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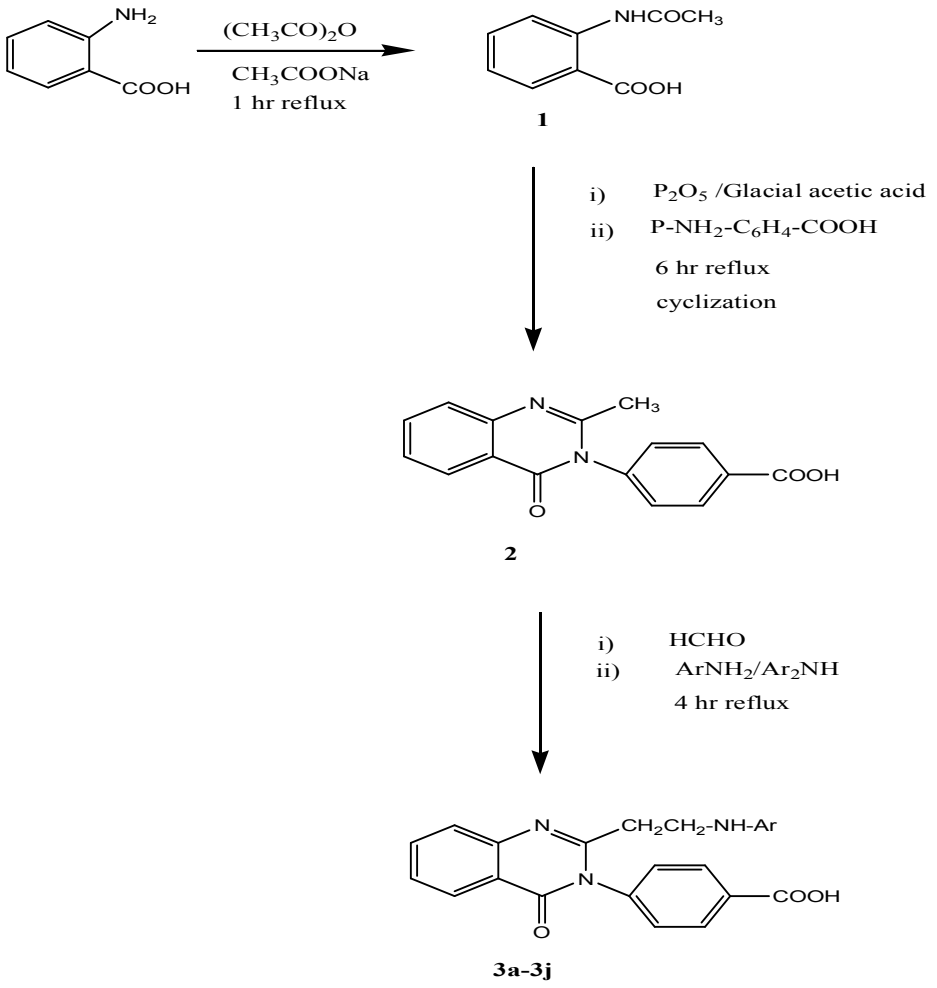
SYNTHESIS OF SOME NEW 2-SUBSTITUTED QUINAZOLIN-4-ONE DERIVATIVES AND THEIR BIOLOGICAL ACTIVTIES

B.KIRUTHIGA*, K.ILANGO, P.VALENTINA, N.UMARANI and RITESH PATEL
Department of Pharmaceutical Chemistry, SRM College of Pharmacy, SRM University, Kattankulathur – 603203, Tamil Nadu
****Corres.author : nithi217@yahoo.co.in***
Phone: (+91) - 44-27453160 Fax: (+91) - 44-27455717

ABSTRACT: A series of mannich bases **(3a-3j)** were synthesized by the reaction of 4-[2-methyl-4-oxo-4H-quinazolin-3-yl] benzoic acid **(2)** with formaldehyde and appropriate amines by conventional technique. The procedure afforded various quinazolinone derivatives with 75% yield. Structures were characterized by means of spectral data. All the synthesized compounds were subjected to biological evaluation for antibacterial, antifungal and anti-inflammatory activities.
KEYWORDS: Quinazolinone, Mannich bases, Antibacterial, Antifungal, Anti-inflammatory activity

