4**, **6**, **9** and **18** exhibited comparable TNF-α (62%–72%) and IL-6 (73%–83%) inhibitory activity. Compounds **13**, **20** and **26** exhibited moderate TNF-α (50%–52%) and IL-6 (62%–67%) inhibitory activity and rest of the compounds show very low to no activity at the same level of concentration (10 μM). It is to be noted that all these active compounds viz. **3**, **4**, **6**, **9**, **16** and **18** are either from urea or thiourea series, surprisingly only compound **26** having Cl at ortho and CF_3 at para position on the benzene ring of sulphonamide terminus from the corresponding sulphonamide series was found to be moderately effective against TNF-α (52%) or IL-6 (66%) and rest are almost very low to no active. This finding implicates that

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Table 2 Antibacterial activity of novel 3-(2-aminoethyl)-2-methylquinazolin-4(3H)-one derivatives containing urea, thiourea and sulphonamide functionalities. (MIC [a] values μg/ml).

Compounds	Gram-positive		Gram-negative	
	Staphylococcus aureus	*Bacillus subtilis*	*Escherichia coli*	*Salmonella typhimurium*
1	–	–	–	–
2	–	–	–	–
3	75	60	80	75
4	80	75	60	70
5	55	65	50	60
6	80	80	65	90
7	15	15	15	20
8	55	50	65	60
9	70	80	65	75
10	15	10	10	10
11	60	55	50	50
12	30	25	30	30
13	110	100	120	110
14	90	80	75	90
15	35	40	30	35
16	110	–	–	–
17	90	110	115	100
18	75	90	90	80
19	65	75	60	55
20	–	–	–	–
21	40	45	45	50
22	70	80	65	75
23	20	20	15	25
24	65	70	60	60
25	15	10	15	10
26	60	65	55	70
27	85	100	75	90
28	10	15	10	10
29	60	50	70	65
Ciprofloxacin	20	15	15	20

–: No activity was observed up to 200 μg/ml.
[a] Values are the average of three readings.

the presence of special chemical space viz. urea or thiourea in the novel 2-methylquinazolin-4(3H)-one scaffold is of immense importance in order to have moderate to potent anti-inflammatory activity.

The structure–activity relationship of these newly synthesized compounds is represented in Table 1 and it can be seen that anti-inflammatory activity can be attributed to the presence of urea or thiourea functionality in 2-methylquinazolin-4(3H)-one scaffold as the most potent compounds **3**, **4**, **6**, **9**, **16** and **18** are the derivatives bearing either urea or thiourea moiety and similar to our previously reported work [31] in this study also none of the members from the corresponding sulphonamide series (compounds **23**–**29**) were found to be a potent anti-inflammatory agent. Here it is to be noted that the nature of the substituent present on the benzene ring of ureido or thioureido terminus is found to have strong influence on the activity which can be confirmed by the fact that the presence of lipophilic H-bond acceptor type functionalities like F, CF_3 or OCF_3 at ortho position is foremost to the moderately potent anti-inflammatory compounds **3**, **4**, **6**, **9**, **16** and **18**. The compounds **3**, **6** and **9** having F, CF_3 and OCF_3 at ortho position on the benzene ring of ureido terminus exhibited 84% - 65% TNF-α and 92% - 75% IL-6 inhibitory activity respectively and proved to be a moderately potent anti-inflammatory agent, while the presence of same substituent at para position on the benzene ring of ureido terminus leading to compounds **7** and **10** was found to have low TNF-α (17%–22%) and IL-6 (25%–31%) inhibitory activity. Similarly, the compounds **16** and **18** having F and CF_3 at ortho position on the benzene ring of thioureido terminus exhibited 78%–72% TNF-α and 89%–83% IL-6 inhibitory activity and proved to be a moderately potent anti-inflammatory agent, while the presence of same substituent at meta position on the benzene ring of thioureido terminus leading to compounds **17** and **19** was found to be inactive against TNF-α and very low IL-6 (11%–14%) inhibitory activity. Also it is to be noted that the electron donating group like OMe at ortho position on the benzene ring of thioureido terminus in compound **13** and lipophilic H-bond acceptor type group like di-CF_3 at meta position on the benzene ring of thioureido terminus in compound **20** show moderate TNF-α (52%–50%) and IL-6 (67%–62%) inhibitory activity, while OMe at meta and para position on the benzene ring of thioureido terminus leading to compound **14** and **15** showed low TNF-α (20%–28%) and IL-6 (35%–42%) inhibitory activity. As of now, though we have no concrete evidence in hand in support of the actual role of urea or thiourea functionalities on this activity, we can at least speculate that the H-bond donor ability of the urea or thiourea (not present in

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Table 3 Antifungal activity of novel 3-(2-aminoethyl)-2-methylquinazolin-4(3H)-one derivatives containing urea, thiourea and sulphonamide functionalities (MIC [a] values μg/ml).

Compounds	*Candida albicans*	*Aspergillus niger*	*Fusarium solani*	*Aspergillus flavus*
1	–	–	–	–
2	–	–	–	–
3	80	75	90	70
4	65	70	80	75
5	65	50	60	70
6	90	75	90	80
7	15	20	10	20
8	65	60	75	55
9	80	75	65	85
10	15	15	10	15
11	80	60	55	60
12	20	20	15	30
13	120	90	110	100
14	90	85	70	80
15	35	35	30	40
16	130	–	–	–
17	90	100	105	90
18	75	80	90	80
19	75	60	55	60
20	–	–	120	–
21	40	45	40	45
22	80	90	75	65
23	25	20	25	25
24	60	65	80	80
25	20	15	15	25
26	70	65	75	60
27	70	75	65	80
28	15	10	10	15
29	60	55	60	65
Miconazole	20	15	15	20

–: No activity was observed up to 200 μg/ml.
[a] Values are the average of three readings.

sulphonamide framework) along with the electronic effect of ortho or para substituent might be responsible for their anti-inflammatory activity.

2.2.2. Antimicrobial activity

The antibacterial activity data are represented in Table 2. As shown in our results, some analogues of this series were found to have even more potency than the standard drug ciprofloxacin while some of them have comparable potency.

The compounds **10**, **25** and **28** exhibited comparable or higher antibacterial activities than ciprofloxacin against each strain tested while compounds **7**, **12**, **15**, **21** and **23** showed moderate to comparable antibacterial activities than ciprofloxacin according to the strain tested. Other compounds exhibited lower to no activities than ciprofloxacin.

