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Synthesis, characterization and biological evaluation of novel 3-amino-1-(phenyl) benzo[*f*]quinoline-3-carbonitrile derivatives

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Abstract
A series of 3-amino-1(phenyl) benzo[*f*]quinoline-3-carbonitrile derivatives were synthesized by one pot Multi Component Reactions (MCRs) with different aromatic aldehyde, 2-Napthylamine and malononitrile using iodine and l-proline as catalyst. The main advantages for present high efficient method are short reaction time and higher yield. All of the synthesized compounds were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, Mass spectroscopy. Antibacterial and antifungal potential of the synthesized derivatives was studied against various bacterial and fungal strains respectively. Few derivatives were found to exhibit good antimicrobial activity.

Keywords: benzo[*f*]quinoline, iodine, aldehyde, malononitrile, 2-Napthylamine, L-proline

Introduction
A new series of Novel 3-amino-1-(phenyl)benzo[f]quinoline-3-carbonitrile analogues was designed and synthesized as microbial inhibitors using quinoline as the lead compounds. One approach to discourse this task involves the development of multi component reactions (MCRs), whereby three or more reactants are clubbed together in a sequential manner to give highly selective products that retain majority of the atoms of the starting material. A general and efficient procedure is described for one pot three component intra-molecular cyclization of 2-napthylamine, aldehydes and malononitrile in methanol or ethanol within very shorter reaction times and higher yield. The catalytic activity of L-proline or iodine in these reactions was tested over a set of aldehydes and amines, signifying that it is reactive in the direction of a variety of functionalities. Multi component reactions (MCRs) have been proven to be a powerful and efficient tool with the main benefits of atom economy, low waste, as well as of the time and work required to carry them out and furnishing diverse molecules for optimization processes for drug discovery research.

The benzo[*f*]quinoline moiety is an vital structural unit in naturally occurring quinolone alkaloids [1], therapeutics, and synthetic analogues with stimulating biological activities [2]. Mutagenicity and tumorigenicity [3], Anticonvulsant Activity, Cardiovascular Activity [4], Anti-inflammatory Activity [5], Antimicrobial Activity [6], antitubercular agents [7], Anticancer [8], antibacterial activity [9], antifungal activity [10], analgesic [11], Antimycobacterial activity, antiallergeticagents [12], in conduct alzheimer's disease [13], so quinoline ring system is of concern in synthetic and medicinal chemistry.

Previously we studied the synthesis of compounds of benzo[f]quinoline series ported by Wang and co-workers synthesized benzoquinoline by the condensation of malononitrile with aromatic aldehydes and tetrahydropyran-4-onein the presence of iodine [14]. 2-naphthylamine, aldehydes and ethyl acetoacetate condense to benzo[f]quinoline by Abu T. Khan [15]. N. G. Kozlov and co-workers synthesis of benzo[f]quinolone by condention of substituted benzaldehydes, 3-acetylpyridine and acetophenone [16-17]. Spiro[benzo [*f*]quinolone-3,3-indoline] formed by Isatin, naphthalen-1-amine, dialkylbut-2-ynedioate, and antimony trichloride as catalyst by Rajiv karmakar and co- workers [18]. We report here the synthesis of these potentially active compounds using malononitrile, aromatic aldehyde and 2-napthylamine as reactants to construct novel series of benzo[*f*]quinolone derivatives bearing cyano substituent [20].

Experimental

Methods, materials and physical measurements

The reagents and solvents used for the synthesis were procured from Merck ltd., SD fine chemicals and LOBA chemie. The melting points of the final derivatives were determined by melting point apparatus using open end capillary method. TLC plates purchased from Merck (TLC silica gel 60 F_{254}) were used for monitoring the completion of reaction. The elemental data were collected using Perkin-Elmer 2400 CHN analyser. IR spectra analysis was obtained using Bruker FT-IR alpha-t (ATR) instrument. Mass spectra data for each derivative was determined using Schmiadzu mass spectrophotometer. and ^{13}CNMR data were obtained using Bruker spectrometer-100MHz.

