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Research Article

ANTICOAGULANT POTENTIAL OF SCHIFF BASES OF 1,3-OXAZINES

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ABSTRACT

A series of Schiff bases of 1, 3-oxazines were synthesized *via* reaction of 1, 3-oxazine-2-amine with substituted benzaldehyde. The title compounds (3a-3r) were characterized with IR, NMR and screened for their anticoagulant activity by measuring prothombin time by Quick's method. The study revealed that most of the synthesized compounds exhibited significant anticoagulant activity amongst which compound **3c, 3f, 3g, 3j, 3o** and **3p** were found to be most active.

Keywords: Schiff bases, 1,3-Oxazines, Anticoagulant activity.

INTRODUCTION

Nitrogen heterocycles are of special interest because they constitute an important class of natural and nonnatural products, many of which exhibit useful biological activities[1]. Investigation of the 1,3-oxazine heterocycles has shown that they possess varied biological properties such as antibacterial[2], analgesic[3], antitubercular[4], anticancer[5] and anticoagulant[6]. Here we described synthesis and anticoagulant potential of Schiff bases of 1,3-oxazines which may inhibit the ability of factor VII_a in complex with tissue factor (TF) to cleve factor X, thus inhibiting clotting activity. Patient with deep vein thrombosis (DVT) and pulmonary embolism (PE), two of the most common thrombotic complications are diagnosed every year. Thrombotic disorders are also 3-fold more likely in people with cancer. Now days, heparin and warfarin and low molecular weight heparin are used. Heparin and coumarin are indirect inhibitors that require intermediate co-factors to mediate their anticoagulant effect.

The coumarin suffers from narrow therapeutic index, while unfractionated heparin suffers from enhanced bleeding complication, patient to patient response variability, heparin induced thrombocytopenia (HIT). Low molecular weight heparin also suffers from similar problems, although the number of bleeding episode is lower and response variability is reduced.

