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SYNTHESIS OF AZETIDINON ES OF AMINOTHIAZOLYL COUMARIN AND THEIR ANTIMICROBIAL SCREENING

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Abstract:

Keeping in view the pharmacological potential of coumarin, thiazoles and azetidinones, the title compound containing these nuclei have been synthesized. Reaction of 3—Bromo-2—Acetyl coumarin with thiourea yield 3—(2—Amino-4— Thiazolyl) coumarin which on treatment with various aromatic aldehydes gave Schiff bases. Schiff bases (4a—h) underwent cyclisation when treated with chloroacetyl chloride in presence of triethyl amine to give substituted 3|-chloro-4|—aryl—1 (4—coumarinyl—1,3—thiazol-2—y1) azetidin--2—one. The constitution of all the above products have been supported by elemental analysis, and spectral studies. Antibacterial activities of the final compounds have been evaluated and all the compounds have shown significant inhibition of bacterial growth.

Keywords: Coumarin, Bromo coumarin, Amino thiazolyl coumarin, antibacterial activity, Schiff bases and Azetidinone.

Introduction:

Azetidine and their derivatives have been extensively explored for their applications in the field of medicines[1.2]. Like wise, azetidin--2—ones are of great importance because of the use of β—Lactam derivatives as an antimicrobial agents. [3] Coumarins constitute an important class of naturally occurring oxygen ring compound[4]. The chemistry of coumarin derivatives continues to draw attention of synthetic organic chemists due to their varied biological activities. Further thiazoles and coumarin derivatives with heterocyclic system at 3rd position exhibit promising biological activities. The growing literature demonstrates that the azetidine derivatives also exhibit better pharmacological properties. Variety of applications of azetidine in the biological studies necessitated us to take up the synthesis of biologically active heterocyclic compounds and study their biological and pharmacological activity.

Experimental:

Chemicals were obtained from Sigma—Aldrich and Merck, and are used as such without further, purification. All solvents (AR or extra pure grade) used for spectroscopic and other physical studies were further purified by literature method[8]. All operations were performed under nitrogen atmosphere using standard glass wares IR—spectra were recorded as KBr disc and in nujol mull on JASCO FT/IR-5300 spectrophotometer. Melting points were determined using a calibrated thermometer by Remi Digital Melting point

apparatus and are uncorrected. Elemental analysis were performed by Central Drug Research Institute, Lucknow NMR (^{1}H) spectra were recorded on a JEOL AL 300 FT NMR spectrometer. All chemical shifts were reported in parts per million relative to TMS as an internal standard in $CDCl_3$. Mass spectra were recorded at 70ev ionizing voltage on a JEOL—D300 MS instrument.

Preparation of Schiff bases:

