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Original article

Click chemistry: Studies on the synthesis of novel fluorous tagged triazol-4-yl substituted quinazoline derivatives and their biological evaluation – Theoretical and experimental validation

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ABSTRACT

The formation of N- and O-propargylated quinazoline derivatives **2**, **3** from quinazol-4-ones **1** was theoretically predicted by optimizations at B3LYP/6-31G* level, analysed kinetically and thermodynamically. Theoretical predictions are validated by experiment to observe the trends and found deviation. Thus, compound **1** was propargylated in basic media to obtain compound **2** and **3** in definite proportions. Each compound was further subjected to [3 + 2] cycloaddition using perfluoroalkyl azides through Click reaction under Sharpless conditions, and obtained a series of novel perfluoroalkyl-1H,1,2,3-triazol-4-yl substituted quinazolines **4**, **5**, and **6.** All the compounds were screened for antimicrobial activity and identified potential compounds.

1. Introduction

The Quinazoline nucleus features in many alkaloids and is known to show a wide range of biological activity [1–3]. A few non-classical quinazoline analogues of folic acid have remarkable antibacterial and antimalarial effects and most prominent is trimetrexate [4]. The specific 3*H*-quinazolin-4-one derivatives known in the art as anti-convulsant [5], CNS depressant [6], muscle relaxant [7], anti-neoplastic [8–10] and antimicrobial agents [11–21]. It is also known that fluorine [22] or trifluoromethyl [23,24] group at an appropriate position in the molecule alters the properties of molecule by promoting activity due to high lipid solubility and enhancement of transport mechanism. The perfluoroalkyl triazoles [25,26], perfluoroalkyl tetrazolo-5-ones [27] and other fluoroalkyl derivatives [28–30] also found to show promising biological activity. Therefore, there is a growing demand for the synthesis of fluorinated molecules in order to find a potential pharmacophore.

In continuation of our efforts toward synthesis of potential molecules such as quinazolines [31–34], pyrido pyrimidines [35], pyrimido[1,2-*b*] indazoles [36,37], we have synthesized a series of O-propargylated quinazolines **2**, N-propargylated quinazolines **3**, perfluoroalkyl-1H,1,2,3-triazol-4-yl substituted O-/N-quinazolines **4**, **5**, **6** and screened for antimicrobial activity. Computational studies were carried out to unravel the observed trends. The prediction for formation of isomers **2** and **3** is validated by experiment in basic media to observe the trend and found deviation. Each isomer is further subjected to [3 + 2] cycloaddition reaction using perfluoroalkyl azides through Click reaction [38,39] under Sharpless conditions. All the final compounds were screened for antimicrobial activity and identified potential compounds.

2. Chemistry

The 2-substituted quinazol-4-ones **1** were initially propargylated using propargyl bromide in acetone and potassium carbonate

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under reflux conditions, obtained two isomers **2**, **3** in definite proportions. The ratio of each isomer is evaluated based on the substituent present in second position. The CF_3 substituent promoted O-propargylated isomer **2** and phenyl substituent favored N-propargylated isomer **3** as major products. However, the 2,6-difluorophenyl substituent gave exclusively N-propargylated isomer **3**. The role of CF_3 is consistent with the earlier reports [40–42] whereas role of phenyl substituent is differed. The change in ratio and mode of formation of products may be due to change in reaction medium and base. Each isomer is separated and characterized.

The isomers **2** and **3** were independently reacted with perfluoroalkyl azides in THF using copper (I) iodide as catalyst to give perfluoroalkyl-1H,1,2,3-triazol-4-yl substituted O-, N-quinazoline derivatives **4a–d**, **5a–b** and **6a–f**. Compound **2** gave product **4** as major and **5** as minor however compound **3** gave exclusive product **6**. The reaction is considered to take place via 1,3-dipolar cycloaddition of azide to alkyne, through a preformed copper acetylide complex formation [43,44]. The reactions are drawn in Scheme 1 and products are tabulated in Tables 1–3.

3. Theoretical interpretations based on computational studies of compounds 2a–c, 3a–c, 4a, 4c, 4e, 6a, 6c, 6e

Computational studies were carried out to unravel the observed trends. Optimizations of the reactants, products and transition states have been carried out at B3LYP/6-31G* level. Solvent calculations are done using Polarized Continuum (overlapping spheres) Model (PCM) and all the calculations are done using G03W program package. The reactivity and feasibility of products with different yields are explained based on the thermodynamic and kinetic stabilities of the products. The transition state and product structures for all the systems along with the activation and reaction energy values (in kcal/mol) are depicted in Fig. 1.