The compound **10** bearing OCF_3 at para position on the benzene ring of ureido terminus is 1.3-fold more potent against S*taphylococcus aureus* (MTCC 96), *Bacillus subtilis* (MTCC 441) and *Escherichia coli* (MTCC 443) while 1.5-fold more potent against S*almonella typhimurium* (MTCC 98) than standard drug ciprofloxacin and found to be the most potent antibacterial agent, but compound **7** bearing CF_3 at para position on the benzene ring of ureido terminus is almost 1.3-fold more potent against S.s *aureus* (MTCC 96) and comparable to other bacterial strains. Compound **25** bearing Br at ortho and CF_3 at para position on the benzene ring of sulphonamide terminus is 1.3-fold more potent against S.s *aureus* (MTCC 96), *B.s subtilis* (MTCC 441) while 1.5-fold more potent against S. *typhimurium* (MTCC 98) than standard drug ciprofloxacin. Interestingly compound **28** bearing OMe at para and meta position on the benzene ring of sulphonamide terminus is 1.5-fold more potent against S.s *aureus* (MTCC 96) and S. *typhimurium* (MTCC 98) while 1.3-fold more potent against *E.s coli* (MTCC 443) than standard drug ciprofloxacin.

Concerning the antifungal activity data represented in Table 3, compounds **10** and **28** exhibited higher antifungal activities, while compounds **7**, **12**, **15**, **21**, **23** and **25** exhibited moderate to comparable antifungal activities than miconazole according to the strain tested.

The compound **10** is 1.3-fold more potent against *Candida albicans* (MTCC 227) and *Aspergillus flavus* (MTCC 277) while 1.5-fold more potent against *Fusarium solani* (MTCC 350) and compound **7** is almost 1.3-fold more potent against *C. albicans* (MTCC 227) and 1.5-fold more potent against *F.s solani* (MTCC 350) than standard drug miconazole. Interestingly compound **28** is 1.3-fold more potent against *C. albicans* (MTCC 227) and *Aspergillus flavus* (MTCC 277) while 1.5-fold more potent against *Aspergillus niger* (MTCC 281), *F.s solani*

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(MTCC 350) than standard drug miconazole and found to be the most potent antifungal agent.

From the above activity data we come to a conclusion that, the compound **10** bearing OCF_3 at para position on the benzene ring of ureido terminus and the compound **28** bearing OMe at para and meta position on the benzene ring of sulphonamide terminus are the most potent antimicrobial agents followed by compound **25** bearing Br at ortho and CF_3 at para position on the benzene ring of sulphonamide terminus. The high potency or comparable activity of compounds **7**, **10**, **23** and **25** may be attributed to the presence of lipophilic H-bond acceptor type groups like CF_3, OCF_3, Cl, and Br at para position on the benzene ring of urea and sulphonamide functionalities while compounds **12** and **28** may be due to the presence of electron donating groups like OMe or Me at meta and para position on the benzene ring of urea and sulphonamide functionalities.

It is clear from our results (Table 2 vs. Table 3) that the SAR of 2-methylquinazolin-4(3H)-one derivatives bearing urea, thiourea and sulphonamide functionalities for antibacterial activity strongly correlates with their SAR of antifungal activity. To our surprise, none of the most active anti-inflammatory agents **3**, **4**, **6**, **9**, **16** and **18** were found to be active antibacterial or antifungal agents against all the bacteria or fungi screened but importantly indicate the low toxicity associated with them and should be considered as ideal anti-inflammatory agents.

3. Conclusion

In conclusion, the intention of the present study was to synthesize and investigate the anti-inflammatory and antimicrobial activities of novel structurally diverse 2-methylquinazolin-4(3H)-one derivatives bearing urea, thiourea and sulphonamide functionalities with the hope of discovering a new structure leads serving as an anti-inflammatory or antimicrobial agents. With little exception, overall it has been observed that the urea or thiourea was found to be favourable in structural feature for the anti-inflammatory activity, while no particular trend was observed for antimicrobial activity. Thus the presence of substituents such as F, CF_3 or OCF_3 at ortho position on the benzene ring of urea or thiourea terminus was found to have strong relevance to the anti-inflammatory activity while CF_3, OCF_3, Cl, and Br at para position and OMe or Me at meta and para position on the benzene ring of urea, thiourea and sulphonamide terminus were found to be effective antimicrobial agents. Thus the nature and position of the substituent were found to be crucial to improve the activity.

4. Experimental

4.1. General

All commercial chemicals and solvents are of reagent grade and were used without further purification. The thin layer chromatography was performed on Merck pre-coated silica gel 60 F_{254} plates, with visualization under UV light. ^{1}H NMR spectra were recorded with a Bruker 300 MHz AVANCE instrument and J values are in Hertz and chemical shifts (δ) are reported in ppm relative to internal tetramethylsilane. IR (Perkin-Elmer FT-IR) spectroscopic technique. The mass spectra were measured with Thermo Finnigan-TSQ Quantum Ultra (triple Quad). The purity of all compounds was determined by HPLC (Waters 2695 Alliance) using column Kromasil C18, solvent acetonitrile & buffer (0.01 M ammonium acetate + 0.5% triethylamine, pH 5.0 with acetic acid). Melting points were determined with a (PEW-340MP) melting point apparatus and are uncorrected.

4.2. Synthesis of 6,7-dimethoxy-2-methyl-4H-benzo[d] [1,3] oxazin-4-one (*1*)

Anthranilic acid (1 equiv) was taken in acetic anhydride (excess) and refluxed under anhydrous condition for 4 h and progress of reaction monitored by TLC in ethyl acetate–petroleum ether (2:8). After completion of reaction, excess of acetic anhydride was then distilled off under reduced pressure and the viscous reaction mass triturated in petroleum ether and obtained solid was filtered to afford title compound as white solid. Yield 78%, mp 178–180 °C; ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 7.32 (s, 1H), 7.02 (s, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 2.10 (s, 3H); MS (APCI); m/z 222.1$[M+H]^+$; HPLC; 98%.

4.3. Synthesis of 3-(2-aminoethyl)-6,7-dimethoxy-2-methylquinazolin-4(3H)-one (*2*)

A mixture of 6,7-dimethoxy-2-methyl-4H-benzo[d] [1,3] oxazin-4-one (**1**) (1 equiv) and 1,2-ethylenediamine (excess) was directly heated at 120 °C for 2 h with continuous stirring and reaction monitored by TLC in ethyl acetate–petroleum ether (4:6). The reaction mixture was then poured in ice cold water and extracted with ethyl acetate. Organic layer was washed by fresh water and brine, dried on Na_2SO_4 and concentrated under reduced pressure to afford crude product, which was purified by silica gel (100–200 #) column chromatography in 30% ethyl acetate petroleum ether as eluent to obtain a title compound as reddish solid. Yield 55%, mp 253–255 °C; ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 7.51 (s, 1H), 7.40 (s, 1H), 4.37 (t, J = 6.0 Hz, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 3.22–3.26 (m, 2H), 3.07 (brs, 2H), 2.92 (s, 3H); MS (APCI); m/z 264.4$[M+H]^+$; HPLC; 95%.