SCHEME



INTRODUCTION

Quinazolinones are versatile nitrogen containing heterocyclic compound, possessing broad spectrum of biological and pharmacological activities such as antimicrobial[1], bronchodilator[2], antihistaminic[3], anti-inflammatory[4], angiotensin(II) receptor antagonist[5], antiherpes[6], antitubercular[7], anti-insecticidal[8] and cardiovascular agent[9]. Earlier reports have shown that the presence of alkyl/aryl/hetero aryl group at 2nd, 3rd position of quinazolinone is beneficial to anti-inflammatory activity. In this regard it was planned to synthesize quinazolin-4-one derivatives by substitution at 2-methyl group with various aryl amines using mannich reaction.

RESULTS AND DISCUSSION

In the present work, ten different quinazolinone derivatives **(3a-3j)** were synthesized. Anthranilic acid undergoes acetylation with acetic anhydride in the presence of anhydrous sodium acetate to give N-acetyl anthranilic acid **(1)** which later undergoes cyclization with phosphorus pentoxide and p-amino benzoic acid to yield 4-(2-methyl-4-oxo-4*H*-quinazolin-3-yl)benzoic acid **(2).** This resultant intermediate was then subjected to mannich reaction in the presence of paraformaldehyde with different primary and secondary aromatic amines to give different substituted aromatic compounds. Spectral data (IR,NMR,Mass) supported the structures assigned. The anti-inflammatory activity of the synthesized compounds **3b, 3c, 3f, 3g** and **3h** showed significant activity. The antibacterial activity of the tested compounds revealed that **3e** and **3f** exhibited moderate activity against *Escherichia coli.*The antifungal screening revealed that **3b** and **3d** were moderately active against *Aspergillus niger* and *Candida albicans,* whereas **3h** was active against *Aspergillus niger.*

BIOLOGICAL ACTIVITY

INVITRO ANTI INFLAMMATORY ACTIVITY

Anti inflammatory activity of the synthesized compounds were carried out by HRBC membrane stabilization method using Diclofenac sodium as standard. The synthesized compounds were made into doses of 1000µg/ml with DMSO as solvent. Percentage inhibition of the compounds were calculated and shown in **Table 1**

ANTIBACTERIAL ACTIVITY

Antibacterial activity was carried out by turbidimetric method[10] using Streptomycin sulphate as standard. Nutrient broth was used as culture medium and DMSO as solvent. Five different concentration of the standard was prepared and the median concentration was selected, the solution of the substance to be examined is appropriately diluted to median concentration of standard.1ml of each concentration of the standard and sample solution was placed in each of the test tube in duplicate. To each test tube 9ml of nutrient medium previously seeded with test organism was added. All the test tubes were placed in an incubator and the growth of the test organism was measured at about 530nm against blank.

ANTIFUNGAL ACTIVITY

Antifungal activity was also carried out by the same method using Ketoconazole as standard. Potato dextrose broth was used as culture medium and DMSO as solvent. The minimum inhibitory concentration values for antibacterial and antifungal activity was tabulated in **Table 2**

EXPERIMENTAL

GENERAL

The melting point of the synthesized compound was taken in an open end capillary tube and was uncorrected. TLC was performed using precoated plates with silica gel–G of 0.25mm thickness. Spots were visualized through the iodine chamber. IR spectra were recorded using KBr discs on Perkin Elmer FTIR spectrometer.^{1}HNMR were recorded on 1HFT-NMR (Bruker Avance II 400MHZ) using $CDCl_3$ and DMSO as solvent system. Mass spectra was also recorded on LC MSD Tranp SL 2010A SHIMADZU

Synthesis of N-acetyl anthranilic acid:

Anthranilic acid (5 gm, 0.036 mole) was mixed with an equimolar quantity of anhydrous sodium acetate (2.9 gm) and acetic anhydride (4.4 ml, 0.041 mole in slight excess) and refluxed on sand bath under anhydrous condition for 1 hr. The reaction mixture was then poured into ice cold water and the crude product was filtered and dried. The dried crude product was recrystallised from ethanol.Yield:72%, m.p:184°C

