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Synthesis and Characterization of Azo Schiff Bases and their β-Lactam Derivatives

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Azo salicylaldehyde (**I5**) was synthesized by reaction of 5-bromo-salicylaldehyde with diazonium salt of 4-nitroaniline by diazotization method. Thus, synthesized azoaldehyde was treated with variable 2-aminobenzothiazoles (**I6a-f**) to synthesize the Schiff bases (**I7a-f**). The β-lactam derivatives (**I8a-f**) were also synthesized. All the newly synthesized compounds were characterized by TLC, UV-visible and FT-IR techniques.

Keywords: Azo salicylaldehyde, Schiff base, 2-Amino-benzothiozole, β-Lactam.

INTRODUCTION

Schiff bases and their β-lactam derivatives exhibited a variety of applications in clinical, biological, analytical and pharmacological activities [1-5]. The Schiff bases (-CH=N-) playes an important function as an organic synthone for newer molecules. In addition, moieties within the azole class have been of great scientific exploitation and interest as these are accompanied with almost all the biological profiles and the pharmacological activities [6-8]. Similarly, the β-lactam ring is part of the core structural feature in an array of drug categories and are active against a wide range of microorganisms [9-11].

In addition, the antimicrobial activity of aldimines and ketimines containing electron-attracting and electron-repelling groups are widely used for industrial purposes and also exhibit a broad range of biological activities [12]. These imines are in a forms of *syn*- or *anti*-oxime and phenolic or amino Schiff bases. The synthesis of compounds containing chloro group or azo moiety exhibit the herbicidal activities [13,14]. The azo group in addition to the other groups in the same compounds exhibit important biological activities like antibacterial, antioxidant and other pharmacological activities [15-18].

Azo unit linked with Schiff bases exhibited a diverse applications in chemical as well as pharmacological activities [19-22]. The β-lactams are one of the most commonly prescribed drug classes with numerous clinical indications generally synthesized by the cyclization of imines and resulted in the formation of 3-carbon and 1-nitrogen ring (β-lactam ring), which is highly reactive [2]. In this present investigation work, we are interested in the combination of azo group with the Schiff base fragment, using 2-aminobenzothiazoles and then further converted the azo Schiff base into β-lactam derivatives.

EXPERIMENTAL

All the reagents were of synthesis grade and purchased from Sigma-Aldrich, USA. The progress of reaction was monitored by TLC. TLC plates were of silica gel coated aluminum plates made by Merck. Physical constants recorded on Equiptronics digital m.p./b.p. apparatus in degree calculus on model EQ-730. The UV-Vis spectra were recorded on Shimadzu UV 1800 series spectrophotometer in the range of wavelength 800-200 nm. FT-IR spectra were recorded on Shimadzu FT-IR spectrometer using KBr pellets in the range of 4000-400 cm^{-1}. ^1H NMR was recorded with delta NMR software (Jeol) in $CDCl_3$ as solvent and TMS as internal standard. The chemical shifts are reported in ppm (δ) downfield from TMS.