4.4. General procedure to synthesize compounds *3*–*12*

To a solution of 3-(2-aminoethyl)-6,7-dimethoxy-2-methylquinazolin-4(3H)-one (**2**) (1 equiv) in THF (10 ml) different substituted isocyanates (1.1 equiv) were added. Resulting reaction mixture was stirred at room temperature for 1–2 h and progress of reaction monitored by TLC in ethyl acetate- petroleum ether (4:6). Resulting reaction mixture was diluted with hexane and obtained solid was filtered to afford crude product, which was purified by silica gel (100–200 #) flash column chromatography in ethyl acetate petroleum ether (40:60) as eluent to obtain a title compound in moderate to good yield.

4.4.1. Synthesis of 1-(2-(6,7-dimethoxy-2-methyl-4-oxoquinazolin-3(4H)-yl) ethyl)-3-(2-fluorophenyl) urea (*3*)

Yield 81%, mp 232–234 °C; ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 8.33–8.35 (m, 1H), 7.99 (td, J = 8.3, 1.5 Hz, 1H), 7.40

(s, 1H), 7.11–7.19 (m, 1H), 7.01–7.08 (m, 2H), 6.88–6.96 (m, 1H), 6.79 (t, J = 6.0 Hz, 1H), 4.12 (t, J = 7.6 Hz, 2H), 3.86 (s, 6H), 3.37–3.46 (m, 2H), 2.58 (s, 3H); IR (KBr) νmax/cm^{-1} 3400 (N–H str.), 3149 (C–H), 1533 (C═O urea), 1245 (C–O), 1193 (C–F), 1064 (C–H), 899 (C–N); MS (APCI); m/z 398.92[M−H]$^-$; HPLC; 97%.

4.4.2. Synthesis of 1-(3-chloro-2-fluorophenyl)-3-(2-(6,7-dimethoxy-2-methyl-4-oxoquinazolin-3(4H)-yl) ethyl) urea (**4**)

White solid, Yield 80%, mp 245–247 °C; ^{1}H NMR (DMSO-d$_6$, 300 MHz, δ ppm): 8.53 (d, J = 1.9 Hz, 1H), 7.88–8.23 (m, 1H), 7.39 (s, 1H), 7.02–7.24 (m, 3H), 6.83 (t, J = 6.0 Hz, 1H), 4.13 (t, J = 6.2 Hz, 2H), 3.86 (s, 6H), 3.36–3.59 (m, 2H), 2.58 (s, 3H); IR (KBr) νmax/cm^{-1} 3450 (N-H str), 3149 (C–H), 1637 (C═O urea), 1366 (C–F), 1230 (C–O), 1173 (C–H), 825 (C–N), 615 (C–Cl); MS (APCI); m/z 432.83[M−H]$^-$; HPLC; 99%.

4.4.3. Synthesis of 1-(2-(6,7-dimethoxy-2-methyl-4-oxoquinazolin-3(4H)-yl) ethyl)-3-(5-fluoro-2-methylphenyl) urea (**5**)

White solid, Yield 83%, mp 244–246 °C; ^{1}H NMR (DMSO-d$_6$, 300 MHz, δ ppm): 7.75 (s, 1H), 7.54–7.61 (m, 1H), 7.35 (s, 1H), 6.96–7.08 (m, 2H), 6.84 (brs, 1H), 6.64 (t, J = 6.0 Hz, 1H), 4.03–4.11 (m, 2H), 3.99 (s, 6H), 3.33–3.42 (m, 2H), 3.21 (brs, 3H), 2.53 (s, 3H); IR (KBr) νmax/cm^{-1} 3400 (N–H str), 3153 (C–H), 1561 (C═O urea), 1300 (C–F), 1240 (C–O), 1173 (C–H), 751 (C–N); MS (APCI); m/z 412.92[M−H]$^-$; HPLC; 96%.

4.4.4. Synthesis of 1-(2-(6,7-dimethoxy-2-methyl-4-oxoquinazolin-3(4H)-yl) ethyl)-3-(2-(trifluoromethyl) phenyl) urea (**6**)

White solid, Yield 79%, mp 243–245 °C; ^{1}H NMR ($CDCl_3$ + Drop of MeOD, 300 MHz, δ ppm): 7.55 (s, 1H), 7.49–7.50 (m, 3H), 7.35 (s, 1H), 7.11–7.19 (m, 1H), 7.02 (s, 1H), 6.48 (t, J = 6.0 Hz, 1H), 4.28 (t, J = 6.6 Hz, 2H), 3.99 (s, 3H), 3.98 (s, 3H), 3.57–3.59 (m, 2H), 2.71 (s, 3H); IR (KBr) νmax/cm^{-1} 3400 (N–H str), 3153 (C–H), 1561 (C═O urea), 1300 (C–F), 1259 (C–O), 1173 (C–H), 751 (C–N); MS (APCI); m/z 451.2[M + H]$^+$; HPLC; 99%.

4.4.5. Synthesis of 1-(2-(6,7-dimethoxy-2-methyl-4-oxoquinazolin-3(4H)-yl) ethyl)-3-(4-(trifluoromethyl) phenyl) urea (7)

White solid, Yield 80%, mp 220–223 °C; ^{1}H NMR (DMSO-d$_6$, 300 MHz, δ ppm): 8.05 (s, 1H), 7.48 (s, 5H), 7.02 (s, 1H), 5.92 (t, J = 6 Hz, 1H), 4.3 (t, J = 6.6 Hz, 2H), 3.99 (s, 3H), 3.98 (s, 3H), 3.56–3.62 (m, 2H), 2.72 (s, 3H); IR (KBr) νmax/cm^{-1} 3400 (N–H str), 3153 (C–H), 1561 (C═O urea), 1300 (C–F), 1241 (C–O), 1173 (C–H), 751 (C–N); MS (APCI); m/z 451.2[M + H]$^+$; HPLC; 97%.