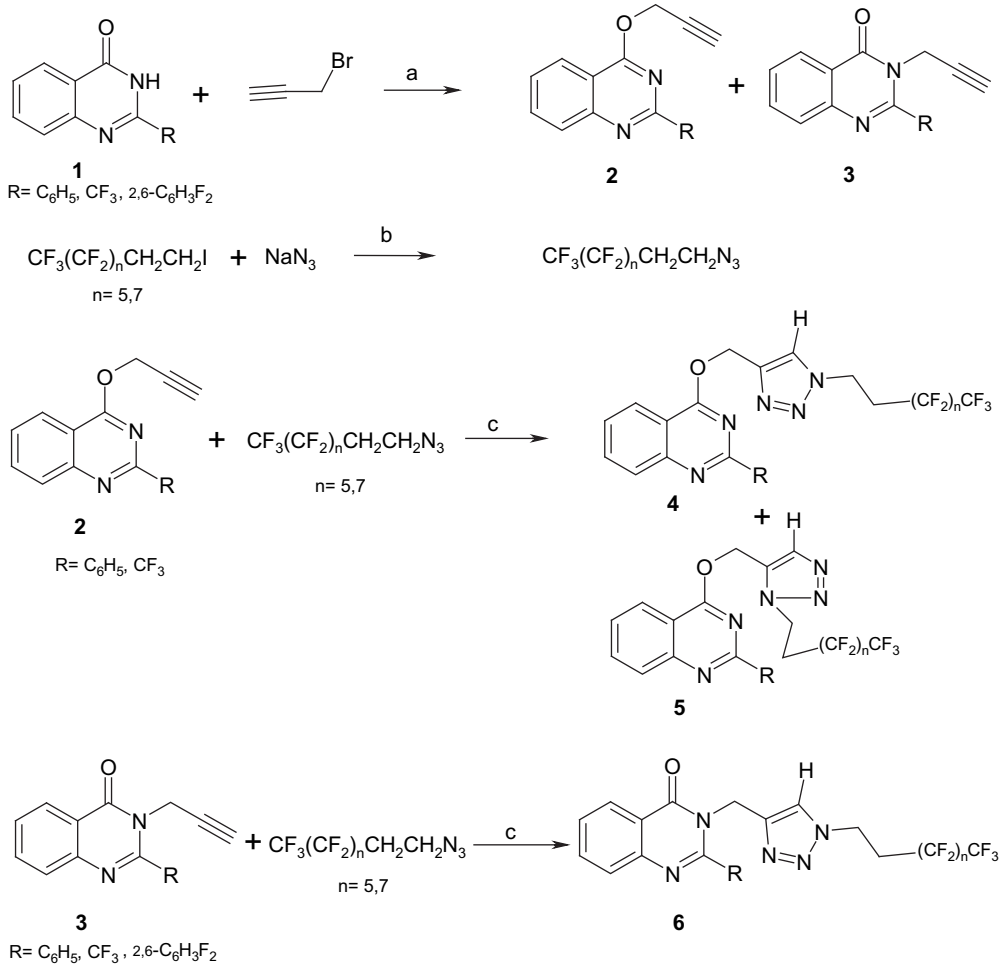
From the Fig. 1 (**3a–c**) it is observed that the substituents CF_3, Ph and 2,6-F_2Ph in second position thermodynamically favor N-propargylated quinazolines **3** and is consistent with the

Table 1
Preparation of compounds **1**.

Entry	Compd. no.	R	m.p. °C	Yield (%)
1	**1a** [31]	C_6H_5	226	84
2	**1b** [42]	CF_3	250	85
3	**1c**	2,6-$C_6H_3F_2$	231	81

Table 2
Preparation of O-, N-propargylated quinazoline derivatives **2a–b** and **3a–c**.

Entry	Compd no.	R	m.p. °C	Yield (%)
1	**2a** [42]	C_6H_5	130	39
2	**3a** [42]	C_6H_5	174	50
3	**2b** [42]	CF_3	101	52
4	**3b** [42]	CF_3	98	32
5	**3c**	2,6-$F_2C_6H_3$	133	86-



Scheme 1. Reagents & conditions: a) K_2CO_3, NaI acetone, reflux. b) Acetone, water, reflux. c) CuI, THF, room temperature.

Table 3
Perfluoroalkyl-1H,1,2,3-triazol-4-yl substituted O-, N-quinazolines (**4a–d**), (**5a**, **5b**), (**6a–f**).

Entry	Compd no.	R	*n*	m.p. °C	Yield (%)
1	**4a**	C_6H_5	5	118	46
2	**5a**	C_6H_5	5	125	40
3	**4b**	C_6H_5	7	128	47
4	**5b**	C_6H_5	7	149	38
5	**4c**	CF_3	5	93	85
6	**4d**	CF_3	7	105	86
7	**6a**	C_6H_5	5	241	85
8	**6b**	C_6H_5	7	160	88
9	**6c**	2,6-$C_6H_3F_2$	5	144	83
10	**6d**	2,6-$C_6H_3F_2$	7	156	87
11	**6e**	CF_3	5	99	81
12	**6f**	CF_3	7	116	80

experimental results except with CF_3. Kinetic stabilities suggest that, phenyl substituent favor O-propargylated quinazolines **2**, CF_3 and 2,6-F_2Ph substituents favor N-propargylated quinazolines is inconsistent with the experimental results except with the 2,6-difluorophenyl substituent. This may be attributed to the small difference in the activation energies 0.4–1.3 kcal/mol and large difference in reaction energies 6–7 kcal/mol for CF_3 and Ph which promote uneven trends. In case of 2,6-F_2Ph substituent, the difference in reaction energies of two isomers is almost 10 kcal/mol which has resulted in exclusive formation of N-propargylated quinazoline derivative. Further [3 + 2] cycloaddition reaction between propargylated quinazolines and alkyl azides are analysed. Theoretical studies on such molecules using Cu as catalyst, along with the mechanism are well established [45]. The alkyl tagged bulky group on the azide nitrogen is replaced with simple alkyl group i.e., 'C_2H_5' for easier computation. Activation energy $\Delta E^{\ddagger}$ and reaction energy ΔE_r values are in kcal/mol given in Table 4.