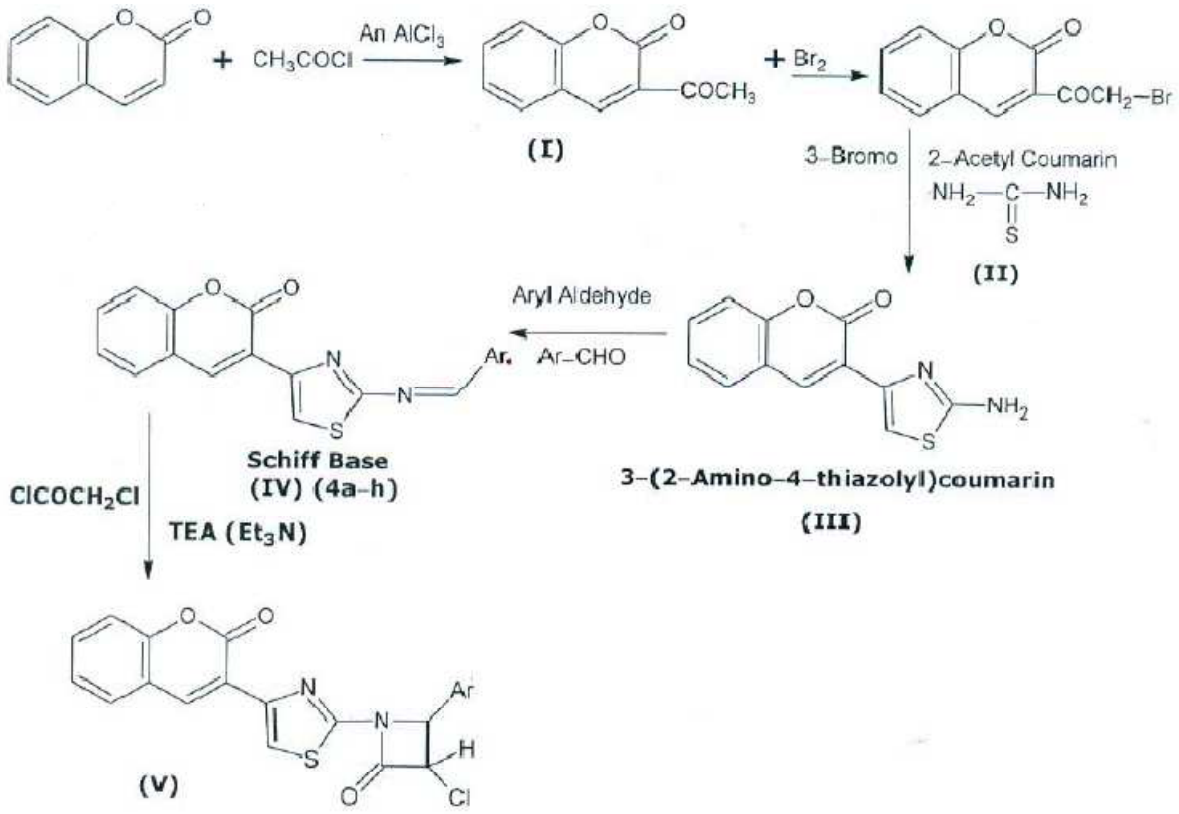
The starting compound 3—(2—bromo acetyl) coumarin was synthesized according to the reported(9) procedure by the bromination of 3—Acetyl coumaiin. Reaction of 3—(2—bromo acetyl) coumarin with thiourea resulted in the formation of 3—(2—amino-4—thiazoly1) coumarin (III)(10) Condensation of this compound with various aldehydes gave the Schiff bases(IV). These on cyclisation with chloroacetyl chloride gave the azetidinones(V). This is a two step process (yield 10-70%) (scheme-1).

Preparation of Schiff Bases(4a—h):

To a solution of 3—(2—Amino-4—thiazoly1) coumarin (2.44 g, 0.01 mole) in 15 mL of ethanol (15 mL) substituted Aromatic aldehyde (1.06 g, 0.01 mol) and 0.5 mL of piperidine as a catalyst was added, and the contents refluxed for about 5-6 hrs. Reaction mixture was cooled to 25°C and poured onto crushed ice, the solid separated was filtered, washed, dried and crystallized from ethanol to give the Schiff bases. The analytical data of all the compound (4a—h) are given in Table-1.

Preparation of 2—Azetidinones (5a—h):

A mixture of appropriate, Schiff bases (0.002 m mole) in Dioxane (30 mL) containing few drops of triethyl amine (TEA) (0.004 m mole) was stirred for one hours. Now chloro acetyl chloride (0.004mmole) (20mL) added and refluxed for half an hour. The reaction mixture was kept at RT for two days. The solvent was allowed to evaporate at RT. After completion of the reaction the contents were poured onto ice cold water, filter and dried. Product was purified by column chromatography over silica gel using 30% ethyl acetate:70% benzene as eluant. Recrystallisation from n—hexane gave various derivatives of substituted 2—Azetidinones in 65% yield. The homogeneity of all the synthesized compounds were checked by TLC using silica gel as adsorbent and visualization was accomplished by UV—light or iodine vapour in a Chamber. The analytical data of the compounds (5a—h) are given in table-2.