4.4.6. Synthesis of 1-(2-chloro-5-(trifluoromethyl) phenyl)-3-(2-(6,7-dimethoxy-2-methyl-4-oxoquinazolin-3(4H)-yl) ethyl) urea (**8**)

White solid, Yield 78%, mp 256–258 °C; ^{1}H NMR (DMSO-d$_6$, 300 MHz, δ ppm): 8.04 (brs, 1H), 7.59–7.74 (m, 2H), 7.36–7.49 (m, 3H), 6.67 (t, J = 6.0 Hz, 1H), 4.21 (t, J = 5.9 Hz, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 3.28–3.41 (m, 2H), 2.59 (s, 3H); IR (KBr) νmax/cm^{-1} 3400 (N-H str), 3153 (C–H), 1561 (C═O urea), 1300 (C–F), 1223 (C–O), 1173 (C–H), 751 (C–N), 615 (C–Cl); MS (APCI); m/z 485.07[M + H]$^+$; HPLC; 97%.

4.4.7. Synthesis of 1-(2-(6,7-dimethoxy-2-methyl-4-oxoquinazolin-3(4H)-yl) ethyl)-3-(2-(trifluoromethoxy) phenyl) urea (**9**)

White solid, Yield 80%, mp 246–249 °C; ^{1}H NMR (DMSO-d$_6$, 300 MHz, δ ppm): 8.21 (s, 1H), 8.10 (dd, J = 8.3, 1.5 Hz, 1H), 7.40 (s, 1H), 7.17–7.35 (m, 2H), 6.96–7.14 (m, 2H), 6.64 (t, J = 6.0 Hz, 1H), 4.12 (t, J = 6.0 Hz, 2H), 3.95 (s, 3H), 3.86 (s, 3H), 3.37–3.60 (m, 2H), 2.57 (s, 3H); IR (KBr) νmax/cm^{-1} 3400 (N–H str), 3153 (C–H), 1561 (C═O urea), 1265 (C–O), 1300 (C–F), 1173 (C–H), 751 (C–N); MS (APCI); m/z 464.92[M−H]$^-$; HPLC; 98%.

4.4.8. Synthesis of 1-(2-(6, 7-dimethoxy-2-methyl-4-oxoquinazolin-3(4H)-yl) ethyl)-3-(4-(trifluoromethoxy) phenyl) urea (**10**)

White solid, Yield 78%, mp 228–230 °C; ^{1}H NMR (DMSO-d$_6$, 300 MHz, δ ppm): 8.82 (s, 1H), 7.39–7.48 (m, 3H), 7.20 (d, J = 8.3 Hz, 2H), 7.04 (s, 1H), 6.45 (t, J = 6.0 Hz, 1H), 4.12 (t, J = 6.4 Hz, 2H), 3.95 (s, 3H), 3.86 (s, 3H), 3.39–3.49 (m, 2H), 2.59 (s, 3H); IR (KBr) νmax/cm^{-1} 3400 (N–H str), 3153 (C–H), 1561 (C═O urea), 1300 (C–F), 1193 (C–O), 1173 (C–H), 751 (C–N); MS (APCI); m/z 464.93[M−H]$^-$; HPLC; 98%.

4.4.9. Synthesis of 1-(2-(6, 7-dimethoxy-2-methyl-4-oxoquinazolin-3(4H)-yl) ethyl)-3-(4-isopropylphenyl) urea (**11**)

White solid, Yield 83%, mp 204–206 °C; ^{1}H NMR (DMSO-d$_6$, 300 MHz, δ ppm):): 8.45 (s, 1H), 7.40 (s, 1H), 7.25 (d, J = 8.7 Hz, 2H), 7.03–7.09 (m, 3H), 6.32 (t, J = 6.0 Hz, 1H), 4.11 (t, J = 6.4 Hz, 2H), 3.95 (s, 3H), 3.86 (s, 3H), 3.32–3.41 (m, 2H), 2.71–2.83 (m, 1H), 2.53 (s, 3H), 1.12–1.25 (m, 6H); IR (KBr) νmax/cm^{-1} 3435 (N–H str), 3148 (C–H), 1637 (C═O urea), 1236 (C–O), 1173 (C–H), 825 (C–N); MS (APCI); m/z 422.87[M–H]$^-$; HPLC; 98%.

4.4.10. Synthesis of 1-(2-(6,7-dimethoxy-2-methyl-4-oxoquinazolin-3(4H)-yl) ethyl)-3-(3, 4-dimethylphenyl) urea (**12**)

White solid, Yield 83%, mp 218–220 °C; ^{1}H NMR (DMSO-d$_6$, 300 MHz, δ ppm): 8.35 (s, 1H), 7.40 (s, 1H), 7.02–7.14 (m, 3H), 6.92–6.99 (m, 1H), 6.30 (t, J = 6.0 Hz, 1H), 4.11 (t, J = 6.2 Hz, 2H), 3.95 (s, 3H), 3.86 (s, 3H), 3.42–3.50 (m, 2H), 2.53 (s, 3H), 2.07–2.18 (m, 6H); IR (KBr) νmax/cm^{-1} 3400 (N–H str), 3153 (C–H), 1561 (C═O urea), 1260 (C–O), 1173 (C–H), 751 (C–N); MS (APCI); m/z 411.07[M + H]$^+$; HPLC; 98%.

4.5. General procedure to synthesize compounds *A13–A22*

To a solution of 3-(2-aminoethyl)-6,7-dimethoxy-2-methylquinazolin-4(3H)-one (**2**) (1 equiv) in THF (10 ml), different substituted isothiocyanates (1.1 equiv) were added. Resulting reaction mixture was stirred at room temperature for 1–2 h and progress of reaction monitored by TLC in ethyl acetate-petroleum ether (4:6). Resulting reaction mixture was diluted with hexane and obtained solid was filtered to afford crude product, which was purified by silica gel (100–200 #) flash column chromatography in ethyl acetate petroleum ether (40:60) as eluent to obtain a title compound in moderate to good yield.

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*4.5.1. Synthesis of 1-[2-(6,7-Dimethoxy-2-methyl-4-oxo-4H-quinazolin-3-yl)-ethyl]-3-(2-methoxy-phenyl)-thiourea (**13**)*

White solid, Yield 86%, mp 178–180 °C; ^{1}H NMR (DMSO-d$_6$, 300 MHz, δ ppm): 9.00 (s, 1H), 7.91 (brs, 1H), 7.52 (d, 1H, *J* = 6.4 Hz), 7.39 (s, 1H), 7.10–7.27 (m, 1H), 7.06 (s, 2H), 6.89 (t, *J* = 7.6 Hz, 1H), 4.20 (t, *J* = 5.9 Hz, 2H), 3.87 (s, 6H), 3.60–3.80 (m, 5H), 2.61 (s, 3H); IR (KBr) νmax/cm^{-1} 3435 (N–H str), 3149 (C–H), 1561 (C═O), 1448 (C═S), 1225 (C–O), 1172 (C–H), 768 (C–N); MS (APCI); *m*/*z* 427.4[M−H]$^-$; HPLC; 99%.