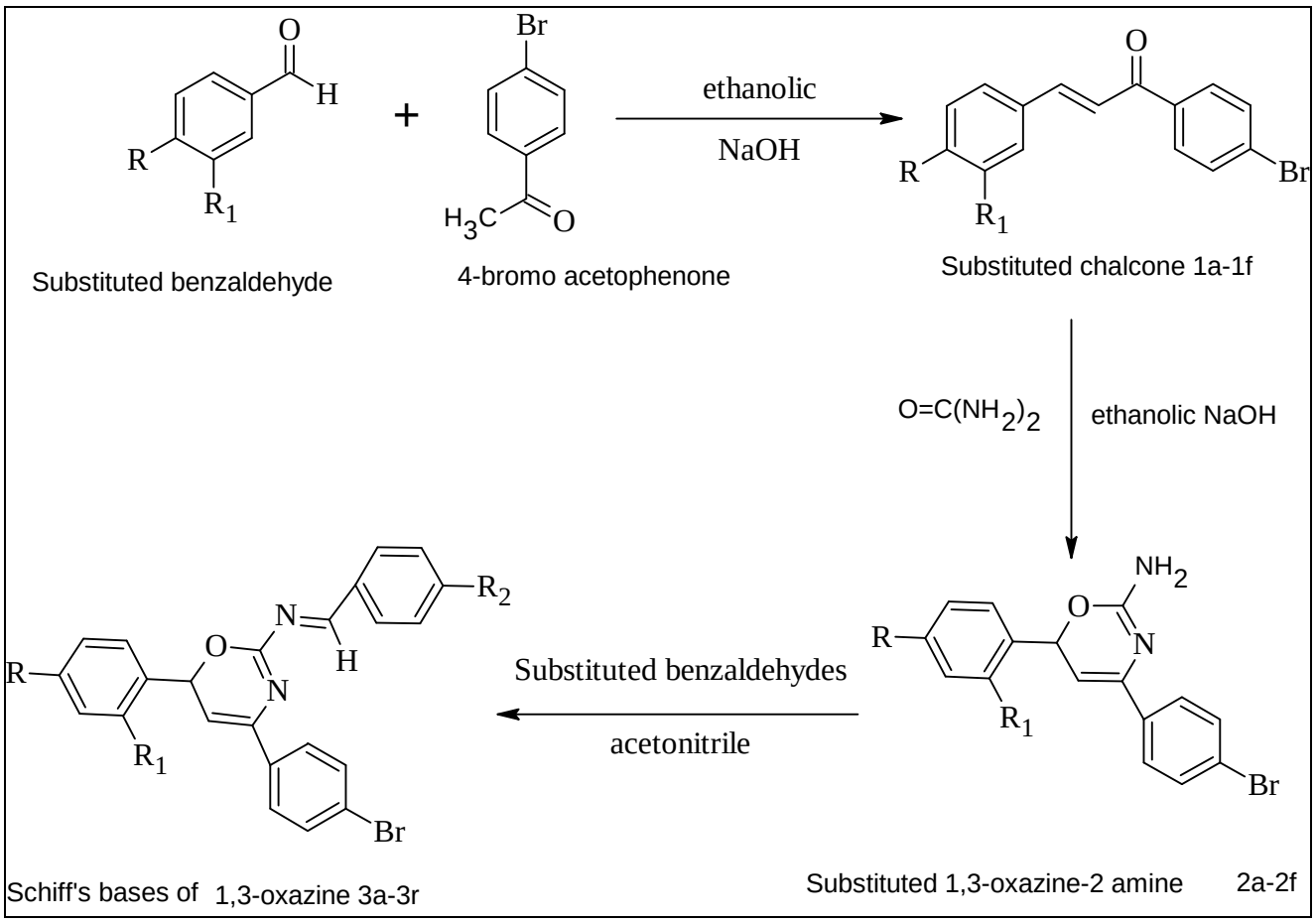

Fig. 1: Synthesis Scheme

Table 1: Various Substituents Used for Schiff's Bases of 1,3-Oxazine (3a-3r)

Compound	R	R_1	R_2
3a	Cl	H	NO_2
3b	$(OCH_3)_3$	H	NO_2
3c	NO_2	H	NO_2
3d	$N(CH_3)_2$	H	NO_2
3e	OCH_3	H	NO_2
3f	H	OH	NO_2
3g	Cl	H	Cl
3h	$(OCH_3)_3$	H	Cl
3i	NO_2	H	Cl
3j	$N(CH_3)_2$	H	Cl
3k	OCH_3	H	Cl
3l	H	OH	Cl
3m	Cl	H	OCH_3
3n	$(OCH_3)_3$	H	OCH_3
3o	NO_2	H	OCH_3
3p	$N(CH_3)_2$	H	OCH_3
3q	OCH_3	H	OCH_3
3r	H	OH	OCH_3

GENERAL PROCEDURE FOR SYNTHESIS OF SUBSTITUTED CHALCONES 1a-1f[7]

A solution of 22 gm of sodium hydroxide in 200 ml of water and 100 gm (122.5 ml) of ethanol was placed in 500 ml bolt hand flask provided with a magnetic stirrer (Remi- capacity 1 litre). The flask was immersed in a bath of a crushed ice poured in 52 gm (0.43 mol) of 4-bromoacetophenone then stirring was started and 46 gm (44 ml,0.43 mol) of pure substituted benzaldehyde was added. The temperature of mix was kept at about 25^0 C and stirred vigorously until the mixture was so thick that stirring is no longer effective (2-3 hr). The stirrer was removed and reaction mixture was left in a refrigerator for overnight. The product was filtered with suction on stirred glass funnel and then washed with cold water until the washing are neutral to litmus then rinsed with 20 ml of ice-cold rectified spirit. The crude chalcone obtained was dried in air. It was recrystallised from rectified spirit.

GENERAL PROCEDURE FOR SYNTHESIS OF SUBSTITUTED 1,3-OXAZINE-2-AMINES 2a-2f[7]

A mixture of chalcone (0.02 mol) and urea (0.02 mol) was dissolved in ethanolic NaOH (10 ml) and stirred for about 2-3 hr with magnetic stirrer. Then 400 ml of cold water was poured into it with continuous stirring for 1 hr. and then kept in refrigerator for 24 hr. Then precipitate obtained was filtered and recrystallized from rectified spirit.

GENERAL PROCEDURE FOR SYNTHESIS OF SCHIFF BASES OF 1,3-OXAZINES 3a-3r[8]

Mixture of substituted aldehydes (0.1 moles) and 4-(4-bromophenyl)-6-(4-substitutedphenyl)-6*H*-1,3-oxazin-2-amine (0.1 moles) in acetonitrile were taken in round bottom flask separately and a few drops of sulphuric acid was added to reaction mixtures. The reaction mixture was refluxed for two hours on a water bath. The clear solution obtained was cooled and poured onto cold water. Pale yellow crystals immediately separated out. The solids separated on filteration were dried and recrystallized from acetic acid.