Substituted 3[l]–chloro–4[l]–aryl–1–(4–coumariniyl–1,3–thiazol–2–yl) azetidin–2–one (5a–h) (Scheme–1)

Where Ar — is referred to as: (a) Phenyl (b) 4—Methoxy phenyl (c) 4—Hydroxy phenyl (d) 2—Hydroxy phenyl (e) 4—Methyl phenyl (f) 3,4—Methylene dioxy phenyl (g) 4—Hydroxy-3—methoxy phenyl (h) 3,4—Dimethoxy phenyl

Antimicrobial Activity:

The synthesized compounds (5a—h) were screened for their antibacterial activity E.coli, P.aeruginoxa, S.aureus, Bacillus Sp. And C.albicans by filter paper disc technique. The minimum inhibitory concentration (MIC) was determined by using tube dilution method according to standard procedure(11). The screening results exhibited the MIC against the micro—organisms in the ranges 125-250 µg/mL. Results are presented in table-3.

Results and Discussion:

The characterization data for some representative compounds (5a—h) has been given. The IR—spectra of the compounds showed a prominent peaks 1615 (—C=N), 1716 cm^{-1} (Lactone —C=O), 1620 acetyl (C=O) consistent with the assigned structures. The ^{1}H—NMR spectrum showed a coumarin C_4—proton as singlet at δ 8.54. The remaining protons were observed in the usual range. A singlet appeared at δ 3.52-3.55 due to —$COCH_3$ proton. The multiplet observed in the range at 6.30-8.82 corresponded to phenylic proton. The IR—spectra of the Schiff base exhibit bands around 1620-30 cm^{-1} for the azomethine group[12 15].Cyclosation of the Schiff base with chloroacetyl chloride [16-18] gave substituted 2—azetidinones.

Antimicrobial activity:

It is evident from the screening data that compounds 5d, 5e, 5f, 5g showed highest degree of inhibition only against E. coli, P. aeruginosa, S.aureus and Bacillus SP at 250 µg/mL while 5a, 5b, 5c and 5h have been found to show good activity against all the bacterial Sp at 250 µg/mL no significant activity was found at 125 µg/rnL concentration.

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Table 1: Analytical data of compounds (4a-h)

Compd.	Molecular Formula Formula	Yield %	M.P. °C	Chemical analysis % Found (Calcd.)			
				C	H	N	S
4a	(C_{19}-$H_{12}N_2O_2S$)	68	160	68.60 (68.67)	3.57 (3.61)	8.40 (8.43)	9.57 (9.63)
4b	(C_{29}-$H_{14}N_2O_3S$)	64	158	66.26 (66.29)	3.80 (3.86)	7.67 (7.73)	8.78 (8.83)
4c	(C_{19}-$H_{12}N_2O_3S$)	58	151	65.44 (65.51)	3.38 (3.44)	7.98 (8.04)	9.12 (9.19)
4d	(C_{19}-$H_{12}N_2O_3S$)	64	155	65.44 (65.51)	3.38 (3.44)	7.97 (8.04)	9.11 (9.19)
4e	(C_{20}-$H_{14}N_2O_2S$)	66	145	69.31 (69.36)	3.97 (4.04)	8.0 (8.09)	9.17 (9.24)

4f	($C_{20}H_{12}N_2O_4S$)	60	164	63.75 (63.82)	3.10 (3.19)	7.37 (7.44)	8.45 (8.51)
4g	($C_{20}H_{14}N_2O_4S$)	55	165	63.41 (63.49)	3.62 (3.70)	7.37 (7.40)	8.40 (8.46)
4h	($C_{21}H_{16}N_2O_4S$)	54	159	64.20 (64.28)	4.0 (4.08)	7.04 (7.14)	8.05 (8.16)

Table 2: Analytical data of compounds (5a-h)