General procedures for the Synthesis of 2-methyl-4-(phenyl) benzo[f]quinoline-3-carbonitrile derivatives

A mixture of substituted aldehyde (0.01 mol), malononitrile (0.01 mol) and 2- naphthylamine (0.01 mol) in methanol (8 mL) with catalytic amount of iodine (0.0001 mol) was stirred at room temperature for 15 minutes, and then reaction mixture was refluxed for 5 hrs. The completion of reaction was monitored periodically by TLC using toluene/acetone (8:2 v/v) as mobile phase. After completion of reaction, the reaction mixture was kept overnight at room temperature. The obtained crystals were filtered and collected.

General procedures for the Synthesis of 2-methyl-4-(phenyl) benzo[f]quinoline-3-carbonitrile derivatives

A mixture of substituted aldehyde (0.01 mol), malononitrile (0.01 mol) and 2- naphthylamine (0.01 mol) in methanol (8 mL) with catalytic amount of l-proline (0.0005 mol) was stirred at room temperature for 15 minutes and then reaction mixture was refluxed for 8 hour. After completion of reaction, the reaction mixture was kept overnight at room temperature and crystals were collected.

Results & Discussion

Chemistry

The synthesis of aim molecules was accomplished by multicomponent reactions (MCRs). Synthesis of 3-amino-1-(2-chlorophenyl)benzo[f]quinoline-2-carbonitrile(C_2) was obtained by cyclocondensation synthesis of 2-chlorobenzaldehyde(0.01 mol), malononitrile(0.01 mol), 2-naphthylamine (0.01 mol) with iodine(0.0001 mol) or l-proline (0.0005 mol) as catalyst was dissolved in methanol (8 ml) into the Round bottle flask and stirring at room temperature for 15 minute precipitate was obtain then reaction mixture was refluxed (Monitored by TLC analysis, Toluene/Acetone (8:2)). After completion of reaction put the reaction on the overnight at room temperature, crystals was formed and filter it.

Characterization

IR data

In IR spectrum of titled compound C_2 shows a sharp absorption peak at 3330cm^{-1} to confirmed the presence of primary amine (-NH_2) group. The stretching band of the nitrile (-CN) group is confirmed by the peak obtain at 2412 cm^{-1}. A sharp peak at 1578 cm^{-1} helped to assign the titled compound is aromatic. A sharp peak of 745 cm^{-1} was representing ortho-disubsitiuted aromatic ring. The presence of chloro (-Cl) group was also confirmed by the sharp absorption band at 691 cm^{-1}. The IR spectrum provides a valuable tool for probing the structure of organic molecules.

^{1}H NMR

In ^{1}HNMR spectra, the presence of hydrogen atoms of primary amine (-NH_2) is confirmed by singlet peak at δ 4.44 ppm in the compound C_2. The aromatic protons in titled compounds C_2 are obtained between δ values 7.61-8.37 ppm.

^{13}C NMR

The carbon atom of the nitrile group (-CN) showed a peak at δ value 123.03 ppm. The δ value at 188.9 ppm peak represented carbon attached with amine. The δ value of benzo[f] quinoline ring was between 124.6 to 141.4 ppm.

Mass Spectra

In mass spectra, the molecular ion peak observed at m/z 330 (329) to confirmed the final compound C_2.

Biological evaluation

In silico study

Lipinski's rule of five was used to appraise the drug-likeness and calculate the essential factors to molecular properties for a drug pharmacokinetics, including ADME (absorption, distribution, metabolism and excretion). Molinspiration website-based software (www.molinspiration.com) was used to obtain certain molecular parameters. According to the Lipinski's rule of five, compounds with number of violations not more than 1 shows good bioavailability and bioactivity. Analysis of molecular structure of each derivative by Molinspiration are depicted in the table-2. The synthesize moiety has some hydrogen bond donors, which show less than 5. The target compound has hydrogen bond acceptors value (3-6) which is ≤ 10 and has molecular weight 295.35g/mol which is < 500 preferable. Besides we calculated the polar surface area (62.71- 108.53) was less than 140 and number of rotatable bonds (1–2), which should be less than 10, These values indicated that this series may present good bioavailability [19]. The prediction of bioactivity scores of these synthesized moiety were calculated by recording the activity scores, as good as Clotrimazole, Ciprofloxacin, Linezolid. Antibiotic drugs of properties like GPCR (G-protein coupled receptors ligand), KI (kinase inhibitor), PI (protease inhibitor), EI (enzyme inhibitor), ICM (ion channel modulator) and NRL (nuclear receptor ligand) are displayed in table-3.