4-(4-Bromophenyl)-6-(4-chlorophenyl)-N-[(E)-(4-nitrophenyl) methylidene]-6H-1,3-oxazin-2-amine (3a)

Yield: 71.46%, M.P.: 140-142^{0}C, IR (KBr, cm^{-1}): 3054.69, 944.94 (C-C-H), 1648.84 (C=N), 1563.99, 1342.21 (NO_2), 1224.58 (C-O), 1178.29 (C-N), 815.74 (C-Cl), 694.248 (C-Br). ^{1}H NMR (300 MHz, TMS) δ: 7.887-7.771 (m, 4H, Ar-Br), 7.633-7.533 (m, 4H, Ar-Cl), 7.297-7.245 (m, 4H, Ar-NO_2), 6.3 (d, 1H, fifth CH oxazine), 6.12 (d, 1H, sixth CH oxazine), 1.612 (s, 1H, CH).

4-(4-Bromophenyl)-6-(3,4,5-trimethoxyphenyl)-N-[(E)(4-nitrophenyl)methylidene]-6H-1,3-oxazin-2-amine (3b)

Yield: 68.43%, M.P.: 152-154^{0}C, IR (KBr, cm^{-1}): 3109.73, 934.83 (C-H), 1623.73 (C=N), 1523.25, 1333.33 (NO_2), 1212.55 (C-O), 1182.44 (C-N), 1093.28 (C-O), 667.55 (C-Br). ^{1}H NMR (300 MHz, TMS) δ: 7.965-7.787 (m, 4H, Ar-Br), 7.723-7.633 (m, 2H, Ar-$(OCH_3)_3$, 7.387-7.255 (m, 4H, Ar-NO_2), 6.3 (d, 1H, fifth CH oxazine), 6.12 (d, 1H, sixth CH oxazine), 2.525-2.625 (s, 9H, OCH_3), 1.721 (s, 1H, CH).

4-(4-Bromophenyl)-6-(nitrophenyl)-N-[(E)(4-nitrophenyl) methylidene]-6H-1,3-oxazin-2-amine (3c)

Yield: 62.71%, M.P.: 140-142^{0}C, IR (KBr, cm^{-1}): 3052, 945 (CCH), 1646 (C=N), 1564, 1377 (NO_2), 1226, 1173 (C-N), 692 (C-Br). ^{1}H NMR (300 MHz, TMS) δ: 7.899-7.772 (m, 4H, Ar-Br), 7.387-6.99 (m, 8H, Ar-NO_2), 6.3 (d, 1H, fifth CH oxazine), 6.12 (d, 1H, sixth CH oxazine), 1.612 (s, 1H, CH).

4-(4-Bromophenyl)-6-(N,N-dimethylaminophenyl)-N-[(E)(4-nitrophenyl)methylidene]-6H-1,3-oxazin-2-amine (3d)

Yield: 65.14%, M.P.: 172-174^{0}C, IR (KBr, cm^{-1}): 2918, 1440 (-CH_3), 1648 (C=N), 1564, 1343 (NO_2), 1223 (C-O), 1173 (C-N), 690 (C-Br). ^{1}H NMR (300 MHz, TMS) δ: 7.903-7.678 (m, 4H, Ar-Br), 7.564-7.454 (m, 4H, Ar-NO_2), 7.343-7.266 (m, 4H, Ar-$N(CH_3)_2$), 6.3 (d, 1H, fifth CH oxazine), 6.12 (d, 1H, sixth CH oxazine), 1.569 (s, 6H, N-CH_3), 1.273 (s, 1H, CH).

4-(4-Bromophenyl)-6-(4-methoxyphenyl)-N-[(E)-(4-nitrophenyl) methylidene]-6H-1,3-oxazin-2-amine (3e)

Yield: 64.44%, M.P.: 130-132^{0}C, IR (KBr, cm^{-1}): 3198.83, 935.83 (C-H), 1694.94 (C=N), 1524.25, 1384.39 (NO_2), 1267.55 (C-O), 1183.42 (C-N), 1093.28 (C-O), 669.53 (C-Br). ^{1}H NMR (300 MHz, TMS) δ: 7.961-7.737 (m, 4H, Ar-Br), 7.713-7.663 (m, 4H, Ar-(OCH_3), 7.357-7.235 (m, 4H, Ar-NO_2), 6.3 (d, 1H, fifth CH oxazine), 6.12 (d, 1H, sixth CH oxazine), 2.525-2.625 (s, 3H, OCH_3), 1.718 (s, 1H, CH).

