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A CONVENIENT SYNTHESIS OF 3-(2-ARYL AMINO)-ETHYLAMINO-*2H*-CHROMEN-2-ONES AND THEIR ANTIMICROBIAL ACTIVITIES

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Abstract: A series of 3-(2-arylamino)ethylamino-*2H*-chromen-2-ones **5(a-f)** have been synthesized from salyciladehyde and spectrally characterized. In vitro antimicrobial activities of synthesized compounds were investigated against Grampositive *S.Aureus* bacteria, Gram-negative *E.Coli* bacteria and fungi *C. Albicans* and *A.Niger* in comparison with standard drugs. Some of the tested compounds showed significant antimicrobial activity.

Keywords: Amino coumarin, aryl amines, salicylaldehyde, antimicrobial.

INTRODUCTION:

Coumarins are a large family of compounds of natural and synthetic origin, which are present with different pharmacological actions.[I] Chemically they are lactones of cinnamic acid. Their structural variety is responsible for the important place that they occupy in the natural product and synthetic organic chemistry realm [II]. Some important studies pay special attention to their antioxidative, anticancer, antiinflammatory, cardioprotective and enzymatic inhibitory properties.[III–IX]. The 3-aminocoumarin motif, while considerably less prevelent, can nonetheless be found in a number of naturally occuring antibiotics, such as novobiocin [X], clorobiocin [XI] and coumermycin A_1 [XII]. Derivatives of 3-aminocoumarins have been found to possess biological activity, including CNS depressant [XIII], antibacterial [XIV], antiallergic [XV] and insect growth regulatory[XVI]. Moreover, 3-aminocoumarin and its derivatives are also known to exhibit interesting photochemical behavior and have found application as fluroscent markers[XVII].

In view of the above mentioned facts, it was envisaged that these active pharmacophores, if linked together would generate novel molecular templates which are likely to exhibit interesting biological properties. In continuation of our interest in the synthesis of biologically heterocycles, we report herein the synthesis and antimicrobial activity of some new 3-(2-arylamino)-ethylamino-*2H*-chromen-2-ones compounds.

EXPERIMENTAL SECTION:

General Methods: Melting points were measured in open capillary and were uncorrected. Column chromatography was performed using silica gel (100-200 mesh size) purchased from Thomas Baker and Thin Layer Chromatography (TLC) was carried out using aluminum sheets pre-coated with silica gel 60 F254 purchased from Merck. IR spectra (KBr) were obtained using Baker WM-4(X) spectro meter (577 model). ^{1}H NMR (400 MHz) and ^{13}C

NMR (100 MHz) spectra were recorded on a Bruker WM-400 spectrometer in DMSO-d_6 with TMS as an internal standard. Mass spectra (ESI) were carried out on a JEOL SX-102 spectrometer. CHN analysis was done by Carlo Erba EA 1108 automatic analyzer. Combustion analyses were found to be within the limits permissible errors. The chemicals and solvents used were of commercial grade and used without further purification unless otherwise stated.

Synthesis of 3-amino coumarin 3:
Salicylaldehyde (0.10 mol) and (0.10 mol) of methyl aminoacetate hydrochloride were mixed and the pH of the mixture was adjusted to 9-10 using triethylamine. The resulting mixture was heated to 90° for 30 minutes. The mixture was allowed to cool to room temperature and stirring was continued until a precipitate formed. The crude product was obtained by filtration and washed with water. The solid was recrystallized from methanol to give 80% of a yellow solid product ; mp: 130-131°C [literature 132-133° C [XXI].

Synthesis of 3-(2-bromoethylamino)-*2H*-chromen-2-one 4:
3-Aminocoumarin (0.10 mol) and 0.15 (mol) of anhydrous sodium acetate was dissolved in 100 mL of dried acetonitrile and the mixture was cooled on an ice-bath. To this 1,2 dibromo ethane (0.10 mol) was added dropwise. The mixture was refluxed for 3h, than allowed to room temperature. The solvent was evaporated under reduced pressure and the residue was washed with water which was directly used to next step.