The theoretical results suggest that, the formation of *anti* product is more feasible and stable than *syn* both kinetically and thermodynamically. This might be mainly due to the steric repulsions arising due to the bulky fluorous alkyl tag attached to the triazole ring.

Table 4
Activation $E^{\ddagger}$, reaction energy E_r values in kcal/mol of **4a, c, e** and **6a, c, e**.

Compd. no.	Conformation	$\Delta E^{\ddagger}$	ΔE_r
4a	Syn	17.00	−70.4
4a	Anti	16.57	−73.0
4c	Syn	16.62	−72.1
4c	Anti	16.44	−73.2
4e	Syn	16.83	−70.6
4e	Anti	16.72	−73.0
6a	Syn	17.64	−70.5
6a	Anti	16.79	−76.8
6c	Syn	19.13	−69.5
6c	Anti	16.74	−75.0
6e	Syn	17.32	−70.7
6e	Anti	17.06	−74.7

4. Antimicrobial activity

4.1. In vitro antibacterial assays

Compounds **2a**, **3a**, **4a–d**, **5b**, **6a–f** were dissolved in acetone and screened for *in vitro* antibacterial activity against gram-positive (*Bacillus subtilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*) and gram-negative (*Pseudomonas aeruginosa*, *Escherichia coli*) bacteria. Compounds **4c** and **5b** showed significant activity against all species of gram-positive and gram-negative bacteria except *E. coli*. Compounds **3a**, **4a–b**, **6a–b** and **6d–f** showed moderate activity and **2a**, **4d** and **6c** showed the least activity. The regioisomer **3a** is more active than compound **2a** and **5b** is more active than compound **4b** against all the bacterial species. The compound **4c** is identified as most active compound. The MIC values of the compounds were compared with those obtained with penicillin and streptomycin. Compound **4c** and **5b** are considered as interesting lead compounds. The details of compounds and their activity profile against various microorganisms are tabulated in Table 5.

4.2. In vitro antifungal activity assays

The *in vitro* antifungal activity of compounds **2a**, **3a**, **4a–d**, **5b**, **6a–f** were screened against the fungal strains, viz., *Candida albicans* (MTCC 227), *Saccharomyces cerevisiae* (MTCC 36) and filamentous fungal cultures like *Rhizopus oryzae* (MTCC 262), *Aspergillus niger* (MTCC 1344), *Aspergillus flavus* (MTCC 277), *Candida rugosa* (NCIM 3462) by agar cup diffusion method. The strains were obtained from the Institute of Microbial Technology, Chandigarh. Compounds **3a**, **6a**, **6e** showed promising activity against most of the fungi at 100 μg/ml. It is found that the inhibition diameter increases with concentration. Compound **4d** is inactive against all the fungal cultures except for *C. albicans* (MTCC 227) and *C. rugosa* (NCIM 3462). The regioisomer **5b** is more active than **4b** and **3a** is more active than **2a**. However, all the compounds **2a**, **4d** and **6c** are

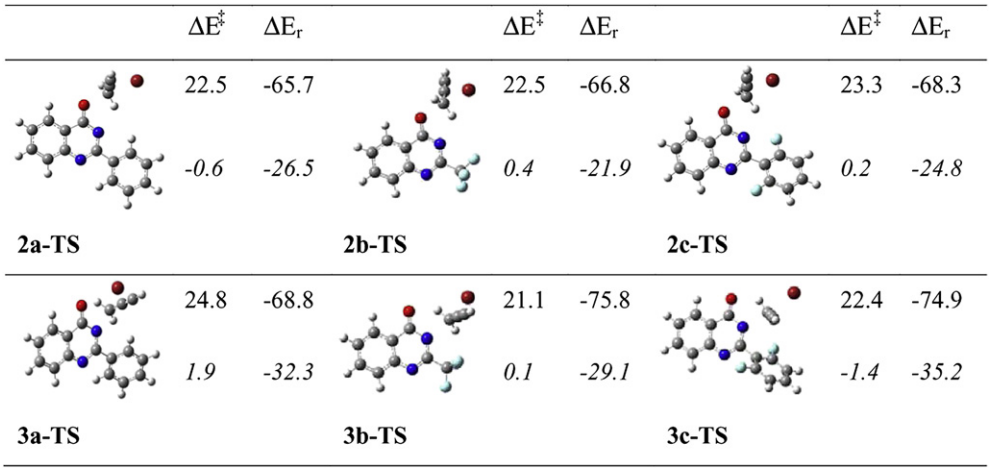


Fig. 1. Structures of the compounds **2a–c**, **3a–c** in their Transition State TS and their activation energy ($\Delta E^{\ddagger}$) and reaction energy (ΔE_r) respectively in gas (normal) and solvent (italics) phases respectively. All the energy values are in kcal/mol.

