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SHORT COMMUNICATION

Synthesis and characterization of novel 2-oxo-4-((4-(3-oxomorpholino)phenyl)amino)-2H-chromene-3-carbaldehyde derivatives

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ABSTRACT

A highly functionalized heterocyclic library were synthesized, characterized and tested for biological evaluation against bacteria and fungus. This novel synthetic rout involves nucleophilic substitution reaction of 4-chloro-2-oxo-2H-chromene-3-carbaldehyde with 4-(4-aminophenyl) morpholin-3-one in the presence of base and methanol as a solvent in good yield and high purity. All the synthesized compound of libraries characterized using ^{1}H NMR, Mass, and IR spectroscopic technique. Also all compound screened for antimicrobial activity against standard drugs.

***Keywords*:** 4-(4-aminophenyl)morpholin-3-one,4-chloro-2-oxo-2H-chromene-3-carbaldehyde, antimicrobial activity

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1. INTRODUCTION

In recent decades, chromenone and its derivatives have attracted considerable attention from medicinal and synthetic organic chemists because of a wide range of biological activities displayed by this class of compounds which is described below. The corresponding 2-substituted-3-carbaldehyde chromenones are molecules of current interest as they have potent biological activity. It is well recognized that incorporation of nitro group into the chromenone skeleton have significant biological activity.[1,2] Vasselin A. D. et al[3] have synthesized a new series of fluoro, methoxy and amino substituted isoflavones and demonstrated as potent antitumor agents. The substituted isoflavones were synthesized using palladium catalyzed coupling methodologies to construct the central aryl carbon-carbon single bond. The new isoflavone derivatives were tested for *invitro* activity in human breast (MDA-MB-468 and MCF-7) and colon (HT29 and HCT-116) cancer cell lines. Low micromolar GI_{50} values were obtained in a number of cases, with the MDA-MB-468 cell line being the most sensitive overall. This study is suggesting that isoflavone derivatives can act as substrates for CYP1A1 bioactivation. Chen S. F. et al[4] have developed a series of nitrocoumarin and nitrochromene derivatives and shown to inhibit the phosphatidylinositol-specific phospholipase C(PLC) (ICW *C*10 pg/mL) isolated from human melanoma. The inhibition of PLC by nitrocoumarin was time-dependent and irreversible.

The inhibition of PLC was shown to interfere with inositide metabolism in whole cells in a manner consistent with their proposed mode of activity. Dauzonne D. et al[5] have synthesized some novel flavone-8-acetic acid derivatives and evaluated for reversible inhibitors of aminopeptidase N(APN/CD13) activity. The cell surface APN/CD13, overexpressed in tumor cells, plays a critical role in angiogenesis. In this context, they have tested a series of novel flavone-8-acetic acid derivatives and found that the 2', 3-dinitroflavone-8-acetic acid proved to be the most efficient and exhibited an IC_{50} of 25 μM which is 2.5 times higher than that of bestatin, the natural known inhibitor of APN/CD13. The presence of other substituents such as OMe groups at the 3 or 4 position of the A phenyl group, or the existence of steric constraints, did not improve selectivity and potency.

The results were indicated that derivatives, which bear a CH_2COOH group in the 8-position and two NO_2 substituents in both 2' and 3 positions inhibited efficiently APN activity and this to the same extent as bestatin. Deletion or replacement of the NO_2 group in the 2'-position gave compounds with a lesser degree of potency against APN activity whereas the presence of an electron-donating methoxy group in the ortho or para position of the nitro substituent led to slightly lowered inhibitory effects.

The main significance of the work is it will provide synthesized and more potent stable molecule for biological response as most of coumarine derivatives has significant biological activity. As we mentioned above, the significance and biological profile of this class of molecule so our continue efforts towards the synthesis of potential heterocyclic molecules

2. EXPERIMENTAL

All chemicals and solvents used to synthesised library were purchased from CDH chemical, Delhi of AR grade and were used without further purification. Melting points were taken in open capillary method and are uncorrected. IR spectra were recorded on FTIR-8400

spectrophotometer (Shimadzu, Kyoto, Japan), using DRS probe KBr pallet. ^{1}H-NMR spectra of the synthesized compounds were recorded on a Bruker-Avance-II (400 MHz) DMSO-*d*6 solvent. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu, Kyoto, Japan). Physical constants of the synthesized compounds are shown in Table.

2. 1. General synthesis of various substituted 4-hydroxy coumarin (int-01)

Various Substituted phenols (0.1 mole) and malonic acid were added to a mixture of phosphorus oxychloride (40 ml) and anhydrous zinc chloride (30 gm) which was preheated to get rid of any moisture. The reaction mixture was heated on a water bath at 70 ºC for 8-10 hours. It was cooled and decomposed with ice and water to afford buff-yellow colored solid. The solid was then filtered and washed thoroughly with water. It was then triturated with 10% sodium carbonate solution and filtered. The filtrate was slowly acidified with dilute HCl till the effervescence ceased. The product was filtered, dried and recrystallized with methanol.