Synthesis of 3-(2-arylamino)ethylamino)-*2H*-chromen-2-ones 5(a-f):
To a solution of compound 3-(2-bromoethylamino)-*2H*-chromen-2-one **4** (1.0 mol) in anhydrous
DMF (50 mL) was added K_2CO_3 (3.0 mole), then stirred for 30 minutes and added the compound of 1,2-dibromoethane (1.2 mol).slowly. The reaction mixture was heated at 60 ^{0} C for 4-5 h (the reaction was monitored by TLC), after completion of the reaction concentrated under *vacuo* obtained crude which was dissolved in DCM and filtered. The DCM layer was concentrated on rota evaporation to get title compounds.

3-(2-(phenylamino)ethylamino)-*2H*-chromen-2-one 5a:
Yield: 75.0 %; IR (KBr, cm^{-1}): 1451, 1487, 1636, 1724, 2998 and 3396. ^{1}H NMR (DMSO-d_6, 400MHz): ð 3.24 (t, 2H, -CH_2), 3. 42 (t, 2H, -CH_2), 6.82-7.13 (m, 5H, Ar-H), 7.38-7.42 (m,2H, Ar-H), 7.52-7.56 (m, 2H,Ar-H), 8.21 (s, 1H, coum-H) ppm. ^{13} C NMR (DMSO-d_6, 100 MHz): ð 46.0, 46.7, 114.3, 116.0, 117.9, 118.2, 121.4, 129.3, 127.6, 126.9, 131.6, 139.2, 149.8, 152.2 ppm. ESI–MS (m/z): 281 (M+1). Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C,72.84; H, 5.75; N, 9.99: Found: C, 72.80; H, 5.71; N, 9.87.

3-(2-(4-chlorophenylamino)ethylamino)-*2H*-chromen-2-one 5b:

Yield: 79.0 %; IR (KBr, cm^{-1}): 1454, 1494, 1638, 1720, 3012 and 3390. ^{1}H NMR (DMSO-d_6, 400 MHz): ð 3.24 (t, 2H, -CH_2), 3. 46 (t, 2H, -CH_2), 6.65-6.68 (dd, 2H, Ar-H), 7.28-7.34 (m, 2H, Ar-H), 7. 42-7.48 (m, 2H, Ar-H), 7.54-7.59 (m, 2H,Ar-H), 8.19 (s, 1H, coum-H) ppm. ^{13} C NMR (DMSO-d_6, 100 MHz): ð 44.6, 44.8, 114.3, 115.3, 117.4, 118.8, 123.2, 126.7, 127.5, 128.3, 129.9, 131.9, 140.2, 147.8, 153.4 ppm. ESI–MS (m/z): 315 (M+1). Anal. Calcd for $C_{17}H_{15}ClN_2O_2$: C,64.87; H, 4.80; N, 8.90: Found: C, 64.80; H, 4.75; N, 8.76.

3-(2-(4-bromophenylamino)ethylamino)-*2H*-chromen-2-one 5c:
Yield: 82.0 %; IR (KBr, cm^{-1}): 1458, 1494, 1642, 1718, 3018 and 3395. ^{1}H NMR (DMSO-d_6, 400 MHz): ð 3.20 (t, 2H, -CH_2), 3. 42 (t, 2H, -CH_2), 6.62-6.70 (dd, 2H, Ar-H), 7.30-7.35 (m, 2H, Ar-H), 7. 42-7.52 (m, 2H, Ar-H), 7.58-7.64 (m, 2H,Ar-H), 8.20 (s, 1H, coum-H) ppm. ^{13} C NMR (DMSO-d_6, 100 MHz): ð 44.0, 44.8, 114.4, 114.9, 117.0, 119.3, 124.2, 126.2, 127.9, 129.2, 130.9, 132.8, 140.8, 148.3, 153.2 ppm. ESI–MS (m/z): 360 (M+1). Anal. Calcd for $C_{17}H_{15}BrN_2O_2$: C,56.84; H, 4.21; N, 7.80: Found: C, 56.80; H, 4.17; N, 7.73.