Table 5
Minimum inhibitory concentration (MIC in μg/ml) of compounds **2a**, **3a**, **4a–d**, **5b**, **6a–f** against various bacterial microorganisms.

Entry	Compd. no.	Gram-positive strains			Gram-negative strains	
		B. subtilis	*S. aureus*	*S. epidermidis*	*E. coli*	*P. aeruginosa*
1	**2a**	150	150	150	150	150
2	**3a**	37.5	37.5	37.5	75	37.5
3	**4a**	150	75	75	75	75
4	**4b**	150	150	150	150	75
5	**4c**	18.75	9.375	9.375	75	37.5
6	**4d**	150	150	150	150	150
7	**5b**	37.5	9.375	9.375	75	37.5
8	**6a**	150	150	150	75	37.5
9	**6b**	150	75	75	15	75
10	**6c**	150	150	150	150	150
11	**6d**	150	150	150	75	75
12	**6e**	150	150	150	75	75
13	**6f**	150	75	75	75	75
14	Streptomycin	6.25	1.56	1.562	3.125	3.125
15	Penicillin	1.526	6.25	3.125	6.25	12.5

Negative control; acetone showed no activity.

6. Experimental

6.1. Chemistry

6.1.1. General methods

Melting points were recorded on Casia-siamia (VMP-AM) melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer FT-IR 240-C spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Gemini varian 200 MHz, Bruker AV 300 MHz and Unity 400 MHz spectrometer in DMSO-d_6 or $CDCl_3$ using TMS as an internal standard. Electron impact (EI) and chemical ionisation mass spectra were recorded on a VG 7070 H instrument at 70 eV. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F_{254} (mesh); Spots were visualized with UV light. Merck silica gel (100–200 mesh) was used for chromatography. CHN analyses were recorded on a Vario EL analyser. Five bacterial test organisms such as *B. subtilis* (MTCC 441), *S. aureus* (MTCC 96), *S. epidermidis* (MTCC 435), *E. coli* (MTCC 443) and *P. aeruginosa* (MTCC 741) were selected and obtained from the Institute of Microbial Technology, Chandigarh.

Table 6
Zone of Inhibition (in mm) of compounds **2a**, **3a**, **4a–d**, **5b**, **6a–f** for various fungal cultures at two concentration levels.

Entry	Compd.	*C. albicans* (μg/ml)		*S. cerevisiae* (μg/ml)		*R. oryzae* (μg/ml)		*A. niger* (μg/ml)		*A. flavus* (μg/ml)		*C. rugosa* (μg/ml)	
		30	100	30	100	30	100	30	100	30	100	30	100
1	**2a**	7	10	–	–	–	–	7	10	–	–	–	–
2	**3a**	7	10	9	12	8	12	7	10	9	12	8	12
3	**4a**	8	11	–	9	–	–	8	11	–	9	–	–
4	**4b**	7	10	7	10	–	10	7	10	7	10	–	10
5	**4c**	8	12	–	9	–	9	8	12	–	9	–	9
6	**4d**	–	9	–	–	–	–	–	9	–	–	–	–
7	**5b**	8	12	–	9	–	12	8	12	–	9	–	12
8	**6a**	9	12	8	12	–	10	9	12	8	12	–	10
9	**6b**	–	9	–	9	–	10	–	9	–	9	–	10
10	**6c**	7	10	–	–	–	–	7	10	–	–	–	–
11	**6d**	7	10	–	9	–	9	7	10	–	9	–	9
12	**6e**	–	9	9	12	8	13	–	9	9	12	8	13
13	**6f**	7	9	–	9	–	–	7	9	–	9	–	–
14	Amphotericin-B (50 μg/ml)	23.5	22	24	25	25	22						

Negative control; acetone showed no activity; well or cup method; the concentrations are expressed in μg/ml and inhibitory zone diameters are expressed in mm.

inactive against all fungal cultures except for *C. albicans* upto a maximum concentration of 100 μg/ml. The compounds **3a** and **6e** are identified as most active compounds. The inhibitory zone diameters of the compounds are compared with those obtained with 50 μg/ml of standard amphotericin. The details of the results have been tabulated in Table 6.

5. Conclusion

A series of novel perfluoroalkyl-1H-1,2,3-triazol-4-yl substituted O-/N-quinazolines **4**, **5** and **6** was synthesized from quinazolinones via propargylation followed by Click reaction. Theoretical interpretations based on computational studies were calculated for the formation of compounds **2** and **3** and are validated by experiments. All the compounds were screened against gram-positive, gram-negative bacterial strains and also fungal strains. Compounds **4c** and **5b** showed significant activity against bacterial strains and compounds **3a**, **6a** and **6e** showed promising activity against fungi.

*6.1.1.1. Preparation of 2-phenyl quinazoline-4 (3H)-one (**1a**).* Ref. [31].

*6.1.1.2. Preparation of 2-(trifluoromethyl) quinazoline-4 (3H)-one (**1b**).* Ref. [42].