2. 2. Synthesis of 4-chloro,3-formayl coumarin (int-2)

To a stirred mixture of 4-hydroxycoumarin (0.06 mol) in anhydrous DMF (0.6 mol) were added drop wise $POCl_3$ (0.18 mol) at –10 °C to –5 °C. The reaction mixture was then stirred for 1 h at room temperature and heated and stirred for 2 h at 60 °C. After the reaction completed, the mixture was poured onto crushed ice under vigorous stirring. After storing the mixture overnight at 0°C the pale yellow solid was collected by filtration and washed successively with Na_2CO_3 (5%) and water, and then was air–dried. Recrystallization from acetone gave 85% of 4-chloro-3-formyl coumarin as a pale yellow powder with m.p. 115–12

2. 3. General synthesis of Schiff base of 4-chloro,3-formayl coumarin with 4-(4-aminophenyl) morpholin-3-one

A mixture of substituted 4-chloro 3-formayl coumarin (0.02 mmol) and 4-(4-aminophenyl) morpholin-3-one (0.02 mmol) were taken into Methanol and 2-3 drops of glacial acetic acid was added as catalyst. Completion of reaction was checked over TLC. If the reaction was not complete warm the reaction mixture and stir further 15 minutes. After completion of the reaction, mixture was poured into crushed ice, filtered and washed with water. Crystallization from chloroform gives Schiff base Yield 68-86%

3. REACTION SCHEME

Table 1. Physical constant of synthesized library.

Code	Molecular formula	Substitution	Molecular Weight	M.P. ºC	Percentage of Yield
V-2a	$C_{20}H_{16}N_2O_5$	H	364	164-166	82
V-2b	$C_{21}H_{17}N_2O_5$	2-Methyl	378	176-178	84

V-2c	$C_{21}H_{17}N_2O_5$	3-Methyl	378	156-158	72
V-2d	$C_{21}H_{17}N_2O_5$	4-Methyl	378	158-160	78
V-2e	$C_{20}H_{15}N_3O_7$	4-Nitro	409	178-180	71
V-2f	$C_{20}H_{15}N_3O_7$	2-Nitro	409	180-182	75
V-2g	$C_{20}H_{15}CIN_2O_5$	2-Chloro	398	146-148	69
V-2h	$C_{20}H_{15}CIN_2O_5$	4-Chloro	398	140-142	82
V-2i	$C_{20}H_{15}BrN_2O_5$	2-Bromo	443	180-182	84
V-2j	$C_{20}H_{15}BrN_2O_5$	4-Bromo	443	188-190	81
V-2k	$C_{22}H_{20}N_2O_5$	2,3-Dimethyl	392	174-176	76
V-2l	$C_{22}H_{20}N_2O_5$	2,5 Dimethyl	392	180-182	78