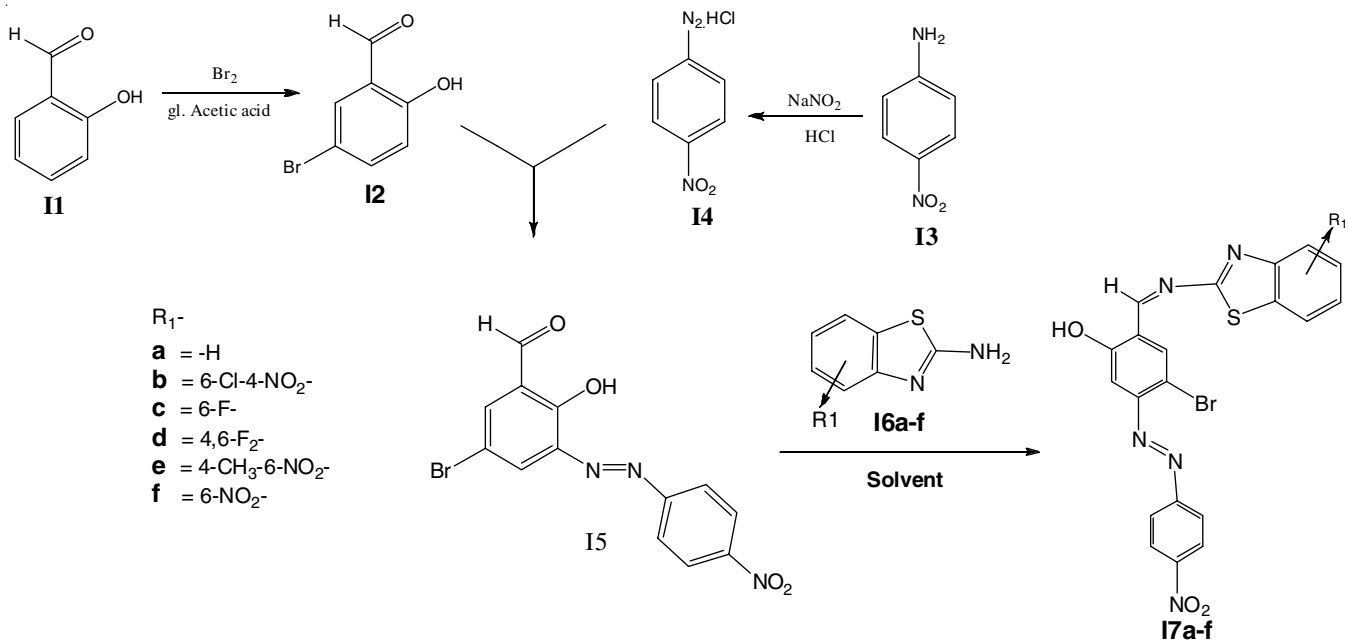
Synthesis of azo salicylaldehyde (I5): In 100 mL beaker charged 5.13 g (0.0372 mol) 4-nitroaniline, added 25 mL conc. HCl and 20 mL distilled water. Cooled the solution to 0 ºC by in ice bath (solution A). In a hard glass tube, charged 3.105 g (0.045 mol) sodium nitrite and dissolved in 15 mL water and cooled the solution to 0 ºC in ice bath (solution B).

When both the solutions attained 0 ºC temperature, solution B was added dropwise in solution A with constant stirring. During addition, temperature of the reaction solution should be maintained below 10 ºC. A pinch of urea was added in order to decompose the excess nitrous acid and filtered the solution.

5-Bromo salicylaldehyde (7.477 g, 0.0372 mol) was added in 35 mL 10 % NaOH solution and stirred till clear solution obained. The solution was cooled to 0 ºC and then added the filtrate slowly to this content with constant stirring. After complete addition, allowed the solution to stand for 10 min in ice bath. Filtered the light orange dye, washed with cold water, recrystallized and stored in an air tight container [16]. Yield: 61.49 %, m.p.: 106-108 ºC, R_f: 0.33. Elemental analysis calcd. (found) % of $C_{13}H_8N_3O_4Br$: C: 44.57 (43.12), H: 2.28 (2.23), N: 12.00 (11.52). IR (KBr, ν_{max}, cm^{-1}): 3225 (-OH *str.*), 3075 (C-H arom.), 2850 (-CHO), 1605 (C=O), 1521 (C=C arom.), 1520, 1350 ($-NO_2$), 1305, 1463 (N=N), 1305 (-CH), 535 (C-Br). UV analysis: 337 and 236 nm.

Synthesis of Schiff base (I7a-f): Equimolar proportion of compound **I5** and relevant benzothiazole (**I6a-f**) was mixed in 250 mL round bottom flask fitted with water condenser and thermometer pocket. To this, added 70 mL toluene and attached Dean and Stark apparatus properly. Few drops of acetic acid was added and allowed to reflux for 4 h and monitored the reaction with TLC. The solvent was removed under reduced pressure after the completion of the reaction. The solid product obtained was washed with ethanol and recrystallized by hot water (**Scheme-I**). The physico-analytical data is given in Table-1.