Compd.	Molecular Formula	Yield %	M.P. °C	Chemical analysis % Found (Calcd.)			
				C	H	N	S
5a	($C_{21}H_{13}N_2O_3SCl$)	68	184	61.62 (61.68)	31.73(31.82)	6.80 (6.85)	7.80 (7.83)
5b	($C_{22}H_{15}N_2O_4SCl$)	63	182	60.13 (60.20)	3.36 (3.42)	6.33 (6.38)	7.22 (7.29)
5c	($C_{21}H_{13}N_2O_4SCl$)	58	174	59.30 (59.36)	3.0 (3.06)	6.57 (6.59)	7.45 (7.53)
5d	($C_{21}H_{13}N_2O_4SCl$)	63	196	59.30 (59.36)	3.0 (3.06)	6.57 (6.59)	7.48 (7.53)
5e	($C_{22}H_{15}N_2O_3SCl$)	68	112	62.44 (62.48)	3.50 (3.55)	6.57 (6.62)	7.50 (7.57)
5f	($C_{22}H_{13}N_2O_5SCl$)	58	154	58.28 (58.34)	2.80 (2.87)	6.12 (6.18)	7.0 (7.07)
5g	($C_{22}H_{15}N_2O_5SCl$)	55	187	58.0 (58.08)	3.22 (3.30)	6.10 (6.16)	6.98 (7.04)
5h	($C_{23}H_{17}N_2O_5SCl$)	53	173	58.82 (58.91)	3.55 (3.62)	5.90 (5.92)	6.78 (6.83)

Compd.	IR (K.Br) cm^{-1} /1H—NMR ($CDCl_3$)
5a	1557 (—C=C), 1615 (—C=N), 1716 (Lactone —C=O), 1492, 1134 (C—N), 1H—NMR ($CDCl_3$), 7.30-7.58 (m, 4H, Ar—H), 7.99 (s, 1H, C_5—H) of thiazole 8.54 (s, 1H, C_4—H of cournarin)
5b	1540 (C=C), 1614 (—C=N), 1713 (Lactone—C=0), 1450, 1158 (—C—N); H—NMR ($CDC1_3$) 7.35-7.55 (m, 3H, Ar—H), 8.0 (s, 1H, C_5—H of thiazole) 8.45 (s, 1H C4—H of coumarin), δ 3.96 (s, 3H, OCH_3)
5c	1540 (C=C), 1605 (—C=N), 1731 (Lactone—C=O), 1490, 1138 (C—N), 1H—NMR ($CDCl_3$), 7.35-7.55 (m, 3H, Ar—H), 8.0 (s, 1H, C_5—H of thiazo1e, 8.45 (s, 1H, C_4—H of coumarin), 9.20 (s, 1H—OH).
5d	1538 (C=C), 1608 (—C=N), 1731 (Lactone —C=O), 7.20 (d, 1H, Ar—H, J=3Hz), 7.75 (d, 1H, Ar—H, J=3 Hz), 8.0 (s, 1H, C_5—H of thiazole), 9.38 (s, 1H, C_4—H) of coumarin; 1439-1156 (C—N) 9.20, s, 1H—OH
5e	1603 (—C=N), 1724 (Lactone —C=O) δ 2.28 (s, 3H, CH), 7.53 (d, 1H, J=8 Hz, Ar—H); 7.62 (s, 1H, C5 of thiazole) 7.69-7.73 (dd, 1H, Ar—H), 7.92 (d, 1H, J=2.4 Hz, Ar—H), 8.08 (s, 1H, C_4—H of coumarin) 1439-1156 (C—N), δ 2.50 (s, 3H, —CH_3)
5f	1538 (C=C); 1625 (—C=N); 1739 (Lactone, C=O) 7.35 (d, 1H, Ar—H,J =3Hz); 7.78, (d, 1H, Ar—H), J=2Hz, 8.10 (s, 1H, C_5—H of thiazole) 8.55 (s, 1H, C_4—H of coumarin) 1433, 1456 (—C—N), δ 6.15 (s, 2H, CH2); 3.70-3.74 (m, 8H, —CH_2—O—CH_2—)
5g	1635 (C=N), 1576 (C=C) 1439, 1156 (C—N), 1719 (Lactone —C=O), 8-10 (s, 1H, of the thiazole) 7.4-7.8 (m, 3H, Ar—H), 8.50 (s, 1H, C_4 of coumarin) δ 3.8 (3H, s, OCH_3); 6.08 broad signal,OH)
5h	1630 (C=N), 1585 (C=C), 1490, 1140 (C—N); δ 3.89 (s, 3H, OCH_3), 7.42-7.79 (m, 6H, Ar—H); 1720 (Lactone—C=O), 8.3 (s, 1H, C_5 of Thiazole) and 8.5 (s, 1H,C_4 of coumarin)