*6.1.1.3. Preparation of (2,6-difluorophenyl) quinazolin-4(3H)-one (**1c**).* The 2-(2,6-difluorophenyl)-4H-benzo(d) (1,3) oxazin-4-one (0.5 g, 1.93 mmol) was treated with aqueous ammonia at room temperature while stirring for 4 h. Excess ammonia was removed by evaporation and quenched with water. The solid obtained was filtered and crude product 2-(2,6-difluoro phenylamido) benzamide thus formed was refluxed in presence of aq. NaOH for 2 h. The reaction mixture was neutralized with acid and separated solid product was filtered, washed with water and dried. The crude product was purified passing through a column packed with silica gel (mesh 60/120) and solvents hexane: ethyl acetate (90:10) as eluents. Yield: 0.42 g (85%); m.p: 234 °C; IR (KBr, cm^{-1}): 1675 (lactam CO), 1553 (C=N), 1457 (C=C); ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.00–7.18 (t, $J = 11.53$ Hz, 2H, Ar–H), 7.57–7.77 (quintet, $J = 7.69$ Hz, 2H, Ar–H), 7.70–7.82 (quintet, $J = 7.69$ Hz, 2H, Ar–H),

8.20–8.30 (*d*, $J = 15.38$ Hz, 1H, Ar–H), 12.60 (s, 1H, NH); EIMS, *m/z*: 259 ($M^+ + 1$); IR (KBr): 1675 (CO) cm^{-1}, 3230 (NH) cm^{-1}. Anal. Calcd. for $C_{14}H_8F_2N_2O$: C, 65.13; H, 3.10; N, 10.85%. Found: C, 65.34; H, 3.39; N, 10.66%.

6.2. Synthesis of 2-substituted-4-(prop-2-ynyloxy) quinazoline (**2a**, **2b**) and 2-substituted-3-(prop-2-ynyl) quinazolin-4(3H)-ones (**3a–c**)

6.2.1. General procedure

Quinazolin-4-one **1** (0.01 mol) was dissolved in acetone (15 ml), K_2CO_3 (0.02 mol), NaI (5 mg) was added. Then, propargyl bromide (0.015 mol) was slowly added drop wise over a period of 15 min at room temperature. Reaction mixture was refluxed for 3–4 h and solvent was removed under reduced pressure. The residue was washed with *n*-hexane repeatedly to remove excess propargyl bromide, added distilled water to remove excess potassium carbonate and solid product separated was filtered, purified by eluting through column using 2% ethyl acetate in *n*-hexane for O-propargylated compound **2** and 8% ethyl acetate in *n*-hexane for N-propargylated compound **3**.

*6.2.1.1. 2-phenyl-4-(prop-2-ynyloxy) quinazoline (**2a**).* Ref. [42].

*6.2.1.2. 4-(prop-2-ynyl)-2-(trifluoromethyl) quinazolin-4-(3H)-one (**2b**).* Ref. [42].

*6.2.1.3. 2-phenyl-3-(prop-2-ynyl) quinazolin-4(3H)-one (**3a**).* Ref. [42].

*6.2.1.4. 3-(prop-2-ynyl)-2-(trifluoromethyl) quinazolin-4-(3H)-one (**3b**).* Ref. [42].

*6.2.1.5. 2-(2,6-difluorophenyl)-3-(prop-2-ynyl) quinazolin-4(3H)-one (**3c**).* Yield: 2.55 g (86.25%); m.p. 133 °C; IR (KBr, cm^{-1}): 1681 (lactam CO), 1593 (C═N), 1472 (C═C); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.35–2.45 (1H, s, C≡CH), 4.68–4.79 (2H, s, CH_2), 7.10–7.25 (2H, m, Ar–H), 7.60–7.69 (3H, m, Ar–H), 7.79–7.89 (1H, m, Ar–H), 8.29–8.39 (1H, d, $J = 12.90$ Hz, Ar–H); EIMS, *m/z*: 297 ($M^+ + 1$); Anal. calcd. for $C_{17}H_{10}F_2N_2O$: C, 68.92; H, 3.40; N, 9.46%. Found: C, 68.73; H, 3.32; N, 9.27%.

6.3. Synthesis of perfluoroalkyl-1H,1,2,3-triazol-4-yl substituted O-, N-quinazolines (**4a–d**), (**5a–b**), (**6a–f**)

6.3.1. General procedure

The propargylated quinazoline **2** or **3** (0.45 mmol) was dissolved in dry THF and CuI (0.025 mmol) was added. Then, 10-azido-1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-heptadecafluorodecane/8-azido-1,1,1,2,2,3,3,4,4,5,5,6,6,-trideca fluorooctane (0.45 mmol) in dry THF was slowly added over a period of 30 min at room temperature under nitrogen atmosphere and continued stirring overnight. The solvent was removed under reduced pressure, the residue was diluted with distilled water and extracted thrice with ethyl acetate. The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated to get the product. The crude product thus obtained was purified by column chromatography after its adsorption onto silica gel (60/120) using 8% ethyl acetate in hexane to separate O-isomer and 20% ethyl acetate in hexane to separate N-isomer.