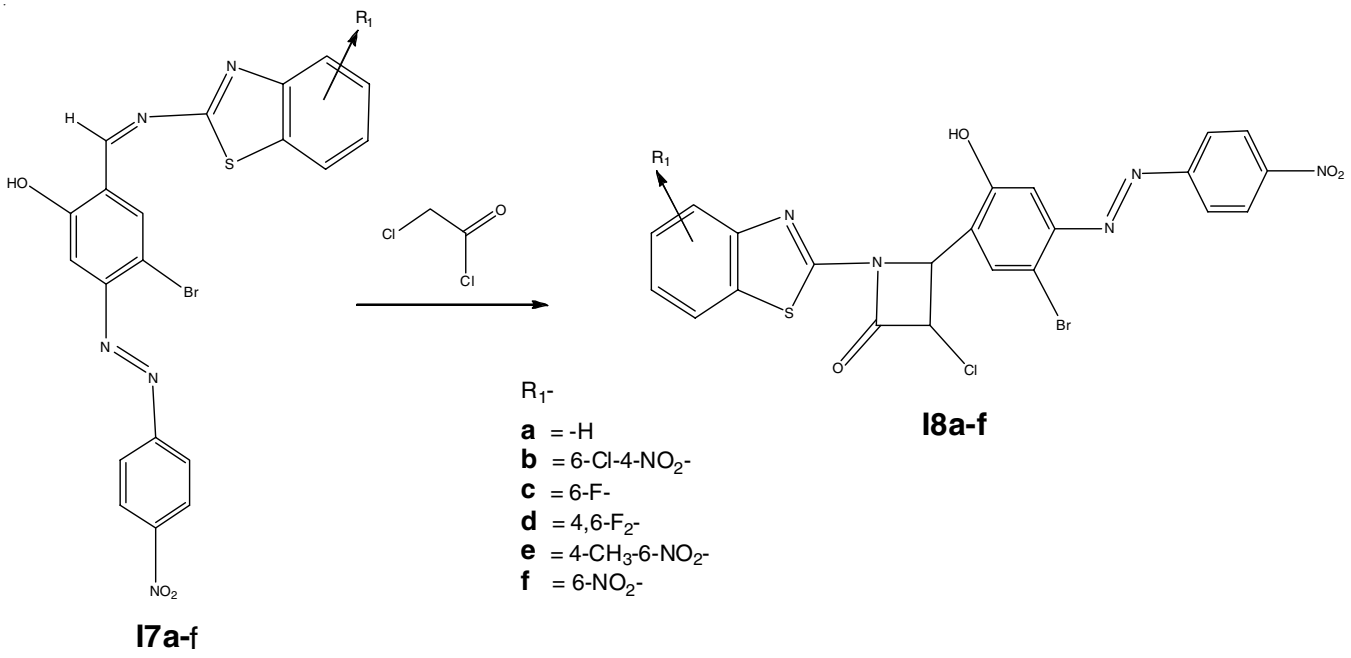
Synthesis of β-lactam derivatives (I8a-f): In 100 mL round bottom flask containing reflux condenser and thermometer pocket in a ice-bath, a mixture of 0.00125 mol of Schiff base (**I7a-f**) and 0.15 mL TEA was dissolved in 20 mL 1,4-dioxane was stirred for 0.5 h. To this cold solution, 0.15 mL (0.00186 mol) chloroacetyl chloride was added slowly added at > 5 ºC. Refluxed the contents for 12-15 h and TLC was checked after 9, 11 and 13 h. After clear TLC, 1,4-dioxane was distilled off and a viscous liquid as the resultant content was obtained. It was washed with 10% $NaHCO_3$ to remove unreacted chloroacetyl chloride, finally washed with cold water and recrystallized by methanol (**Scheme-II**). The physico-analytical data is given in Table-2.