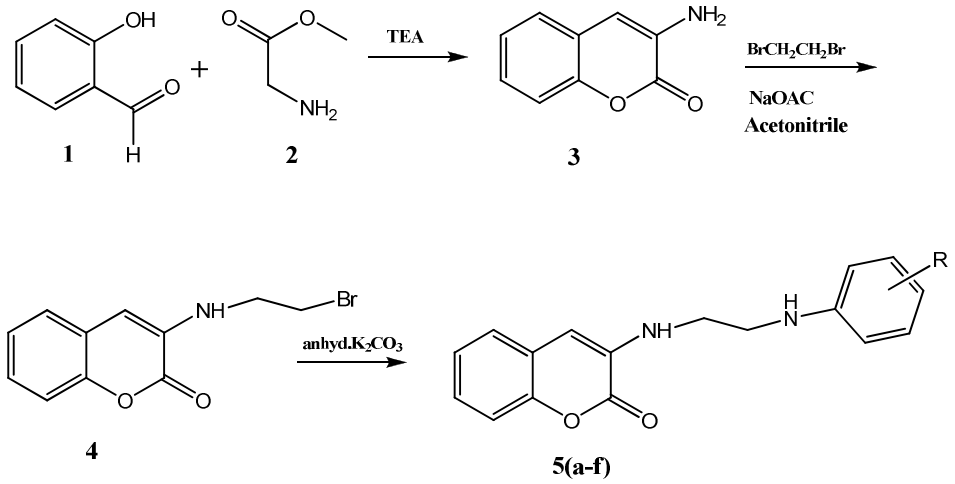
3-(2-(4-methoxyphenylamino)ethylamino)-*2H*-chromen-2-one 5d:
Yield: 68.0%; IR (KBr, cm^{-1}): 1452, 1495, 1642, 1718, 3012 and 3398. ^{1}H NMR (DMSO-d_6, 400 MHz): ð 3.24 (t, 2H, -CH_2), 3. 40 (t, 2H, -CH_2), 6.62-6.64 (dd, 2H, Ar-H), 7.12-7.15 (m, 2H, Ar-H), 7.48-7.53 (m, 2H, Ar-H), 7.58-7.62 (m, 2H, Ar-H), 8.20 (s, 1H, coum-H) ppm. ^{13} C NMR (DMSO-d_6, 100 MHz): ð 45.0, 45.4, 56.2, 114.2, 116.3, 117.4, 117.8, 121.2, 126.4, 126.9, 129.8, 139.2, 142.2, 153.7, 162.8 ppm.ESI–MS(m/z):311(M+1). Anal. Calcd for $C_{18}H_{18}N_2O_3$: C,69.66; H, 5.85; N, 9.03: Found: C, 69.62; H, 5.80; N, 8.98.

3-(2-(4-nitrophenylamino)ethylamino)-*2H*-chromen-2-one 5e:
Yield: 71.0%; IR (KBr, cm^{-1}): 1448, 1492, 1642, 1722, 3018 and 3402. ^{1}H NMR (DMSO-d_6, 400 MHz): ð 3.24 (t,2H, -CH_2), 3. 44 (t, 2H, -CH_2), 6.89-6.92 (dd, 2H, Ar-H), 7.42-7.50 (m, 2H, Ar-H), 7.56-7.62 (m, 2H, Ar-H), 7.92-7.96 (dd, 2H, Ar-H), 8.20 (s, 1H, coum-H) ppm. ^{13} C NMR (DMSO-d_6, 100 MHz): ð 45.2, 45.0, 113.5, 114.4, 117.7,118.2, 121.4, 126.4, 127.3, 128.4, 129.4, 137.4, 139.2, 154.7, 160.8 ppm.ESI–MS(m/z):326(M+1). Anal. Calcd for $C_{17}H_{15}N_3O_4$: C,62.76; H, 4.65; N, 12.92: Found: C, 62.72; H, 4.60; N, 12.88.