*6.3.1.1. 2-Phenyl-4-((1-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)-1H-1,2,3-triazol-4-yl)methoxy) quinazoline (**4a**).* Yield: 0.134 g (46.0%); m.p. 118 °C; IR (KBr, cm^{-1}): 1577 (C═N), 1422 (C═C), 1239 (C–O–C); ^{1}H NMR (300 MHz, Acetone-d_6): δ 2.78–2.87 (2H, m, CH_2), 4.68–4.78 (2H, *t*, $J = 10.74$ Hz, CH_2), 5.80 (2H, s, OCH_2), 7.20–7.31 (1H, *d*, $J = 20$ Hz, Ar–H), 7.40–7.51 (3H, m, Ar–H, 1H, *t*, $J = 10.64$ Hz, Ar–H, 1H, s, Ar–H (triazole)), 7.72–7.79 (1H, m, Ar–H), 7.88–7.95 (1H, d, $J = 20$ Hz, Ar–H), 8.10–8.81 (1H, d, $J = 20$ Hz, Ar–H), 8.51–8.62 (1H, m, Ar–H); EIMS, *m/z*: 650 ($M^+ + 1$); Anal. calcd. for $C_{25}H_{16}F_{13}N_5O$: C, 46.19; H, 2.48; N, 10.78%. Found: C, 46.33; H, 2.56; N, 10.90%.

6.3.1.2. 2-Phenyl-4-((1-(3,3,4, 4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)-1H-1,2,3-triazol-4-yl)methoxy) quinazoline (4b). Yield: 0.158 g (47.0%); m.p. 128 °C; IR (KBr, cm^{-1}): 1577 (C═N), 1497 (C═C), 1239 (C–O–C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.78–2.98 (2H, m, CH_2), 4.65–4.75 (2H, *t*, $J = 10.74$ Hz, CH_2), 5.85 (2H, s, OCH_2), 7.42–7.55 (3H, m, Ar–H, 1H, *t*, $J = 6.2$ Hz, Ar–H, 1H, s, Ar–H (triazole)), 7.75–7.85 (1H, *t*, $J = 10.74$ Hz, Ar–H), 7.95–8.00 (1H, d, $J = 8.03$ Hz, Ar–H), 8.13–8.20 (1H, d, $J = 8.0$ Hz, Ar–H), 8.58–8.65 (2H, m, Ar–H); EIMS, *m/z*: 750 ($M^+ + 1$); Anal. calcd. for $C_{27}H_{16}F_{17}N_5O$: C, 43.27; H, 2.15; N, 9.35%. Found: C, 43.01; H, 2.05; N, 9.18%.

*6.3.1.3. 4-((1-(3,3,4, 4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(trifluoromethyl) quinazoline (**4c**).* Yield: 0.244 g (84.77%); m.p. 93 °C; IR (KBr, cm^{-1}): 1572 (C═N), 1499 (C═C), 1200 (C–O–C); ^{1}H NMR (300 MHz, Acetone-d_6): δ 2.80–2.83 (2H, m, CH_2), 4.41–4.70 (2H, *t*, $J = 9.67$ Hz, CH_2), 5.44 (2H, s, OCH_2), 7.31–7.62 (1H, m, Ar–H), 7.71 (1H, s, Ar–H), 7.62–7.81 (2H, d, $J = 12.90$ Hz Ar–H), 8.12–8.30 (1H, d, $J = 15$ Hz, Ar–H); EIMS, *m/z*: 642 ($M^+ + 1$); Anal. calcd. for $C_{20}H_{11}F_{16}N_5O$: C, 37.46; H, 1.73; N, 10.92%. Found: C, 37.30; H, 1.61; N, 10.77%.

*6.3.1.4. 4-((1-(3,3,4, 4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(trifluoro methyl) quinazoline (**4d**).* Yield: 0.286 g (85.91%); m.p. 105 °C; IR (KBr, cm^{-1}): 1595 (C═N), 1510 (C═C), 1225 (C–O–C); ^{1}H NMR (300 MHz, Acetone-d_6): δ 2.72–2.99 (2H, m, CH_2), 4.50–4.80 (2H, *t*, $J = 10$ Hz, CH_2), 5.45 (2H, s, OCH_2), 7.41–7.72 (1H, m, Ar–H), 7.75 (1H, s, Ar–H), 7.64–7.85 (2H, d, $J = 10$ Hz, Ar–H), 8.18–8.39 (1H, d, $J = 15$ Hz, Ar–H); EIMS, *m/z*: 742 ($M^+ + 1$); Anal. calcd. for $C_{22}H_{11}F_{20}N_5O$: C, 35.64; H, 1.50; N, 9.45%. Found: C, 35.50; H, 1.39; N, 9.39%.

*6.3.1.5. 2-Phenyl-4-((3-(3,3,4, 4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)-3H-1,2,3-triazol-4-yl)methoxy) quinazoline (**5a**).* Yield: 0.117 g (40.10%); m.p. 125 °C; IR (KBr, cm^{-1}): 1566 (C═N), 1422 (C═C), 1239 (C–O–C); ^{1}H NMR (300 MHz, Acetone-d_6): δ 2.69–2.91 (2H, m, CH_2), 4.55–4.66 (2H, m, CH_2), 5.79 (2H, s, OCH_2), 7.15–7.21 (1H, d, $J = 20$ Hz, Ar–H), 7.37–7.48 (3H, m, Ar–H, 1H, *t*, $J = 10.24$ Hz, Ar–H, 1H, s, Ar–H (triazole)), 7.60–7.79 (1H, m, Ar–H), 7.89–7.95 (1H, d, $J = 20$ Hz, Ar–H), 8.08–8.12 (1H, d, $J = 20$ Hz, Ar–H), 8.50–8.60 (1H, m, Ar–H); EIMS, *m/z*: 650 ($M^+ + 1$); Anal. calcd. for $C_{25}H_{16}F_{13}N_5O$: C, 46.24; H, 2.48; N, 10.78%. Found: C, 46.02; H, 2.28; N, 10.59%.