Scheme-I: Synthesis of azo Schiff bases

TABLE-1
PHYSICO-ANALYTICAL DATA OF SYNTHESIZED AZO SCHIFF BASES (**I7a-f**)

Compd.	-R_1	m.f. (m.w., g/mol)	Colour (m.p., °C)	Yield (%) (R_f value)	Elemental analysis (%): Calcd. (found)		
					C	H	N
I7a	-H	$C_{20}H_{12}N_5O_3SBr$ (482)	Light brown (109-111)	90.27 (0.40)	49.79 (48.54)	2.49 (2.75)	14.52 (14.20)
I7b	6-Cl, 4-NO_2	$C_{20}H_{10}N_6O_5SBrCl$ (561.5)	Yellow (102-104)	86.90 (0.44)	42.74 (41.53)	1.78 (1.63)	14.96 (13.68)
I7c	6-F	$C_{20}H_{11}N_5O_3SBrF$ (500)	Light yellow (170-172)	87.70 (0.43)	48.00 (47.65)	2.2 (2.15)	14.00 (13.75)
I7d	4,6-F_2	$C_{20}H_{10}N_5O_3SBrF_2$ (518)	Light brown (106-108)	76.03 (0.50)	46.33 (45.63)	1.93 (1.86)	13.59 (13.26)
I7e	4-CH_3, 6-NO_2	$C_{21}H_{13}N_6O_5SBr$ (541)	Yellow (91-93)	85.92 (0.47)	46.58 (45.65)	2.40 (2.38)	15.53 (15.25)
I7f	6-NO_2	$C_{20}H_{11}N_6O_5SBr$ (527)	Light brown (94-96)	70.55 (0.46)	45.54 (44.68)	2.08 (1.98)	15.94 (15.85)



Scheme-II: Synthesis of β-lactam derivatives

TABLE-2
PHYSICO-ANALYTICAL DATA OF SYNTHESIZED β-LACTAM DERIVATIVES (**I8a-f**)

Compd.	-R_1	m.f. (m.w., g/mol)	Colour (m.p., °C)	Yield (%) (R_f value)	Elemental analysis (%): Calcd. (found)		
					C	H	N
I8a	-H	$C_{22}H_{13}N_5O_4SBrCl$ (558.5)	Brown (267-269)	78.26 (0.49)	47.27 (46.59)	2.34 (2.30)	12.53 (12.45)
I8b	6-Cl, 4-NO_2	$C_{22}H_{11}N_6O_6S\ BrCl_2$ (639)	Dark brown (72-74)	81.53 (0.50)	41.40 (40.89)	1.74 (1.71)	13.17 (13.11)
I8c	6-F	$C_{22}H_{12}N_5O_4SBrClF$ (576.5)	Dark brown (60-62)	77.94 (0.58)	45.81 (44.56)	2.10 (2.05)	12.14 (11.95)
I8d	4,6-F_2	$C_{22}H_{11}N5O4SBrClF_2$ (594.5)	Light brown (242-244)	74.39 (0.55)	44.43 (43.95)	1.86 (1.79)	11.77 (11.44)
I8e	4-CH_3, 6-NO_2	$C_{23}H_{14}N_6O_6SBrCl$ (617.5)	Brown (205-207)	83.33 (0.57)	44.73 (44.12)	2.27 (2.15)	13.61 (13.21)
I8f	6-NO_2	$C_{22}H_{12}N_6O_6SBrCl$ (603.5)	Light brown (73-75)	80.79 (0.51)	43.74 (43.02)	1.99 (1.91)	13.92 (13.87)

RESULTS AND DISCUSSION

In the present work, *p*-nitrophenyldiazonium chloride reacted with 5-bromo salicylaldehyde to obtain azo salicylaldehyde and then to get relevant azo-schiff bases by reacting azo salicylaldehyde with substituted 2-aminobenzothiazoles as shown in **Scheme-I**.

The UV-vis spectrum in ethanol for compound **I5** shows two bands at 337 and 236 nm which are attributed due to n→π* and π→π* transition, respectively. The characteristic stretching frequencies of compound **I5** exhibited the band at 3225 cm^{-1} indicates the stretching vibration of -OH group. A band at 3075 cm^{-1} was due to aromatic -C-H bond stretching vibration and frequency at 2850 cm-1 was due to -C-H stretching of aldehyde group. Moreover, bands at 1520 and 1350 cm^{-1} indicated the stretching vibration of -NO_2 group. The lower IR band at 535 cm^{-1} was due to stretching vibration of C-Br group.