2-[4-(4-Bromophenyl)-2-{[(1E)-(4-nitrophenyl)methylene] amino}-6H-1,3-oxazin-6-yl]phenol (3f)

Yield: 53.76%, M.P.:128-130^{0}C, IR (KBr, cm^{-1}): 3456.84 (OH), 1649.67 (C=N), 1544.74, 1343.83 (NO_2), 1223.78 (C-O), 1163.23(C-N), 638.92 (C-Br). ^{1}H NMR (300 MHz, TMS) δ: 7.983-7.773 (m, 4H, Ar-Br), 7.453-7.221 (m, 4H, Ar-(OH)), 7.357-7.235 (m, 4H, Ar-NO_2), 6.3 (d, 1H, fifth CH oxazine), 6.12 (d, 1H, sixth CH oxazine), 4.231-4.442 (s, H, OH), 1.718 (s, 1H, CH).

4-(4-Bromophenyl)-6-(4-chlorophenyl)-N-[(E)-(4-chlorophenyl)-methylidene]-6H-1,3-oxazin-2-amine (3g)

Yield: 69.68%, M.P.:144-146^{0}C, IR (KBr, cm^{-1}): 3154.19, 954.44 (C-C-H), 1628.54 (C=N), 1224.58 (C-O), 1178.29 (C-N), 815.74, 824.34 (C-Cl), 694.24 (C-Br). ^{1}H NMR (300 MHz, TMS) δ: 7.876-7.745 (m, 8H, Ar-Cl), 7.867-7.754 (m, 4H, Ar-Br), 6.3 (d, 1H, fifth CH oxazine), 6.12 (d, 1H, sixth CH oxazine), 1.687 (s, 1H, CH).

4-(4-Bromophenyl)-6-(3,4,5-trimethoxyphenyl)-N-[(E)-(4chlorophenyl)methylidene]-6H-1,3-oxazin-2-amine (3h)

Yield: 66.12%, M.P.: 148-150^{0}C, IR (KBr, cm^{-1}): 3154.19, 954.44 (C-C-H), 1628.54 (C=N), 1224.58 (C-O), 1178.29 (C-N), 815.74, 824.34 (C-Cl), 694.24 (C-Br). ^{1}H NMR (300 MHz, TMS) δ: 7.963-7.754 (m, 4H, Ar-Br), 7.871-7.743 (m, 4H, Ar-Cl), 7.723-7.633 (m, 2H, Ar-$(OCH_3)_3$, 6.3 (d, 1H, fifth CH oxazine), 6.12 (d, 1H, sixth CH oxazine), 2.538-2.485 (s, 9H ,OCH_3), 1.731 (s, 1H, CH).

4-(4-Bromophenyl)-N-[(1E)-(4-chlorophenyl)methylidene]-6-(4-nitrophenyl)-6H-1,3-oxazin-2-amine (3i)

Yield: 61.45%, M.P.:140-142^{0}C, IR (KBr, cm^{-1}): 3054.79, 987.14 (C-C-H), 1609.12 (C=N), 1274.09 (C-O), 1148.29 (C-N), 825.33, 846.04 (C-Cl), 664.24 (C-Br). ^{1}H NMR (300 MHz, TMS) δ: 7.887-7.699 (m, 4H, Ar-Cl), 7.876-7.769 (m, 4H, Ar-Br), 7.387-6.99 (m, 4H, Ar-NO_2), 6.3 (d, 1H, fifth CH oxazine), 6.12 (d, 1H, sixth CH oxazine), 1.612 (s, 1H, CH).