Table 2: IR (KBr) crn^{-1}/1H—NMR ($CDCl_3$) data of (4a—h)

Table 3: Antimicrobial activity data of compounds (5a—h)

Compd.	E.coli		P.aeruginosa		S.aureus		Bacillus Sp		C.Albicans	
5a	—	++	—	++	—	++	—	++	—	—
5b	—	++	—	++	—	++	—	++	—	—
5c	—	++	—	++	—	++	—	++	—	—
5d	—	+++	—	+++	—	+++	—	+++	—	—
5e	—	+++	—	+++	—	+++	—	+++	—	—
5f	—	+++	—	+++	—	+++	—	+++	—	—
5g	—	+++	—	+++	—	+++	—	++	—	—
5h	—	+++	—	++	—	++	—	++	—	—
Amikacin	—	++++	—	++++	—	++++	—	+++	—	—
Grescofulvin	—	—	—	—	—	—	—	—	—	++++

(—)<6mm, (+) = 7—10mm (++)—11—15 mm (+++); 16—21 mm, (++++) 22—28 mm.

REFERENCES :

1. G.Weber, F. Buccheri, R. Mato and P.Salozzo, J. Heterocycl. Chem; 15, 1978, 1537.
2. J.S. Stephenton, E. Vorella, E.D. Micromastaras and N.E. Alexander, J.Heterocycl. Chem; 16, 1978, 1373.
3. G.A. Koppel, Small ring heterocycles (Wiley Interscience, New York) 1993.
4. R.D.H. Murrary, J. Mendez and S.A.Brown, The natural coumarins, Occurrence, Chemistry and Biochemistry (Wiley lnterscience, New York) 1982.
5. V.V. Mulwad & J.M.Shiradkar, Ind. J. Heterocycl. Chem. 11, 2002, 199.
6. M.D. Friedmann, P.L. Stoller, T.H. Porter & K. Folkers, J. Med. Chem; 16, 2002, 1314.
7. S.N.Sawhney, S.P.Singh & S.K. Arora, Ind. J. Chem. 15B, 1977, 729.
8. W.L.F. Armarego & D.D.Perrin, Purification of laboratory chemicals, 4th edn. (Butterworth, Heinemann, Oxford) 1997; OX28DP.
9. E.D.Elliot, J. Amer. Chem. Soc; 73 (1951) 754.

10 B.M.Gurupadiah, E.Jayachandran, B.S.Kumar, A.N.Nagappa & LUG Nargund, Ind. J. Heterocycl. Chem. 7 (1998) 213.

11 W.Kemp. Organic Spectroscopy, 2nd Edition Basingtake, Macmillan U.S.A.

12 J.W.Akitt, NMR and Chemistry, 2nd Edn. Chapman & Hall 1983.

13 E.Breitmair and W.Voelter, 13C-NMR spectroscopy (High resolution methods and applications in organic chemistry and biochemistry (VCH, Publication, Germany) 1990.

14 F.W.Wehri, A.P.Marchand and S.Wlhrli, Interpretation of Carbon 13 NMR— spectra (John Wiley, Singapore 1989).

15 G.C. Levy, R.L. Lichter and G.L.Nelson, Carbon-13 Nuclear Magnetic Resonance Spectroscopy 2nd Ed. Wiley New York 1980.

16 N.C.Desai, A.M.Bhavsar, M.D.Shah and G.D.Vyas, Ind. J. Chem. 39B, 2000, 277.

17 R.K.Tiwari, Devendra Singh, Jaspal Singh, A.K.Chillar, Ramesh Chandra and A.K.Verma, Eur. J. Med, Chem. 41, 2006, 40.

18 S.Prasanna, E.Manivannan & S.C.Chaturvedi, Ind.J.Chem. 43B, 2004, 2349.