Table 1: Physical properties of compounds:-

Sr. No	Substitution R	Molecular Formula	Molecular Weight g/mol	Melting point °C	Yield% iodine	Yield% l-proline
1	H	C20H12N3	295.33g/mol	207°C	68	60
2	2-Cl	$C_{20}H_{12}ClN_3$	329.78g/mol	144-48°C	80	70
3	4-Cl	C20H12ClN3	329.78g/mol	158°C	88	80
4	3-NO2	C20H12N4O2	340.33g/mol	205°C	62	64
5	2-NO2	C20H12N4O2	340.33g/mol	202°C	65	60
6	3-Cl	C20H12ClN3	329.78g/mol	160-64°C	85	70
7	4-OCH3	C21H15N3O	325.36g/mol	138°C	92	75
8	3-OH	C20H13N3O	311.33g/mol	140°C	54	58

Table 2: Essential factors to molecular properties for a drug pharmacokinetics

Compound	Molecular Weight	Atoms	H donor	lop P	H Acceptor	TPSA	Number of Rotatable Bonds	Volume	Violations
Clotrimazole	331.35	24	6	-0.70	2	74.57	3	285.46	0
Ciprofloxacin	344.85	25	2	5.47	0	17.83	4	309.52	1
Linezolid	337.5	24	7	0.92	1	71.11	4	295.40	0
1	295.35	23	3	4.64	2	62.71	1	267.43	0
2	329.79	24	3	5.27	2	62.71	1	280.96	1
3	329.79	24	3	5.31	2	62.71	1	329.79	1
4	340.34	26	6	4.57	2	108.53	2	290.76	0
5	340.34	26	6	4.55	2	108.53	2	290.76	0
6	329.79	24	3	5.29	2	62.71	1	280.96	1
7	325.37	25	4	4.69	2	71.94	2	292.97	0
8	311.34	24	4	4.13	3	82.94	1	275.44	0

Table 3: Bioactivity scores of compounds

No.	compound	GPCR ligand	Ion Channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Ref.	Clotrimazole	0.12	-0.04	-0.07	-0.19	-0.21	0.28
Ref.	Ciprofloxacin	0.17	0.30	0.14	-0.21	-0.13	0.42
Ref.	Linezolid	0.07	-0.14	-0.04	-0.46	0.46	0.12
1	H	0.15	-0.09	0.48	-0.26	-0.15	0.23
2	2-Cl	0.15	-0.10	0.49	-0.23	-0.16	0.19
3	4-Cl	0.14	-0.09	0.44	-0.26	-0.17	0.19
4	3-No2	-0.02	-0.14	0.31	-0.32	-0.25	0.11
5	2-NO2	-0.07	-0.15	0.27	-0.43	-0.30	0.05
6	3-Cl	0.14	-0.10	0.44	-0.24	-0.19	0.20
7	4-OCH3	0.09	-0.16	0.40	-0.25	-0.17	0.16
8	3-OH	0.18	-0.04	0.53	-0.09	-0.13	0.29

Antimicrobial activity

Zone of inhibition test was carried out aginst each strain of gram positive bacteria (*B. subtilis*), gram negative bacteria (*E. coli*) and fungi (*A. niger*). The results obtained were moderate in comparison to that of the standard drugs used against the same microbial strains as shown in table-4.