*4.5.2. 1-[2-(6,7-Dimethoxy-2-methyl-4-oxo-4H-quinazolin-3-yl)-ethyl]-3-(3-methoxy-phenyl)-thiourea (**14**)*

White solid, Yield 84%, mp 181–183 °C; ^{1}H NMR (DMSO-d$_6$, 300 MHz, δ ppm): 9.58 (s, 1H), 7.89 (brs, 1H), 7.34 (s, 1H), 7.06–7.18 (m, 1H), 7.00 (s, 1H), 6.87 (brs, 1H), 6.76 (d, 1H, *J* = 7.2 Hz), 6.65 (t, 1H, *J* = 7.6 Hz), 4.20 (t, *J* = 5.9 Hz, 2H), 3.86 (s, 6H), 3.54–3.82 (m, 5H), 2.55 (s, 3H); IR (KBr) νmax/cm^{-1} 3435 (N–H str), 3148 (C–H), 1637 (C═O), 1448 (C═S), 1244 (C–O), 1172 (C–H), 768 (C–N); MS (APCI); *m*/*z* 427.4[M + H]$^+$; HPLC; 98%.

*4.5.3. Synthesis of 1-[2-(6,7-Dimethoxy-2-methyl-4-oxo-4H-quinazolin-3-yl)-ethyl]-3-(4-methoxy-phenyl)-thiourea (**15**)*

White solid, Yield 87%, mp 176–178 °C; ^{1}H NMR (DMSO-d$_6$, 300 MHz, δ ppm): 9.43 (s, 1H), 7.69 (brs, 1H), 7.39 (s, 1H), 7.15 (d, 2H, *J* = 9.1 Hz), 6.86 (d, 2H, *J* = 9.1 Hz), 6.65 (t, 1H, *J* = 7.6 Hz), 4.21 (t, *J* = 5.9 Hz, 2H), 3.86 (s, 6H), 3.69–3.82 (m, 5H), 2.60 (s, 3H); IR (KBr) νmax/cm^{-1} 3435 (N–H str), 3149 (C–H), 1561 (C═O), 1448 (C═S), 1195 (C–O), 1172 (C–H), 768 (C–N); MS (APCI); *m*/*z* 427.6[M−H]$^-$; HPLC; 98%.

*4.5.4. Synthesis of 1-[2-(6, 7-Dimethoxy-2-methyl-4-oxo-4H-quinazolin-3-yl)-ethyl]-3-(2-fluoro-phenyl)-thiourea (**16**)*

White solid, Yield 83%, mp 173–175 °C; ^{1}H NMR (DMSO-d$_6$, 300 MHz, δ ppm): 9.36 (s, 1H), 8.01 (brs, 1H), 7.44 (s, 1H), 7.39 (d, 1H, *J* = 2.7 Hz), 7.22–7.26 (m, 2H), 7.14 (t, 1H, *J* = 1.8 Hz), 7.05 (s, 1H), 4.20 (t, *J* = 6 Hz, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.77–3.79 (m, 2H), 2.59 (s, 3H); IR (KBr) νmax/cm^{-1} 3395 (N–H str.), 3154 (C–H), 1690 (C═O), 1540 (C═S), 1355 (C–F), 1203 (C–O), 1023 (C–H), 762 (C–N); MS (APCI); *m*/*z* 417.53[M + H]$^+$; HPLC; 99%.

*4.5.5. Synthesis of 11-[2-(6, 7-Dimethoxy-2-methyl-4-oxo-4H-quinazolin-3-yl)-ethyl]-3-(3-fluoro-phenyl)-thiourea (**17**)*

White solid, Yield 86%, mp 179–182 °C; ^{1}H NMR (DMSO-d$_6$, 300 MHz, δ ppm): 9.78 (s, 1H), 8.10 (brs, 1H), 7.39 (s, 1H), 7.27–7.34 (m, 2H), 7.05–7.09 (m, 2H), 6.94 (t, 1H, *J* = 6.3 Hz), 4.23 (t, *J* = 5.7 Hz, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.77–3.80 (m, 2H), 2.59 (s, 3H); IR (KBr) νmax/cm^{-1} 3395 (N–H str.), 3154 (C–H), 1650 (C═O), 1540 (C═S), 1355 (C–F), 1230 (C–O), 1023 (C–H), 762 (C–N); MS (APCI); *m*/*z* 417.47[M + H]$^+$; HPLC; 99%.

*4.5.6. Synthesis of 1-[2-(6, 7-Dimethoxy-2-methyl-4-oxo-4H-quinazolin-3-yl)-ethyl]-3-(2-trifluoromethyl-phenyl)-thiourea (**18**)*

White solid, Yield 85%, mp 183–185 °C; ^{1}H NMR (DMSO-d$_6$, 300 MHz, δ ppm): 9.86 (s, 1H), 8.17 (brs, 1H), 7.82 (s, 1H), 7.57–7.65 (m, 1H), 7.51 (t, 1H, *J* = 1.8 Hz), 7.37–7.46 (m, 2H), 7.04 (s, 1H), 4.24 (t, *J* = 5.9 Hz, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.77–3.79 (m, 2H), 2.60 (s, 3H); IR (KBr) νmax/cm^{-1} 3435 (N–H str.), 3100 (C–H), 1637 (C═O urea), 1530 (C═S), 1372 (C–F), 1259 (C–O), 1200 (C–H), 902 (C–N); MS (APCI); *m*/*z* 465.25[M−H]$^-$; HPLC; 97%.

*4.5.7. Synthesis of 1-[2-(6, 7-Dimethoxy-2-methyl-4-oxo-4H-quinazolin-3-yl)-ethyl]-3-(3-trifluoromethyl-phenyl)-thiourea (**19**)*

White solid, Yield 84%, mp 187–189 °C; ^{1}H NMR (DMSO-d$_6$, 300 MHz, δ ppm): 9.22 (s, 1H), 8.15 (brs, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.42–7.48 (m, 2H), 7.39 (s, 1H), 7.06 (s, 1H), 4.20 (t, *J* = 5.9 Hz, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.78–3.80 (m, 2H), 2.59 (s, 3H); IR (KBr) νmax/cm^{-1} 3435 (N–H str.), 3100 (C–H), 1603 (C═O urea), 1530 (C═S), 1372 (C–F), 1240 (C–O), 1200 (C–H), 902 (C–N); MS (APCI); *m*/*z* 465.17[M−H]$^-$; HPLC; 98%.