Synthesis of 4-(2-methyl-4-oxo-quinazolin-3-yl) benzoic acid

N-acetyl anthranilic acid (4 gm, 0.029 mole) was added to a mixture of 4- amino benzoic acid (3.52 gm, 0.033 mole), phosphorus pentoxide (3.649 gm, 0.033 mole) and glacial acetic acid (15 ml). Further the mixture was refluxed under anhydrous condition for 6 hrs. The reaction mixture was then poured into 10% sodium bicarbonate solution (50 ml) and crude product was filtered and dried. The dried crude product was recrystallised from ethanol. Yield:93.5%, m.p:218°C

General method of Synthesis of 4-(2-arylaminoethyl-4-oxo-4H-quinazolin-3-yl) benzoic acid

A mixture of 4-(2-methyl-4-oxo-4H-quinazolin-3-yl) benzoic acid (0.01 mole), various substituted amines (0.02 mole) and paraformaldehyde (0.02 mole) were taken in methanol (80 ml) and the reaction mixture was refluxed for 4 hrs. The completion of reaction was monitored by TLC. The excess of the solvent was distilled off and the residue was recrystallised from acetone.

Physical and Spectral Analysis

3a: Yield:73.2%, m.p:147ºC, IR cm^{-1} (KBr):3371 (N-H), 1038(C-N), 1689(C=O), 1595(C=C), 1505(C-NO_2), 3078(C-H), ^{1}HNMR: δppm 1.4 (t, 2H, CH_2), 3.15 (q, 2H, CH_2), 4.1 (t, 1H, NH), 6.2-8.2 (m, 12H, Ar-H), 11.01 (s, 1H, COOH), MS (m/z):430.41(M^+)
3b: Yield:73.4%, m.p:165ºC, IR cm^{-1} (KBr):3403 (N-H), 1023 (C-N), 1687 (C=O), 1595 (C=C), 1571 (C-NO2), 2929 (C-H), 1408 (C-O-H), 1261 (C-O), ^{1}HNMR: δppm 1.3 (t, 2H, CH2), 2.9 (q, 2H, CH2), 4.1 (t, 1H, NH), 6.1-8.1 (m, 12H, Ar-H), 11.00 (s, 1H, COOH),
MS (m/z):430.44(M^+)
3c: Yield:75.2%, m.p:175ºC, IR cm^{-1} (KBr): 3364 (N-H), 1016 (C-N), 1688 (C=O), 1601 (C=C), 1530 (C-NO_2), 3075 (C-H), 1433 (C-O-H), 1263 (C-O) ^{1}HNMR: δppm 1.4 (t, 2H, CH_2), 3.15 (q, 2h, CH_2), 4.1 (t, 1H, NH), 6-8 (m, 12H, Ar-H), 11.01 (s, 1H, COOH), MS (m/z):431.31(M^+)
3d: Yield:74.8%, m.p:172ºC, IR cm^{-1} (KBr): 3311 (N-H), 1005 (C-N), 1688 (C=O), 1596 (C=C), 2917 (C-H), 1408 (C-O-H), 1258 (C-O), ^{1}HNMR: δppm 1.3 (t, 2H, CH_2), 3.00 (q, 2H, CH_2), 4.2 (t, 1H, NH), 6-8 (m, 13H, Ar- H), 11.02 (s, 1H, COOH), MS (m/z):385.43(M^+)
3e: Yield:75.2%, m.p:168ºC, IR cm^{-1} (KBr):3374 (N-H), 1024 (C-N), 1689 (C=O), 1594 (C=C), 531 (C-Br), 2930 (C-H), 1408 (C-O-H), 1260 (C-O), ^{1}HNMR: δppm 1.3 (t, 2H, CH_2), 3.05 (q, 2H, CH_2), 4.1 (t, 1H, NH), 6.18 (m, 12H, Ar-H), 11.00 (s, 1H, COOH), MS (m/z):464.44(M^+)
3f: Yield:74.2%, m.p:206ºC, IR cm^{-1} (KBr): 3308 (N-H), 1024 (C-N), 1687 (C=O), 1595 (C=C), 631 (C-C1), 2928 (C-H), 1408 (C-O-H), 1261 (C-O), ^{1}HNMR: δppm 1.4 (t, 2H, CH_2,), 3.15 (q, 2H, CH_2), 4.2 (t, 1H, NH), 6.2-7.9 (m, 12H, Ar-H), 11.00 (s, 1H, COOH), MS (m/z):420.21(M^+)
3g: Yield: 74.8%, m.p:201ºC, IR cm^{-1} (KBr):3309 (N-H), 1004 (C-N), 1689 (C=O), 1595 (C=C), 698 (C-C1), 2928 (C-H), 1408 (C-O-H), 1252 (C-O), ^{1}HNMR: δppm 1.2 (t, 2H, CH_2,), 3.15 (q, 2H, CH_2), 4.3 (t, 1H, NH), 6.3-7.9 (m, 12H, Ar-H), 11.4 (s, 1H, COOH), MS (m/z):420.20(M^+)
3h: Yield:73.2%, m.p:126ºC, IR cm^{-1} (KBr):3311 (N-H), 1017 (C-N), 1688 (C=O), 1595 (C=C), 2920 (C-H), 1405 (C-O-H), 1260 (C-O), ^{1}HNMR: δppm 1.3 (t, 2H, CH_2,), 3.12 (q, 2H, CH_2), 4.3 (t, 1H, NH), 6.3-8.0 (m, 15H, Ar-H), 11.4 (s, 1H, COOH), MS (m/z):435.61(M^+)
3i: Yield:73.6%, m.p:131ºC, IR cm^{-1} (KBr):3306 (N-H), 1017 (C-N), 1686 (C=O), 1594 (C=C), 3046 (C-H), 1397 (C-O-H), 1262 (C-O), ^{1}HNMR: δppm 1.2 (t, 2H, CH_2,), 3.5 (q, 2H, CH_2), 6.3-7.8 (m, 19H, Ar-H), 11.23 (s, 1H, COOH), MS (m/z):511.41(M^+)
3j: Yield:74.2%, m.p:159ºC, IR cm^{-1} (KBr):3363 (N-H), 1018 (C-N), 1679 (C=O), 1599 (C=C), 500 (C-Br), 3065 (C-H), 1409 (C-O-H), 1258 (C-O), ^{1}HNMR: δppm 1.5 (t, 2H, CH_2,), 3.29 (q, 2H, CH_2), 4.3 (t, 1H, NH), 6.2-8.2 (m, 10H, Ar-H), 11.00 (s, 1H, COOH),
MS (m/z):378.24(M^+)