4-(4-Bromophenyl)-6-(N,N-dimethylaminophenyl)-N-[(E)(4-chlorophenyl) methylidene]-6H-1, 3-oxazin-2-amine (3j)

Yield: 71.27%, M.P.: 170-172^{0}C, IR (KBr, cm^{-1}): 3254.19, 937.17 (C-C-H), 1611.13 (C=N), 1218.90 (C-O), 1128.79 (C-N), 875.04, 835.12 (C-Cl), 667.24 (C-Br). ^{1}H NMR (300 MHz, TMS) δ: 7.932-7.743 (m, 4H, Ar-Br), 7.864-7.754 (m, 4H, Ar-Cl), 7.343-7.266 (m, 4H, Ar-N$(CH_3)_2$), 6.3 (d, 1H, fifth CH oxazine), 6.12 (d, 1H, sixth CH oxazine), 1.569 (s, 6H, N-CH_3), 1.189 (s, 1H, CH).

4-(4-Bromophenyl)-N-[(1E)-(4-chlorophenyl)methylidene]-6-(4-methoxyphenyl)-6H-1,3-oxazin-2-amine (3k)

Yield: 68.93%, M.P.: 126-128^{0}C, IR (KBr, cm^{-1}): 3084.89, 945.89 (C-C-H), 1657.97 (C=N), 1234.76 (C-O), 1158.29 (C-N), 834.74, 814.34 (C-Cl), 654.73 (C-Br). ^{1}H NMR (300 MHz, TMS) δ: 7.943-7.777 (m, 4H, Ar-Br), 7.857-7.735 (m, 4H, Ar-Cl), 7.773-7.643 (m, 4H, Ar-(OCH_3), 6.3 (d, 1H, fifth CH oxazine), 6.12 (d, 1H, sixth CH oxazine), 2.575-2.653 (s, 3H, OCH_3), 1.518 (s, 1H, CH).

2-[4-(4-Bromophenyl)-2-{[(1E)-(4-chlorophenyl)methylidene] amino}-6H-1,3-oxazin-6-yl]phenol (3l)

Yield: 57.08%, M.P.: 128-130^{0}C, IR (KBr, cm^{-1}): 3194.19, 984.44 (C-C-H), 1638.54 (C=N), 1298.58 (C-O), 1147.29 (C-N), 825.74, 814.34 (C-Cl), 665.63 (C-Br). ^{1}H NMR (300 MHz, TMS) δ: 7.963-7.763 (m, 4H, Ar-Br), 7.857-7.735 (m, 4H, Ar-Cl), 7.431-7.217 (m, 4H, Ar-(OH)), 6.3 (d, 1H, fifth CH oxazine), 6.12 (d, 1H, sixth CH oxazine), 4.431-4.2874 (s, H, OH), 1.764 (s, 1H, CH).

4-(4-Bromophenyl)-6-(4-chlorophenyl)-N-[(1E)-(4-methoxy phenyl)methylidene]-6H-1,3-oxazin-2-amine (3m)

Yield: 61.75%, M.P.: 140-142^{0}C, IR (KBr, cm^{-1}): 3054.69, 944.94 (C-C-H), 1648.84 (C=N), 1224.58, 1089.23 (C-O), 1178.29 (C-N), 825.74 (C-Cl), 684.48 (C-Br). ^{1}H NMR (300 MHz, TMS) δ: 7.876-7.745 (m, 4H, Ar-Cl), 7.867-7.754 (m, 4H, Ar-Br), 7.276-7.104 (m, 4H, Ar-OCH_3), 6.3 (d, 1H, fifth CH oxazine), 6.12 (d, 1H, sixth CH oxazine), 2.543-2.647 (s, 3H ,OCH_3), 1.689 (s, 1H, CH).

4-(4-Bromophenyl)-6-(3,4,5-trimethoxyphenyl)-N-[(1E)(4-methoxyphenyl) methylidene]-6H-1, 3-oxazin-2-amine (3n)

Yield: 63.56%, M.P.: 150-152^{0}C, IR (KBr, cm^{-1}): 3209.73, 964.83 (C-H), 1633.73 (C=N), 1223.55, 1045 (C-O), 1182.44 (C-N), 697.27 (C-Br). ^{1}H NMR (300 MHz, TMS) δ : 7.965-7.787 (m, 4H, Ar-Br), 7.723-7.633 (m, 2H, Ar-$(OCH_3)_3$, 7.226-7.114 (m, 4H, Ar-OCH_3), 6.3 (d, 1H, fifth CH oxazine), 6.12 (d, 1H, sixth CH oxazine), 2.535-2.413 (s, 3H ,OCH_3), 2.525-2.625 (s ,9H, OCH_3), 1.721 (s, 1H, CH).