*6.3.1.6. 2-Phenyl-4-((3-(3,3,4, 4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)-3H-1,2,3-triazol-4-yl) methoxy) quinazoline (**5b**).* Yield: 0.128 g (38.00%); m.p. 149 °C; IR (KBr, cm^{-1}): 1577 (C═N), 1460 (C═C), 1210 (C–O–C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.66–2.88 (2H, m, CH_2), 4.51–4.61 (2H, *t*, $J = 15$ Hz, CH_2), 5.89 (2H, s, OCH_2), 7.38–7.49 (4H, m, Ar–H), 7.68–7.79 (2H, m, Ar–H), 7.89–7.95 (1H, d, $J = 20$ Hz, Ar–H), 8.07–8.11 (1H, d, $J = 20$ Hz, Ar–H), 8.50–8.60 (2H, d, $J = 20$ Hz, Ar–H); EIMS, *m/z*: 750 ($M^+ + 1$); Anal. calcd. for $C_{27}H_{16}F_{17}N_5O$: C, 43.27; H, 2.15; N, 9.35%. Found: C, 42.02; H, 2.03; N, 9.02%.

*6.3.1.7. 2-Phenyl-3-((1-(3,3,4, 4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)-1H-1,2,3-triazol-4-yl)methyl) quinazolin-4(3H)-one (**6a**).* Yield: 0.248 g (85.21%); m.p. 241 °C; IR (KBr, cm^{-1}): 1678 (lactam CO), 1606 (C═N), 1496 (C═C); ^{1}H NMR (300 MHz, Acetone-d_6): δ 2.85–

3.00 (2H, m, CH_2), 4.61–4.83 (2H, m, CH_2), 5.25 (2H, s, NCH_2), 7.40–7.61 (4H, m, Ar–H), 7.57–7.78 (3H, m, Ar–H), 7.74–7.95 (1H, *t*, $J = 10.34$ Hz, Ar–H), 7.99 (1H, s, Ar–H), 8.13–8.41 (1H, m, Ar–H); EIMS, *m/z*: 650 ($M^+ + 1$); Anal. calcd. for $C_{25}H_{16}F_{13}N_5O$: C, 46.24; H, 2.48; N, 10.78%. Found: C, 46.09; H, 2.28; N, 10.60%.

*6.3.1.8. 2-Phenyl-3-((1-(3,3,4, 4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)-1H-1,2,3-triazol-4-yl)methyl) quinazolin-4(3H)-one (**6b**).* Yield: 0.297 g (88.12%); m.p. 160 °C; IR (KBr, cm^{-1}): 1677 (lactam CO), 1585 (C═N), 1473 (C═C); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.61–2.81 (2H, m, CH_2), 4.61–4.80 (2H, *t*, $J = 10$ Hz, CH_2), 5.19 (2H, s, NCH_2), 7.47–7.66 (6H, m, Ar–H), 7.63–7.77 (1H, d, $J = 13.34$ Hz, Ar–H), 7.78–7.97 (1H, *t*, $J = 10$ Hz, Ar–H), 8.15–8.30 (2H, d, $J = 20$ Hz, Ar–H); EIMS, *m/z*: 750 ($M^+ + 1$); Anal. calcd. for $C_{27}H_{16}F_{17}N_5O$: C, 43.27; H, 2.15; N, 9.35%. Found: C, 43.01; H, 2.08; N, 9.26%.

*6.3.1.9. 2-(2,6-difluorophenyl)-3-((1-(3,3,4, 4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)-1H-1,2,3-triazol-4-yl)methyl) quinazolin-4(3H)-one (**6c**).* Yield: 0.256 g (83.20%); m.p. 144.0 °C; IR (KBr, cm^{-1}): 1676 (lactam CO), 1596 (C═N), 1471 (C═C); ^{1}H NMR (200 MHz, Acetone-d_6): δ 2.80–3.00 (2H, m, CH_2), 4.65–4.76 (2H, *t*, $J = 9.67$ Hz, CH_2), 5.19 (2H, s, NCH_2), 7.10–7.20 (2H, *t*, $J = 12.90$ Hz, Ar–H), 7.51–7.70 (3H, m, Ar–H), 7.75–7.84 (1H, d, $J = 12.90$ Hz, Ar–H), 7.90 (1H, s, Ar–H), 8.20–8.30 (1H, d, $J = 12.90$ Hz, Ar–H); EIMS, *m/z*: 686 ($M^+ + 1$); Anal. calcd. for $C_{25}H_{14}F_{15}N_5O$: C, 43.81; H, 2.06; N, 10.22%. Found: C, 43.65; H, 1.94; N, 10.08%.