*4.5.8. Synthesis of 1-(3, 5-Bis-trifluoromethyl-phenyl)-3-[2-(6, 7-dimethoxy-2-methyl-4-oxo-4H-quinazolin-3-yl)-ethyl]-thiourea (**20**)*

White solid, Yield 84%, mp 181–184 °C; ^{1}H NMR (DMSO-d$_6$, 300 MHz, δ ppm): 10.17 (s, 1H), 8.42 (brs, 1H), 8.15–8.29 (m, 2H), 7.75 (s, 1H), 7.39 (t, 1H, *J* = 1.8 Hz), 7.06 (s, 1H), 4.25 (t, *J* = 6 Hz, 2H), 3.93 (s, 3H), 3.87 (s, 3H), 3.80–3.82 (m, 2H), 2.60 (s, 3H); IR (KBr) νmax/cm^{-1} 3435 (N–H str.), 3100 (C–H), 1533 (C═O urea), 1530 (C═S), 1372 (C–F), 1223 (C–O), 1200 (C–H), 902 (C–N); MS (APCI); *m*/*z* 535.60[M + H]$^+$; HPLC; 98%.

*4.5.9. Synthesis of 1-(4-Chloro-phenyl)-3-[2-(6, 7-dimethoxy-2-methyl-4-oxo-4H-quinazolin-3-yl)-ethyl]-thiourea (**21**)*

White solid, Yield 81%, mp 182–184 °C; ^{1}H NMR (DMSO-d$_6$, 300 MHz, δ ppm): 9.70 (s, 1H), 8.02 (brs, 1H), 7.29–7.50 (m, 5H), 7.05 (s, 1H), 4.22 (t, *J* = 6 Hz, 2H), 3.94 (s, 3H), 3.87 (s, 3H), 3.73–3.78 (m, 2H), 2.59 (s, 3H); IR (KBr) νmax/cm^{-1} 3390 (N–H str.), 3137 (C–H), 1561 (C═O), 1519 (C═S), 1230 (C–O), 1173 (C–H), 773 (C–N), 615 (C–Cl); MS (APCI); *m*/*z* 433.75[M + H]$^+$; HPLC; 98%.

*4.5.10. Synthesis of 1-[2-(6, 7-Dimethoxy-2-methyl-4-oxo-4H-quinazolin-3-yl)-ethyl]-3-p-tolyl-thiourea (**22**)*

White solid, Yield 85%, mp 176–178 °C; ^{1}H NMR (DMSO-d$_6$, 300 MHz, δ ppm): 9.54 (s, 1H), 7.82 (brs, 1H), 7.40 (s, 1H), 7.04–7.17 (m, 5H), 4.22 (t, *J* = 5.9 Hz, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.29–3.43 (m, 2H), 2.60 (s, 3H), 2.26 (s, 3H); IR (KBr) νmax/cm^{-1} 3567 (N–H str.), 3137 (C–H), 1690 (C═O), 1519 (C═S), 1265 (C–O), 1173 (C–H), 773 (C–N); MS (APCI); m/z 413[M + H]$^+$; HPLC; 97%.

*4.6. General procedure to synthesize compounds **A23–A29***

To a solution of 3-(2-aminoethyl)-6,7-dimethoxy-2-methylquinazolin-4(3H)-one (**2**) (1 equiv) in DCM (10 ml), different substituted sulphonyl chlorides (1.1 equiv) and triethylamine (1.1 equiv) were added. Resulting reaction mixture was stirred at room temperature for 1–2 h and progress of reaction monitored by TLC in ethyl acetate- petroleum ether mixture (3:7). Resulting reaction mixture was diluted with DCM and water

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added. Separated organic layer was washed by fresh water and brine, dried on Na_2SO_4 and concentrated under reduced pressure to afford crude product, which was purified by silica gel (100–200 #) flash column chromatography in ethyl acetate petroleum ether (30:70) as eluent to obtain a title compound in moderate to good yield.

4.6.1. Synthesis of 4-Bromo-N-[2-(6, 7-dimethoxy-2-methyl-4-oxo-4H-quinazolin-3-yl)-ethyl]-benzenesulphonamide (**23**)

White solid, Yield 84%, mp 187–189 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 8.09 (s, 1H), 7.64–7.70 (m, 4H), 7.35 (s, 1H), 7.05(brs, 1H), 4.06 (brs 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.16 (brs, 2H), 2.59 (s, 3H); IR (KBr) νmax/cm^{-1} 3435 (N–H str.), 3142 (C–H), 1533 (C═O), 1434 (SO_2NH), 1236 (C–O), 1168 (C–H), 765 (C–N), 673 (C–Br); MS (APCI); *m*/*z* 483.9[M + H]$^+$; HPLC; 97%.

4.6.2. Synthesis of N-[2-(6, 7-Dimethoxy-2-methyl-4-oxo-4H-quinazolin-3-yl)-ethyl]-4-trifluoromethyl-benzenesulphonamide (**24**)

White solid, Yield 87%, mp 184–186 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 7.94 (d, J = 6.9 Hz, 2H), 7.65 (d, J = 6.9 Hz, 2H), 7.28 (s, 1H), 6.77 (s, 1H), 6.55(brs, 1H), 4.29 (brs, 2H), 3.92 (s, 6H), 3.49 (brs, 2H), 2.68 (s, 3H); MS (APCI); IR (KBr) νmax/cm^{-1} 3417 (N–H str), 3147 (C–H), 1560 (C═O), 1443 (SO_2NH), 1355 (C–F), 1260 (C–O), 1159 (C–H), 765 (C–N); *m*/*z* 472.3[M−H]$^+$; HPLC; 98%.