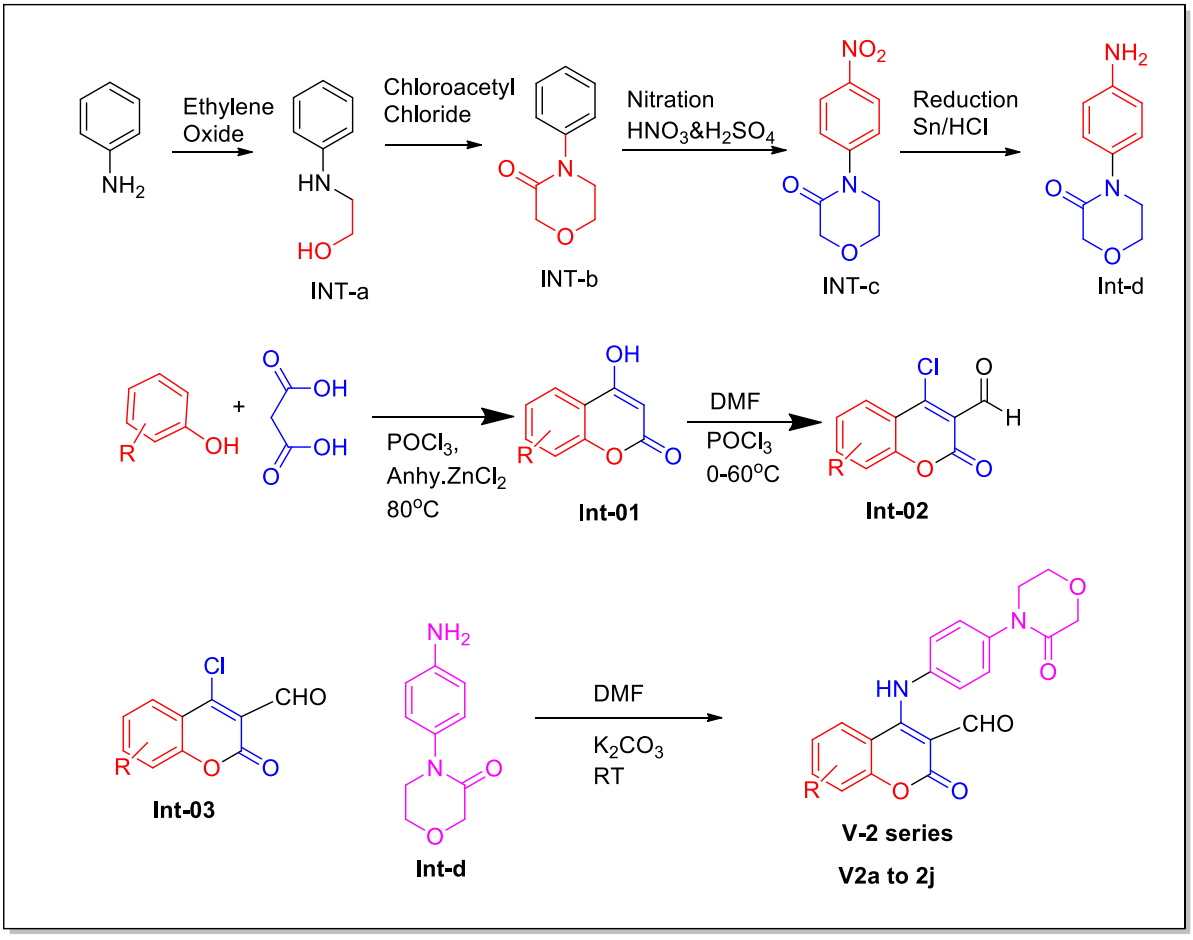

Figure 1. Reaction scheme.