*6.3.1.10. 2-(2,6-difluorophenyl)-3-((1-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)-1H-1,2,3-triazol-4-yl)methyl) quinazolin-4(3H)-one (**6d**).* Yield: 0.305 g (86.50%); m.p. 156.0 °C; IR (KBr,cm^{-1}): 1675 (lactam CO), 1595 (C═N), 1472 (C═C); ^{1}H NMR (300 MHz, Acetone-d_6): δ 2.90–3.00 (2H, m, CH_2), 4.74–4.85 (2H, *t*, $J = 9.67$ Hz, CH_2), 5.28 (2H, s, NCH_2), 7.15–7.24 (2H, m, Ar–H), 7.50–7.61 (1H, m, Ar–H), 7.65–7.74 (3H, m, Ar–H), 7.94–8.10 (1H, d, $J = 10$ Hz, Ar–H), 8.28–8.37 (1H, m, Ar–H); EIMS, *m/z*: 786 ($M^+ + 1$); Anal. calcd. for $C_{27}H_{14}F_{19}N_5O$: C, 41.29; H, 1.80; N, 8.92%. Found: C, 41.35; H, 1.92; N, 9.01%.

*6.3.1.11. 3-((1-(3,3,4, 4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)-1H-1,2,3-triazol-4-yl)methyl)-2-(trifluoromethyl) quinazolin-4(3H)-one (**6e**).* Yield: 0.234 g (81.15%); m.p. 99 °C; IR (KBr, cm^{-1}): 1695 (lactam CO), 1612 (C═N), 1472 (C═C); ^{1}H NMR (300 MHz, Acetone-d_6): δ 2.95–3.04 (2H, m, CH_2), 4.65–4.73 (2H, *t*, $J = 10.34$ Hz, CH_2), 5.80 (2H, s, NCH_2), 7.76–7.85 (1H, m, Ar–H), 8.03–8.11 (2H, m, Ar–H), 8.25–8.35 (2H, *t*, $J = 15$ Hz, Ar–H); EIMS, *m/z*: 642 ($M^+ + 1$); Anal. calcd. for $C_{20}H_{11}F_{16}N_5O$: C, 37.46; H, 1.73; N, 10.92%. Found: C, 37.61; H, 1.85; N, 10.80%.

*6.3.1.12. 3-((1-(3,3,4, 4,5,5,6,6,7,7,8,8, 9,9,10,10,10-heptadecafluoro decyl)-1H-1,2,3-triazol-4-yl)methyl)-2-(trifluoromethyl) quinazolin-4(3H)-one (**6f**).* Yield: 0.267 g (80.20%); m.p. 116 °C; IR (KBr, cm^{-1}): 1695 (lactam CO), 1616 (C═N), 1429 (C═C); ^{1}H NMR (300 MHz, Acetone-d_6): δ 3.05–3.16 (2H, m, CH_2), 4.80–4.90 (2H, *t*, $J = 15$ Hz, CH_2), 5.85 (2H, s, NCH_2), 7.75–7.86 (1H, m, Ar–H), 8.05–8.14 (2H, m, Ar–H), 8.24–8.32 (2H, *t*, $J = 15$ Hz, Ar–H).EIMS, *m/z*: 742 ($M^+ + 1$); Anal. calcd. for $C_{22}H_{11}F_{20}N_5O$: C, 35.64; H, 1.50; N, 9.45%. Found: C, 35.71; H, 1.60; N, 9.62%.

6.4. Antimicrobial activity

6.4.1. Antibacterial activity: procedure

Five bacterial test organisms such as *B. subtilis* (MTCC 441), *S. aureus* (MTCC 96), *S. epidermidis* (MTCC 435), *E. coli* (MTCC 443) and *P. aeruginosa* (MTCC 741) were selected and obtained from the Institute of Microbial Technology, Chandigarh. Cultures of test organisms were maintained on Nutrient agar slants and were sub-cultured in Petri dishes prior to testing. The media used was Nutrient agar, Nutrient broth procured from Himedia Laboratories, Mumbai. The minimum inhibitory concentration was determined by broth dilution method [46].

6.4.2. Antifungal activity: procedure

Antifungal activity is studied by agar cup diffusion method [46]. The readymade potato dextrose agar (PDA) medium (Himedia, 39 g) was suspended in distilled water (1000 ml) and heated to boiling until it dissolved completely. The medium and Petri dishes were autoclaved at pressure of 15 lb/inch for 20 min. Agar cup bioassay was employed for testing antifungal activity. The medium was poured into sterile Petri dishes under aseptic conditions in a laminar flow chamber. When the medium in the plates solidified, 0.5 ml of (week old) culture of test organism was inoculated and uniformly spread over the agar surface with a sterile L-shaped rod. Solutions were prepared by dissolving the compound in acetone and different concentrations (30 μg/ml, 100 μg/ml) were made. After inoculation, cups were scooped out with 6 mm sterile cork borer and the lids of the dishes were replaced. To each cup, different concentrations (30 μg/ml, 100 μg/ml) of test solutions were added. Controls were maintained with acetone and amphotericin-B (50 μg/ml). The treated and the controls were kept at 28 °C for 48 h. Inhibition zones were measured and the diameter was calculated in millimeter.

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