4-(4-Bromophenyl)-N-[(1E)-(4-methoxyphenyl)methylidene]-6-(4-nitrophenyl)-6H-1,3-oxazin-2-amine (3o)

Yield: 63.86%, M.P.: 142-144^{0}C, IR (KBr, cm^{-1}): 3129.73, 984.83 (C-H), 1623.73 (C=N), 1543.15, 1338.31 (NO_2), 1212.55, 1097.13 (C-O), 1182.44 (C-N), 667.55 (C-Br). ^{1}H NMR (300 MHz, TMS) δ: 7.876-7.769 (m, 4H, Ar-Br), 7.387-6.99 (m, 4H, Ar-NO_2), 7.289-7.107 (m, 4H, Ar-OCH_3), 6.3 (d, 1H, fifth CH oxazine), 6.12 (d, 1H, sixth CH oxazine), 2.543-2.453 (s, 3H, OCH_3), 1.612 (s, 1H, CH).

4-(4-Bromophenyl)-6-(N,N-dimethylaminophenyl)-N-[(1E)-(4-methoxyphenyl) methylidene]-6H-1, 3-oxazin-2-amine (3p)

Yield: 67.89%, M.P.: 172-174^{0}C, IR (KBr, cm^{-1}): 3018.41, 1470.57 (-CH_3), 1648.47(C=N), 1213.12, 1045.67 (C-O), 1143.67 (C-N), 693.12 (C-Br). ^{1}H NMR (300 MHz, TMS) δ: 7.903-7.678 (m, 4H, Ar-Br), 7.343-7.266 (m, 4H, Ar-N$(CH_3)_2$), 7.276-7.104 (m, 4H, Ar-OCH_3), 6.3 (d, 1H, fifth CH oxazine), 6.12 (d, 1H, sixth CH oxazine), 2.593-2.476 (s, 3H ,OCH_3), 1.548 (s, 6H, N-CH_3), 1.283 (s, 1H, CH).

4-(4-Bromophenyl)-6-(4-methoxyphenyl)-N-[(1E)-(4-methoxy phenyl)methylidene]-6H-1,3-oxazin-2-amine (3q)

Yield: 65.13%, M.P.: 136-138^{0}C, IR (KBr, cm^{-1}): 3109.73, 984.83 (C-H), 1613.73 (C=N), 1233.27, 1041.34 (C-O), 1162.34 (C-N), 687.17 (C-Br). ^{1}H NMR (300 MHz, TMS) δ: 7.943-7.777 (m, 4H, Ar-Br), 7.781-7.693 (m, 4H, Ar-(OCH_3), 7.267-7.109 (m, 4H, Ar-OCH_3), 6.3 (d, 1H, fifth CH oxazine), 6.12 (d, 1H, sixth CH oxazine), 2.583-2.478 (s, 3H, OCH_3), 1.514 (s, 1H, CH).

2-[4-(4-Bromophenyl)-2-{[(E)-(4-nitrophenyl)methylidene] amino}-6H-1,3-oxazin-6-yl]phenol (3r)

Yield: 68.93%, M.P.: 126-128^{0}C, IR (KBr, cm^{-1}): 3356.74 (OH), 1637.36 (C=N), 1303.07, 1037.83 (C-O), 1166.13 (C-N), 678.02 (C-Br). ^{1}H NMR (300 MHz, TMS) δ: 7.963-7.763 (m, 4H, Ar-Br), 7.476-7.211 (m, 4H, Ar-(OH), 7.273-7.114 (m, 4H, Ar-OCH_3), 6.3 (d, 1H, fifth CH oxazine), 6.12 (d, 1H, sixth CH oxazine), 4.486-4.2974 (s, H ,OH), 2.574-2.456 (s ,3H ,OCH_3), 1.764 (s, 1H, CH).

Determination of Prothrombin Time (PT) by Quick's Method[9]

Pipette out 0.1 ml of plasma in small test tube. Add 0.1 ml of brain thromboplastin and mix. Wait for 2 min and add pre warmed calcium chloride solution at 37°C, mix and start the stop watch. Hold the tube in front a source of light and keep tilting the test tube gently. At first appearance of fibrin clot stop the watch immediately and record the time as control reading. Pipette 0.1 ml of plasma in small test tube; add 0.1 ml of 100 mg/ml test compound solution. Incubate for 5 min and repeat the procedure to record the elongation in mean prothrombin time.