4.6.3. Synthesis of 2-Bromo-N-[2-(6, 7-dimethoxy-2-methyl-4-oxo-4H-quinazolin-3-yl)-ethyl]-4-trifluoromethyl-benzenesulphonamide (**25**)

White solid, Yield 82%, mp 185–187 °C; ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 8.24 (d, J = 7.8 Hz, 1H), 7.93 (s, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.44 (s, 1H), 6.99 (s, 1H), 6.42 (brs, 1H), 4.32 (brs 2H), 3.99 (s, 6H), 3.41–3.43 (m, 2H), 2.70 (s, 3H); IR (KBr) νmax/cm^{-1} 3435 (N–H str.), 3142 (C–H), 1533 (C═O), 1434 (SO_2NH), 1330 (C–F), 1225 (C–O), 1168 (C–H), 765 (C–N), 673 (C–Br); MS (APCI); *m*/*z* 552[M + H]$^+$; HPLC; 98%

4.6.4. Synthesis of 2-Chloro-N-[2-(6, 7-dimethoxy-2-methyl-4-oxo-4H-quinazolin-3-yl)-ethyl]-4-trifluoromethyl-benzenesulphonamide (**26**)

White solid, Yield 85%, mp 184–186 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 7.77 (d, J = 7.2 Hz, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.27–7.32 (s, 1H), 7.04 (s, 2H), 6.99 (brs, 1H), 4.28 (brs 2H), 3.86 (s, 6H), 3.04–3.09 (m, 2H), 2.50 (s, 3H); IR (KBr) νmax/cm^{-1} 3400 (N–H str.), 3142 (C–H), 1540 (C═O), 1418 (SO_2NH), 1340 (C–F), 1203 (C–O), 1100 (C–H), 935 (C–N), 615 (C–Cl); MS (APCI); *m*/*z* 506[M−H]$^+$; HPLC; 99%.

4.6.5. Synthesis of N-[2-(6, 7-Dimethoxy-2-methyl-4-oxo-4H-quinazolin-3-yl)-ethyl]-5-fluoro-2-methyl-benzenesulphonamide (**27**)

White solid, Yield 84%, mp 183–185 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 7.65–7.68 (m, 1H), 7.58 (s, 1H), 7.16–7.09 (m, 2H), 6.99 (s, 1H), 6.42 (brs, 1H), 4.29 (t, J = 6 Hz, 2H), 3.99 (s, 3H), 3.97 (s, 3H), 3.44–3.42 (m, 2H), 2.71 (s, 3H), 2.55 (s, 3H); IR (KBr) νmax/cm^{-1} 3417 (N–H str), 3147 (C–H), 1540 (C═O), 1443 (SO_2NH), 1355 (C–F), 1230 (C–O), 1159 (C–H), 765 (C–N); MS (APCI); *m*/*z* 436.1[M + H]$^+$; HPLC; 98%.

4.6.6. Synthesis of N-[2-(6, 7-Dimethoxy-2-methyl-4-oxo-4H-quinazolin-3-yl)-ethyl]-3, 4-dimethoxy-benzenesulphonamide (**28**)

White solid, Yield 83%, mp 181–183 °C; ^{1}H NMR (DMSO-d_6, 300 MHz, δ ppm): 8.41 (d, J = 7.5 Hz, 1H), 8.13 (d, J = 7.2 Hz, 1H), 7.91–7.97 (m, 1H), 7.43 (s, 1H), 7.06 (s, 1H), 6.19 (brs, 1H), 4.39 (t, J = 5.4 Hz, 2H), 3.88 (s, 6H), 3.86 (s, 6H), 3.47–3.43 (m, 2H), 2.62 (s, 3H); IR (KBr) νmax/cm^{-1} 3400 (N–H str.), 3142 (C–H), 1537 (C═O), 1418 (SO_2NH), 1236 (C–O), 1100 (C–H), 935 (C–N); MS (APCI); *m*/*z* 464.3[M + H]$^+$; HPLC; 96%.

4.6.7. Synthesis of N-[2-(6, 7-Dimethoxy-2-methyl-4-oxo-4H-quinazolin-3-yl)-ethyl]-3-methyl-benzenesulphonamide (**29**)

White solid, Yield 85%, mp 184–186 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 7.89 (s, 1H), 7.55 (s, 2H), 7.35–7.39 (m, 3H), 7.04 (brs, 1H), 4.05 (t, J = 5.9 Hz, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.08–3.10 (m, 2H), 2.72 (s, 3H), 2.34 (s, 3H); IR (KBr) νmax/cm^{-1} 3435 (N–H str.), 3148 (C–H), 1540 (C═O), 1445 (SO_2NH), 1230 (C–O), 1160 (C–H), 765 (C–N); MS (APCI); *m*/*z* 418[M + H]$^+$; HPLC; 98%.

4.7. Biological assay

4.7.1. Anti-inflammatory assay

Pro-inflammatory cytokine production by lip polysaccharide (LPS) in THP-1 cells was measured according to the method described by Hwang et al. (1993). During assay, THP-1 cells were cultured in RPMI 1640 culture medium (Gibco BRL, Paisley, UK) containing 100 U/mL penicillin and 100 mg/mL streptomycin containing 10% foetal bovine serum (FBS, JRH). Cells were differentiated with phorbol myristate acetate (PMA, Sigma). Following cell plating, the test compounds in 0.5% DMSO were added to each well separately and the plate was incubated for 30 min at 37 °C. Finally, LPS (*E. coli* 0127:B8, Sigma Chemical Co., St. Louis, MO) was added, at a final concentration of 1 μg/mL in each well. Plates were further incubated at 37 °C for 24 h in 5% CO_2. After incubation, supernatants were harvested, and assayed for TNF-α and IL-6 by ELISA as described by the manufacturer (BD Biosciences).

4.7.2. Antibacterial assay

Newly synthesized compounds were screened for their antibacterial activity against selected Gram-positive organisms viz. S.s *aureus* (MTCC 96), *B.s subtilis* (MTCC 441) and Gram-negative organisms viz. *E.s coli* (MTCC 443), S. *typhimurium* (MTCC 98) bacterial strains by the agar well diffusion method with little modification (Sridhar et al., 2004). Different concentrations (10–200 μg/ml) of test compounds were prepared in DMSO. The bacterial suspension was spread over nutrient agar plates and the well with of 6 mm diameter was punched with sterile cork borer. The sample (50 μL) was added to the well and the plates were incubated at 37 °C for 24 h. Respective solvent control (DMSO) was kept and ciprofloxacin was used as standard antibacterial agent. The lowest concentration of compound which completely inhibits the bacterial growth

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was taken as minimum inhibitory concentration (MIC). Minimum inhibitory concentrations (MIC) were noted (Table 2).