Similarly, azo Schiff base and β-lactam derivatives were synthesized and characterized successfully (Table-3). The β-lactam ring was occurred by the reaction of Schiff bases with chloroacetyl chloride in dioxane solvent and in IR spectrum the carbonyl group was seen between 1710 and 1730 cm^{-1}.

TABLE-3
UV AND FT-IR SPECTRAL DATA OF AZO SCHIFF BASES (**I7a-f**) AND β-LACTAMS DERIVATIVES (**I8a-f**)

Compd.	IUPAC name	λ_{max} (nm)	FT-IR (ν_{max}, cm^{-1})
I7a	2-(Benzothiazol-2-yliminomethyl)-4-bromo-6-(4-nitro-phenylazo)-phenol	220, 279, 344	3365 (C-OH), 3076 (C-H arom.), 1662 (C=N), 1550 (C=C arom.), 1454 (N=N), 1342 (NO_2), 1091 (C-O), 806 (C-S), 547 (C-Br)
I7b	4-Bromo-2-[(6-chloro-4-nitro-benzothiazol-2-ylimino)-methyl]-6-(4-nitro-phenylazo)-phenol	223, 374	3468 (C-OH), 3089 (C-H arom.), 1654 (C=N), 1531 (N=N), 1460 (C=C arom.), 1091 (C-O), 815 (C-S), 1350, 1342 (C-NO_2), 887 (C-Cl), 443 (C-Br)

I7c	4-Bromo-2-[(6-fluoro-benzothiazol-2-ylimino)-methyl]-6-(4-nitro-phenylazo)-phenol	249, 353	3383 (C-OH), 2964 (C-H arom.), 1616 (C=N), 1480 (C=C arom.), 1512 (N=N), 1456, 1342 (C-NO_2), 1099 (C-F), 812 (C-S), 524 (C-Br)
I7d	4-Bromo-2-[(4,6-difluoro-benzothiazol-2-ylimino)-methyl]-6-(4-nitro-phenylazo)-phenol	205, 234, 371	3230 (C-OH), 2954 (C-H arom.), 1672 (C=N), 1502 (N=N), 1470 (), 1450, 1342 (C-NO_2), 1096 (C-F), 510 (C-Br), 821 (C-S)
I7e	4-Bromo-2-[(4-methyl-6-nitro-benzothiazol-2-ylimino)-methyl]-6-(4-nitro-phenylazo)-phenol	231, 252, 340	3483 (C-OH), 3100 (C-H arom.), 2962 (C-H alkyl), 1662 (C=N), 1517 (N=N), 1490 (C=C arom.), 1483, 1342 (C-NO_2), 887 (C-Cl), 806 (C-S), 525 (C-Br)
I7f	4-Bromo-2-[(6-nitro-benzothiazol-2-ylimino)-methyl]-6-(4-nitro-phenylazo)-phenol	229, 247, 345	3531 (C-OH), 2964 (C-H arom.), 1656 (C=N), 1590 (C=C arom.), 1514 (N=N), 1342 (C-NO_2), 806 (C-S), 464 (C-Br)
I8a	1-Benzothiazol-2-yl-4-[5-bromo-2-hydroxy-3-(4-nitro-phenylazo)-phenyl]-3-chloro-azetidin-2-one	220, 277, 371	3373 (C-OH), 2920 (C-H alkyl), 1589 (C=N), 1522 (), 1444 (N=N), 1304 (C-NO_2), 807 (C-Cl), 765 (C-S), 550 (C-Br)
I8b	4-[5-Bromo-2-hydroxy-3-(4-nitro-phenylazo)-phenyl]-3-chloro-1-(6-chloro-4-nitro-benzothiazol-2-yl)-azetidin-2-one	238, 399	3468 (C-OH), 2920 (C-H alkyl), 1628 (C=N), 1500 (C-NO_2), 1343 (N=N), 1248 (C-NO_2), 815 (C-Cl), 723 (C-S), 550 (C-Br)
I8c	4-[5-Bromo-2-hydroxy-3-(4-nitro-phenylazo)-phenyl]-3-chloro-1-(6-fluoro-benzothiazol-2-yl)-azetidin-2-one	202, 371	3397 (C-OH), 2920 (C-H alkyl), 1606 (C=N), 1545, 1254 (C-NO_2), 1332 (N=N), 1254 (C-NO_2), 1450 (C-F), 807 (C-Cl), 695 (C-S), 650 (C-Br)
I8d	4-[5-Bromo-2-hydroxy-3-(4-nitro-phenylazo)-phenyl]-3-chloro-1-(4,6-difluoro-benzothiazol-2-yl)-azetidin-2-one	219, 257, 371	3384 (C-OH), 2965 (C-H alkyl), 1578 (C=N), 1466, 1254 (C-NO_2), 1332 (N=N), 1450 (C-F), 846 (C-Cl), 801 (C-S), 650 (C-Br)
I8e	4-[5-Bromo-2-hydroxy-3-(4-nitro-phenylazo)-phenyl]-3-chloro-1-(4-methyl-6-nitro-benzothiazol-2-yl)-azetidin-2-one	221, 261, 350	3451 (C-OH), 2920 (C-H alkyl), 1623 (C=N), 1449, 1259 (C-NO_2), 1329 (N=N), 846 (C-Cl), 795 (C-S), 630 (C-Br)
I8f	4-[5-Bromo-2-hydroxy-3-(4-nitro-phenylazo)-phenyl]-3-chloro-1-(6-nitro-benzothiazol-2-yl)-azetidin-2-one	221, 352	3445 (C-OH), 2960 (C-H alkyl), 1595 (C=N), 1444 (C-NO_2), 1326 (N=N), 1259 (C-NO_2), 846 (C-Cl), 795 (C-S), 640 (C-Br)