RESULTS AND DISCUSSION

Initially six compounds **(1a-1f)**, which are substituted chalcones were synthesized. Subsequently six compounds **(2a-2f)** were synthesized with substitution of 4-bromophenyl at 4th position and phenyl substitution on 6th position of 1,3-oxazine-2-amine. The Schiff bases **(3a-3r)** of 1,3-oxazine has been synthesized with formation of imine group with substituted phenyl ring at 2 position of 1,3-oxazine ring. Various substituents and physicochemical data of title compounds are tabulated in Table 1 and 2 respectively.

In the first step, 4-bromoacetophenone and substituted aromatic aldehyde reacted in the presence of sodium hydroxide to give substituted chalcones (Claisen-Schmidt condensation). In second step, substituted chalcones reacted with urea to produce 4-(4-bromophenyl)-6-(substituted phenyl)-6H-1,3-oxazin-2-amine analogues. In third step, these compounds was reacted with substituted aromatic aldehydes to produce 4-(4-bromophenyl)-6-(substituted phenyl)-2-{[(1E)-(substitutedphenyl) methylidenene]-6H-1,3-oxazin-amine.

Melting points of the synthesized compounds were determined in an open capillary tube and hence are uncorrected. The structures of the title compounds were established on the basis of spectral data. The IR spectra were recorded on a Jasco FTIR 4100 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian NMR 300 MHz spectrometer using $CDCl_3$ as solvent with TMS as an internal standard. Purity of the synthesized compounds was checked by silica gel G plate using benzene and methanol as mobile phase.

The anticoagulant activity was carried out using Diagnose thrombo reagent which is rabbit brain thromboplastin reagent in liquid form by Quick's method and measured the time taken for the clot to form. Result showed that most of the synthesized compounds exhibited significant anticoagulant activity amongst them compound **3c, 3f, 3g, 3j, 3o** and **3p** were found to be most active.

Table 2: Physical Data of Synthesized Compounds (3a-3r)

Compound	Molecular Formula	Molecular Weight	% Yield	M .P.^{0}C	R_f Value
3a	$C_{23}H_{15}BrClN_2O$	486.18	71.46	140-142	0.83
3b	$C_{27}H_{22}BrN_3O_6$	568.41	68.43	152-154	0.61
3c	$C_{23}H_{15}BrN_4O_5$	506.28	62.71	140-142	0.75
3d	$C_{25}H_{21}BrN_4O_3$	505.36	65.14	172-174	0.65
3e	$C_{25}H_{18}BrN_2O_4$	491.33	53.76	128-130	0.53
3f	$C_{23}H_{16}BrN_3O_4$	478.29	64.44	130-132	0.47
3g	$C_{23}H_{15}BrCl_2N_2O$	486.18	69.68	144-146	0.90
3h	$C_{27}H_{22}BrClN_2O_4$	540.83	66.12	148-150	0.58
3i	$C_{23}H_{15}BrClN_3O_3$	496.74	61.45	140-142	0.73
3j	$C_{25}H_{21}BrClN_3O$	494.81	71.27	170-172	0.69
3k	$C_{24}H_{18}BrClN_2O_2$	481.76	57.08	128-130	0.56
3l	$C_{23}H_{16}BrClN_2O_2$	467.74	68.93	126-128	0.51
3m	$C_{24}H_{18}BrClN_2O_2$	481.76	61.75	140-142	0.61
3n	$C_{28}H_{25}BrN_2O_5$	553.44	63.56	150-152	0.49
3o	$C_{24}H_{18}Br\ N_3O_4$	492.32	63.86	142-144	0.56
3p	$C_{26}H_{24}BrN_3O_2$	490.39	67.89	172-174	0.53
3q	$C_{25}H_{21}BrN_2O_3$	477.34	53.78	132-134	0.37
3r	$C_{23}H_{19}BrN_3O4$	478.29	65.13	136-138	0.29

Table 3: Anticoagulant Activity of Title Compounds (3a-3r)

Compound	Prothrombin Time (Time in sec)
Control	25.66
Std	122.5
3a	74.33
3b	68.16
3c	113.33
3d	68.66
3e	75
3f	115.5
3g	120.16
3h	33.66
3i	77.5
3j	121
3k	29.5
3l	29.5
3m	25.66
3n	22.83
3o	106.33
3p	118.12
3q	43.66
3r	30

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