4.7.3. Antifungal assay

Newly synthesized compounds were screened for their antifungal activity against *C. albicans* (MTCC 227), *Aspergillus niger* (MTCC 281), *F.s solani* (MTCC 350) and *Aspergillus flavus* (MTCC 277) by the agar well diffusion method with little modification (Sridhar et al., 2004). Normal saline was used to make a suspension of spores of fungal strain. The fungal suspension was spread over potato dextrose agar plates and the wells of 6 mm diameter were punched with sterile cork borer. The sample (50 μL) was added to the well and the plates were incubated at 37 °C for 2–3 days. Respective solvent control (DMSO) was kept and miconazole was used as standard antifungal agent. The lowest concentration of compound which completely inhibits the fungal growth was taken as minimum inhibitory concentration (MIC). Minimum inhibitory concentrations (MIC) were noted (Table 3).

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References

Alagarsamy, V., Muthukumar, V., Pavalarani, N., Vasanthanathan, P., Revathi, R., 2003a. Biol. Pharm. Bull. 26, 557.
Alagarsamy, V., Murugananthan, G., Venkateshaperumal, R., 2003b. Biol. Pharm. Bull. 26, 1711.
Alagarsamy, V., Rajasolomon, V., Meena, R., Ramseshe, K.V., 2005. Biol. Pharm. Bull. 28, 1091.
Barrett, C.T., Barrett, J.F., 2003. Curr. Opin. Biotechnol. 14, 621.
Bombardier, C., Laine, L., Reicin, A., Shapiro, D., Burgos-Vargas, R., Davis, B., Day, R., Ferraz, M.B., Hawkey, C.J., Hochberg, M.C., Kvien, T.K., Schnitzer, T.J.N., 2000. Eng. J. Med. 343, 1520.
Chao, Q., Deng, L., Shih, H., Leoni, L.M., Genini, D., Carson, D.A., Cottam, H.B., 1999. J. Med. Chem. 42, 3860.
Cohen, M.L., 1992. Science 257, 1050.
Cohen, M.L., 2000. Nature 406, 762.
Dinakaran, M., Selvam, P., Declercq, E., Sridhar, S.K., 2003. Biol. Pharm. Bull. 26, 1278.
Dominic, S.C., Raj, M.D., 2009. Semin. Arthritis Rheum. 38, 382.
Grover, G., Kini, S.G., 2006. Eur. J. Med. Chem. 41, 256.
Hwang, C., Gatanaga, M., Granger, G.A., Gatanaga, T., 1993. J. Immunol. 151, 5631.
Kamal, A., Bharathi, E.V., Ramaiah, M.J., Dastagiri, D., Reddy, J.S., Viswanath, A., Sultana, F., Pushpavalli, S.N.C.V.L., Pal-Bhadra, M., Srivastava, H.K., Sastry, G.N., Juvekar, A., Sen, S., Zingde, S., 2010. Bioorg. Med. Chem. 18, 526.
Kashaw, S.K., Kashaw, V., Mishra, P., Jain, N.K., 2008. ARKIVOC 14, 17.
Kashaw, S.K., Kashaw, V., Mishra, P., Jain, N.K., Stables, J.P., 2009. Eur. J. Med. Chem. 44, 4335.
Kashaw, S.K., Kashaw, V., Mishra, P., Jain, N.K., Stables, J.P., 2011. Med. Chem. Res. 20, 738.
Keche, A.P., Hatnapure, G.D., Tale, R.H., Rodge, A.H., Birajdar, S.S., Kamble, V.M., 2012a. Bioorg. Med. Chem. Lett. 22, 3445.
Keche, A.P., Hatnapure, G.D., Tale, R.H., Rodge, A.H., Kamble, V.M., 2012b. Bioorg. Med. Chem. Lett. 22, 3445.
Krishnamoorthy, S., Honn, K.V., 2006. *Cancer Metast. Rev.* 25, 481.
Kumar, A., Sharma, S., Bajaj, A.K., Sharma, S., Panwar, H., Singh, N., Srivastava, V.K., 2003. Bioorg. Med. Chem. 11, 5293.
Maggio, B., Daidone, G., Raffa, D., Plescia, S., Mantione, L., Cutuli, V.M.C., Mangano, N.G., Caruso, A., 2001. Eur. J. Med. Chem. 36, 737.
Mhaske, S.B., Argade, N.P., 2006. Tetrahedron 62, 9787.
Mohamed, M.S., Kamel, M.M., Kassem, E.M.M., Abotale, N., AbdElmoez, S.I., Ahmed, M.F., 2010. Eur. J. Med. Chem. 45, 3311.
Nanda, A.K., Ganguli, S., Chakraborty, R., 2007. Molecules 12, 2413.
Panneerselvam, P., Rather, B.A., Reddy, D.R.S., Kumar, N.R., 2009. Eur. J. Med. Chem. 44, 2328.
Papadakis, K.A., Targan, S.R., 2000. Inflamm. Bowel. Dis. 6, 303.
Patel, N.B., Patel, V.N., 2010. Pharma. Chem. J. 44, 438.
Shishoo, C.J., Ravikumar, T., Jain, K.S., Rathod, I.S., Gandhi, T.P., Satia, M.C., 1999. Ind. J. Chem. 38, 1075.
Silverstien, F.E., Faich, G., Goldstien, J.L., Simon, L.S., Pincus, T., Whelton, A., Makuch, R., Eisen, G., Agrawal, N.M., Stenson, W.F., Burr, A.M., Zhao, W.W., Kent, J.D., Lefkowith, J.B., Verburg, K.M., Gies, G.S., 2000. J. Am. Med. Assoc. 284, 1247.
Sridhar, R., Perumal, P.T., Etti, S., Shanmugam, G., Ponnuswamy, M.N., Prabavathyc, V.R., Mathivanan, N., 2004. Bioorg. Med. Chem. Lett. 14, 6035.
Srivastava, A.V.K., Kumar, A., 2002. Eur. J. Med. Chem. 37, 873.
Srivastava, A.V.K., Kumar, A., 2004. Bioorg. Med. Chem. 12, 1257.
Suresha, G.P., Suhas, R., Kapfo, W., Gowda, D.C., 2011. Eur. J. Med. Chem. 46, 2530.
Tale, R.H., Rodge, A.H., Hatnapure, G.D., Keche, A.P., 2011a. Bioorg. Med. Chem. Lett. 21, 4648.
Tale, R.H., Rodge, A.H., Hatnapure, G.D., Keche, A.P., Patil, K.P., Pawar, R.P., 2011b. Med. Chem. Res.. http://dx.doi.org/10.1007/s00044-011-9943-3.
Venkataraman, S., Meera, R., Dev, P.P., 2010. J. Chem. Pharm. Res. 2, 461.

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