TABLE-4
^{1}H NMR SPECTRAL DATA (δ VALUES, ppm) OF β-LACTAM DERIVATIVES (**I8a-f**)

Compd.	-CH aromatic	-CH benzothiazole	-CH propiolactam	-OH aromatic
I8a	8.10 (s, 2H), 7.80 (s, 2H), 7.75 (s, 1H), 7.10 (s, 1H)	7.60 (s, 1H), 7.40 (s, 1H), 7.20 (s, 2H)	5.0 (d, 1H), 4.75 (d, 1H)	5.30 (s, 1H)
I8b	8.55 (s, 2H), 8.25 (s, 2H), 7.75 (s, 1H), 6.80 (s, 1H)	8.75 (s, 1H), 8.70 (s, 1H)	5.30 (d, 1H), 5.55 (d, 1H)	5.25 (s, 1H)
I8c	8.29 (s, 2H), 7.40 (s, 2H), 7.25 (s, 1H), 7.30 (s, 1H)	7.60 (s, 1H), 7.35 (s, 1H), 7.45 (s, 1H)	5.30 (d, 1H), 5.35 (d, 1H)	5.25 (s, 1H)
I8d	8.25 (s, 2H), 8.10 (s, 2H), 6.90 (s, 1H), 6.80 (s, 1H)	7.40 (s, 1H), 7.30 (s, 1H)	5.25 (d, 1H), 5.55 (d, 1H)	5.25 (s, 1H)
I8e	8.20 (s, 2H), 8.00 (s, 2H), 7.30 (s, 1H), 7.20 (s, 1H)	7.90 (s, 1H), 7.80 (s, 1H), 2.30 (s, 3H)	5.50 (d, 1H), 4.90 (d, 1H)	4.90 (s, 1H)
I8f	8.80 (s, 2H), 8.50 (s, 2H), 7.35 (s, 1H), 7.40 (s, 1H)	8.35 (s, 1H), 7.80 (s, 1H), 7.60 (s, 1H)	5.80 (d, 1H), 5.25 (d, 1H)	5.25 (s, 1H)

The ^{1}H NMR analysis β-lactam derivatives measured in $CDCl_3$ solvent with TMS as an internal reference showed the two peak at ~ 5 ppm was attributed to propiolactam and another peak at ~ 4.5 ppm was attributed to -OH of aromatic ring. The peaks in the range 6.9-9.2 ppm were due to aromatic protons (Table-4).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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