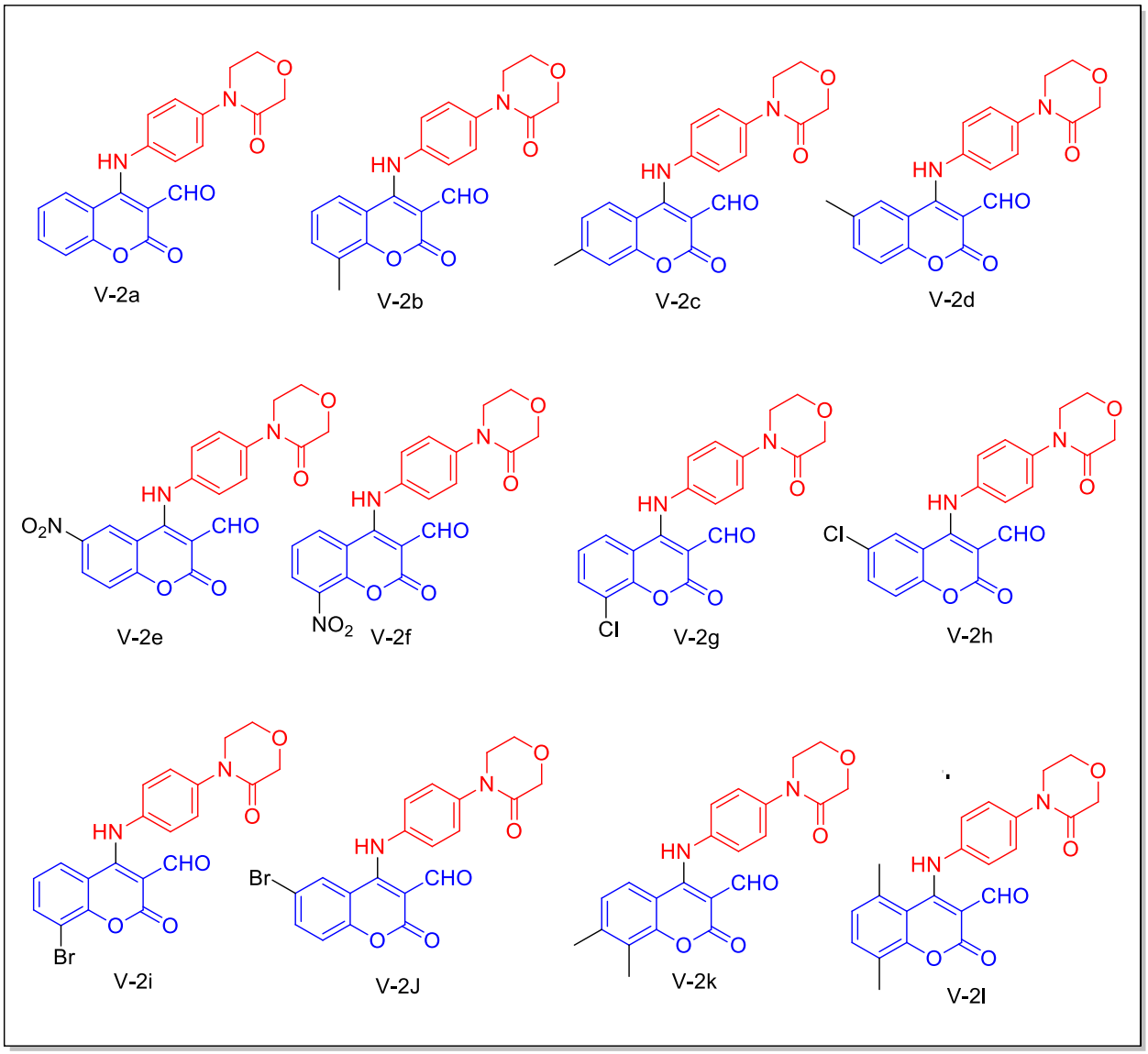

Figure 2. Structure of synthesized library.

4. SPECTRAL DATA OF SYNTHESIZED COMPOUND

2-oxo-4-((4-(3-oxomorpholino)phenyl)amino)-2H-chromene-3-carbaldehyde (V-2a)
Yellow solid, Rf Value 0.42 (Ethyl acetate:Hexane 8:2), M.P-164-166 ºC, IR (KBR pallet) in CM^{-}, 3088.31 (C-H Str. In aromatic), 2969.83 (C-H Str. In alkane), 2877.15 & 2762.75 (C-H Str. In aldehyde), 3516.45 (N-H Str. In 2º amine), 1668.34 (C=O Str. In amide) 1727.71 (C=O Str. In aldehyde) 1117.94 (C-O Str. In ethers) 838.65 (p- disub. Aromatic) 756.15 (o- disub. Aromatic) ^{1}H NMR (400Hz, $CDCl_3$) in δ $_{PPM}$: 9.20-9.50 (Singlet, 1H of -CHO), 7.50-8.70 (Complex, 8H aromatic), 3.90-4.0 (Triplet, 2H of $–CH_2$), 4.0-4.10 (Triplet, 2H of $–CH_2$), 4.30-4.35 (Singlet, 2H of $–CH_2$), 3.30-3.40 (Singlet, 1H of –NH)

MS (m/z): 364(M^+), Ana.calculated for Molecular formula $C_{20}H_{16}N_2O_5$ is C; 65.93%, H; 4.43%, N; 7.69% found C; 65.90%, H; 4.39%, N; 7.64%

8-methyl-2-oxo-4-((4-(3-oxomorpholino)phenyl)amino)-2H-chromene-3carbaldehyde (V-2b)

Yellow solid, Rf Value 0.41 (Ethyl Acetate:Hexane - (8:2), M.P-176-178 ºC, IR (KBR pallet) in CM^{-}: 3103.46(C-H Str. In aromatic), 2952.91(C-H Str. In alkane), 3444.47 (N-H Str. In 2º amine), 1676.87 (C=O Str. In amide) 1734.53 (C=O Str. In aldehyde) 1236.25 (C-O Str. In ethers) 838.50 (p- disub. Aromatic), 1465.46 (C=C Str. In aromatic), 1292.54 (C-N Str. In amine) ^{1}H NMR (400Hz, $CDCl_3$) in δ_{PPM}: 9.20-9.30 (Singlet, 1H of -CHO), 7.20-8.80 (Complex, 7H aromatic), 3.90-4.0 (Triplet, 2H of $–CH_2$), 4.10-4.20 (Triplet, 2H of $–CH_2$), 4.40-4.50 (Singlet, 2H of $–CH_2$) MS (m/z): 378(M^+), Ana. calculated for Molecular formula $C_{21}H_{18}N_2O_5$ is C; 66.66%, H; 4.79%, N; 07.40 % found C; 66.61%, H; 4.74%, N; 07.36 %

5. CONCLUSION

We have prepared a library of novel 4-(4-aminophenyl) morpholin-3-one containing different coumarin derivatives by chloramine coupling reaction using inorganic base and DMF as solvent at low temperature which results in 2-oxo-4-((4-(3-oxomorpholino)phenyl)amino)-2H-chromene-3-carbaldehyde derivatives. The formation of 2-oxo-4-((4-(3-oxomorpholino) phenyl)amino)-2H-chromene-3-carbaldehyde by this method was first developed by us. All synthesized compounds were obtained in good to moderate yield. All synthesized compounds were characterized by IR, NMR and Mass spectrometry

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