Table 4: Biological activity of compounds

Sample No	Gram Negative Baceria *E. coli*			Gram Positive Baceria *B. subtilis*			Fungi *A. niger*		
	Zone of Inhibition in mm			Zone of Inhibition in mm			Zone of Inhibition in mm		
	250 µg/ml	500 µg/ml	1000 µg/ml	250 µg/ml	500 µg/ml	1000 µg/ml	250 µg/ml	500 µg/ml	1000 µg/ml
1	12	14	14	8	-	-	-	6	11
2	-	-	-	-	-	-	11	15	10
3	12	14	18	-	-	-	10	7	5
4	8	10	7	7	8	10	11	13	9
5	9	10	-	-	10	12	10	11	7
6	10	8	9	8	8	10	5	-	-
7	-	-	-	-	-	-	5	10	11
8	12	12	-	-	-	-	-	-	-
Fluconazole	-	-	-	-	-	-	21	20	19
Ciprofloxacin	24	24	23	23	22	22	-	-	-

Characterization details

3-amino-1-phenylbenzo[*f*]quinoline-2-carbonitrile (C1) white solid; m.p.:170°C;IR (ATR): 3412, 3071, 2233,1610, 1540, 971, 703 cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$): δ_H 4.64 (s, 2H, -NH2),6.51-7.99 (m, 11H, Ar-H) ppm;^{13}C NMR (100 MHz, DMSO-d_6): δc 167.2, 93.1, 153.7, 110.3, 147.5, 125.2, 132.0, 129.1, 127.5, 127.3, 127.3, 127.5, 116.9,137.9, 127.4, 129.3, 129.3 ppm; MS (m/z): 317.50 [M^++Na].

3-amino-1-(2-chlorophenyl)benzo[*f*]quinoline-2-carbonitrile (C2) orange solid; m.p.:144-48°C; IR (ATR): 3057, 2412, 1578, 745, 691 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$):δ_H 4.44(s, 2H, -NH2),7.26- 8.37 (m, 10H, Ar-H) ppm;^{13}C NMR (100 MHz, DMSO-d_6): δc 167.2, 93.6, 110.3, 147.8, 125.2, 132.0, 123.1, 127.5, 127.3, 127.3, 127.5, 127.5, 116.9, 138.9, 132.1, 129.3, 130.7, 127.4, 128.8 ppm; MS (m/z): 330[M^++H].

3-amino-1-(4-chlorophenyl)benzo[*f*]quinoline-2-carbonitrile (C3)dark yellow solid; m.p.:158°C; IR (ATR): 3397,3033, 2221, 1633, 1528, 826, 703 cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$): δ_H 4.58 (s, 2H, -NH2),7.52-8.54 (m, 10H, Ar-H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δc 166.4, 95.1, 153.7, 110.3, 147.3, 125.5, 132.0, 129.3, 126.4, 127.2, 127.2, 127.5, 127.9, 115.7, 136.0, 128.8, 134.8, 129.3, 128.8 ppm; MS (m/z): 330.87 [M^+].

3-amino-1-(3-nitrophenyl)benzo[*f*]quinoline-2-carbonitrile (C4) light yellow solid; m.p.:235°C; IR (ATR): 3310,2952, 2213, 1626, 1528, 810, 702 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 5.32 (s, 2H, -NH_2),7.22-8.80 (m, 10H, Ar-H) ppm;^{13}C NMR (100 MHz, DMSO-d_6): δc 168.3, 91.7, 153.7, 112.5, 152.0, 125.2, 131.3, 128.5, 127.4, 127.4, 127.5, 114.8, 133.2, 122.7, 150.2, 124.4, 133.2 ppm; MS (m/z): 341.56 [M^+].

3-amino-1-(2-nitrophenyl)benzo[*f*]quinoline-2-carbonitrile (C5) light white solid; m.p.:222°C; IR (ATR): 2922, 2232, 1724, 1524, 1347, 750, 703 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 4.45 (s, 2H, $-NH_2$), 6.77-8.66 (m, 10H, Ar-H) ppm;^{13}C NMR (100 MHz, DMSO-d_6): δc 157.2, 102.2, 154.7, 113.2, 152.8, 125.7, 132.2, 132.2, 127.5, 125.7, 125.7, 125.4, 118.6, 133.6, 152.0, 133.4, 130.0 ppm; MS (m/z): 360.69 [M^++Na].