3-(2-(3,5-dimethyl-1H-pyrazol-1-yl)ethylamino-*2H*-chromen-2-one 5f:
Yield: 62.0%; IR (KBr, cm^{-1}): 1440, 1488, 1640, 1720, 3108 and 3388. ^{1}H NMR (DMSO-d_6, 400 MHz): ð 2.32(s,3H,-CH_3), 2.46 (s, 3H, -CH_3), 4.12 (t, 2H,-CH_2), 5.72 (t, 2H, -CH_2), 6.52 (s, 1H, Pyrazol-H), 7.46-7.52 (m, 2H, Ar-H), 7.54-7.58 (m, 2H, Ar-H), 8.22 (s, 1H, coum-H) ppm. ^{13} C NMR (DMSO-d_6, 100 MHz): ð 12.6, 14.8, 42.4, 48.4, 52.3, 117.9, 114.2, 117.9, 118.5, 121.4, 126.4, 127.2, 129.5, 139.8, 148.2, 160.2 ppm. ESI–MS(m/z): 284 (M+1). Anal. Calcd for $C_{16}H_{17}N_3O_2$: C,67.83; H, 6.05; N, 14.83: Found: C, 67.74; H, 5.98; N, 14.76.

RESULTS AND DISCUSSION:
The synthetic strategies adopted for the synthesis of the target compounds are depicted in **Scheme-1**. After investigating published methods [XVIII-XX], we found that if equivalent amounts of salicylaldehyde and methyl aminoacetate hydrochloride were reacted in water at pH 9-10, 3-aminocoumarin was formed in 80 % yield. Intermediate **4** are prepared in a straight-forward manner by the reaction of dibromoethane with 3-aminocoumarin **3** in the presence of sodium acetate in acetonitrile solvent.. The compound 3-(2-bromoethylamino)-*2H*-chromen-2-one **4** is reacted with appropriate amines under basic conditions to give corresponding desired compounds **5(a-f)**. The structures of all the newly synthesized compounds were elucidated on the basis of their spectral (IR, NMR and mass) and elemental analyses data. The synthesized compounds **5(a-f)** were also assayed for their antimicrobial activity.

Scheme-1:



Antimicrobial activity:

Antimicrobial activities of synthesized compounds **5(a-f)** were tested using the agar disc diffusion method. They were dissolved in DMSO. Final inoculums of 20 µl suspension of each bacterium and fungus used. Nutrient agar (antibacterial activity) and sabouraud's dextrose agar medium (antifungal activity) was prepared and sterilized by an autoclave and transferred to previously sterilized petridishes. The solidified plates were then seeded with 20 µl bacterial suspensions (freshly prepared in saline). Cups were cut in the solidified medium using sterile cork borer about 10 mm diameter. The cut agar disk was removed by a splayed-out pen nib. Sample solution (50µl) of 125µl g/ml concentration (calculated from tube dilution method) was loaded in each cup under sterile condition. The plates were left for 30 min to allow the diffusion of compounds at room temperature. Antibiotic of ciprofloxacin (50µl) and fluconazole (50µl) were used as positive control, while DMSO used as negative control. Then the plates were incubated for 24 h at 37 ± 1°C for antibacterial activity and 48 h at 37 ± 1°C for antifungal activity. The zone of inhibition was calculated by measuring the minimum dimension of the zone of no microbial growth around the each disc [XXII].

Table-1: Minimum inhibitory concentration (MIC, µg/ml) of synthesized compounds 5(a-f)

	Bacterial strains (+ Ve and –Ve)		**Fungal strains**	
Compound	***S. aureus***	***E. coli***	***C. albicans***	***A. niger***
5a	10	11	9	9
5b	12	10	12	14
5c	14	17	9	8
5d	16	18	12	12
5e	18	20	10	15
5f	17	21	12	14
Ciprofloxacin	25	25		
Flucanazole			16	16

All the synthesized compounds have shown positive antibacterial activity against *S. aureus, E. Coli,* but they are less active as compared to standard ciprofloxacin. The compounds **5c, 5d, 5e** and **5f** shows greatest activity against *S. aureus and E. Coli* respectively and show positive activity against *C. Albicans and A Niger*. The compounds **5b, 5d, 5e** and **5f** showed the greatest activities among the synthesized compounds and they have less activity as compared to standard fluconazole.

CONCLUSIONS:

In conclusion, we synthesized a series of 3-(2-arylamino)ethylamino-*2H*-chromen-2-ones from salycilaldehyde. All the synthesised compounds characterized from IR, ^{1}H NMR and ^{13}C NMR spectroscopy and Mass spectrometry and screened for antimicrobial activity against S. *Aureus and E.Coli* and fungi *Candida albicans and A. Niger*. Some compound shows greatest activity.

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