CONCLUSION

Novel derivatives containing quinazolinone nucleus have been synthesized and screened for their biological activities. The synthesized compounds were characterized by IR, ^{1}HNMR and Mass spectral data. All the synthesized compounds show characteristic absorption peaks in IR, NMR and mass spectra. Expected molecular ion peak fragments were observed for the entire compounds in mass spectra. The synthesized compounds were subjected to various biological activities like invitro anti-inflammatory, antibacterial and antifungal. The activity suggests that novel quinazolinone derivative of aromatic compounds showed moderate antibacterial and anti fungal activities. Anti-inflammatory activity revealed that all the synthesized compounds have shown significant activity when compared with that of standard by HRBC membrane stabilization method.

TABLE 1: ANTI-INFLAMMATORY ACTIVITY

COMPOUND	Ar	% INHIBITION
3a	o- nitrophenyl	40.50
3b	m- nitrophenyl	59.33
3c	p- nitrophenyl	61.24
3d	phenyl	37.00
3e	p- bromophenyl	27.56
3f	2- chlorophenyl	56.38
3g	4- chlorophenyl	54.58
3h	1-naphthyl	51.14
3i	N-phenyl-1-naphthyl	33.46
3j	m-bromophenyl	22.48
Standard	---	76.80
Control	---	---

TABLE 2: ANTIBACTERIAL ACTIVITY (MIC)

COMPOUNDS	MIC for Anti-Bacterial Activity (µg/ml)				MIC for antifungal activity(µg/ml)	
	E. coli	*B. subtilus*	*S. aureus*	*K. pneumonia*	*A.niger*	*C.albicans*
3a	105	113	145	127	165	167
3b	109	120	133	134	130	132
3c	115	122	122	122	165	165
3d	115	135	128	135	140	125
3e	98	128	115	155	166	140
3f	117	115	145	130	140	140
3g	98	133	122	128	165	130
3h	122	128	121	145	132	167
3i	107	113	134	115	168	141
3j	114	115	129	154	163	165

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