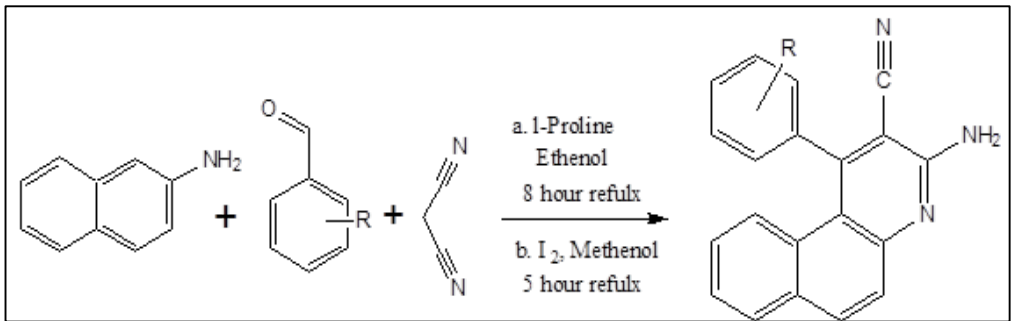
3-amino-1-(3-chlorophenyl)benzo[*f*]quinoline-2-carbonitrile (C6) brown solid; m.p.:160-64°C; IR (ATR): 3320, 2240, 1640, 1540, 792, 696 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 6.51 (s, 2H, $-NH_2$), 7.32-8.72(m, 10H, Ar-H) ppm;^{13}C NMR (100 MHz, DMSO-d_6): δc 167.2, 96.2, 162.2, 114.3, 147.8, 125.2, 132.0, 129.1, 128.3,128.3, 127.5, 115.2, 139.6, 127.4, 134.8, 129.3, 130.7, 125.5 ppm; MS (m/z): 351.86 [M^++Na].

3-amino-1-(4-methoxyphenyl) benzo[*f*]quinoline-2-carbonitrile (C7) green solid; m.p.:168°C; IR (ATR): 2925, 2216,1720,1610, 1274, 1017, 828, 685 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ_H 3.83 (s, 3H, $-CH_3$)6.12 (s, 2H, $-NH_2$), 7.02-8.82(m, 10H, Ar H) ppm;^{13}C NMR (100 MHz, DMSO-d_6): δc 168.9, 94.6, 153.7, 114.0, 152.3, 126.4, 132.0, 129.3, 127.4, 127.4, 125.8, 129.5, 130.5, 128.5, 114.8, 161.5, 55.8, 114.9, 128.4 ppm; MS (m/z): 327.25 [M^+].

3-amino-1-(3-hydroxyphenyl)benzo[*f*]quinoline-2-carbonitrile (C8)white solid; m.p.:140°C;IR (ATR): 3085, 2236, 1747,1536, 1345, 808, 760 cm^{-1};^1H NMR (200 MHz, $CDCl_3$): δ_H 5.52 (s, 2H, $-NH_2$), 6.82-8.32(m, 10H, Ar-H), 9.84 (s, 1H, -OH) ppm;^{13}C NMR (100 MHz, DMSO-d_6): δc 166.5, 86.5, 145.3, 112.7, 152.6, 125.9, 133.0, 129.8, 127.5, 126.7, 127.3, 124.3, 120.2, 139.3, 112.8, 159.3, 116.5, 118.6, 130.8 ppm; MS (m/z): 333.25 [M^++Na].

Reaction Scheme

Synthesis of 2-methyl-4-(R-phenyl) benzo[f]quinoline-3-carbonitrile



R= 2-Cl, 3-Cl, 2-NO_2, 3-NO_2, 4-OCH_3.

Conclusion

This research work was focused on the rational approach in design and development of benzo[f]quinoline-3-carbonitrile via one pot three component process. A series of quinoline derivatives were prepared, in silico study and virtual screening of oral bioavailability by Molinspiration online software was undertaken leading to good results.

All quinoline derivatives showed excellent results in the analysis of Lipinski's Rule of five for MW, log P, and HBA/HBD counts, clog P ≤ 5, and MW was less than 500 g/mol, Moreover, the nRotb ≤ 10, Polar surface area (PSA) < 140 $A^{\circ 2}$. These results showed that in violates zero or one in all criteria, which indicates that good lipophilicity and solubility in oral bioavailability. The Virtual screening comparison result of aim moieties was GPCR ligand, Ion Channel modulator, Kinase inhibitor, nuclear receptor ligand, Protease inhibitor, Enzyme inhibitor showed good result for antibioactivity.

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