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Synthesis, Characterization and biological activity of 4-Aryl 3-Chloro N-Substituted 2-Azetidinones

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Abstract : In the present invention relates to Synthesis of new 2-Azetidinone derivatives from 2, 6-Dimethylbenzenamine. Condensation, amination and cyclocondensation reactions were involved. They are an important class of Hetero cyclic compounds that have a wide range of pharmaceutical and medicinal applications. The structures of synthesized compound -s were confirmed by using IR, ^{1}H NMR, and Mass spectroscopy. Further these synthesized derivatives were subjected to biological activity.
Key Words : 2, 6-Dimethylbenzenamine, Schiff bases, 2-Azetidinones and biological activity.

Introduction:

The most popular used antibiotics like Cephalosporins, Penicillin,Nocardicins contains β-lactam ring.2-azetidinones commonly known as β-lactams.These compounds have wide range of biological activities, such as Anti tubercular[1],Anti inflammatory[2], Anticon- vulasnt[3],Anesthetic[4],Anti viral[5],Anti microbial[6], Hypolipidemic activity[7], Vasodilator[8],CNS depressant[9-11] and Neuromuscular transmission activity[12].That's why I was synthesized different derivatives of 2-azetidinone.These derivatives are prepared from the starting material 2,6-dimethyl benzenamine.The synthesized compounds were confirmed by using IR,H^1 NMR and Mass studies and these compounds are tested for biological activity.

Materials And Method:

All chemicals and solvents, reagents used in the present study were of commercial grade. All the melting points of the synthesized compounds were determined by open capillary .The purity of the compounds was checked by using precoated TLC plates (MERCK).IR spectra were recorded using KBr on Perkin Elmer spectrophotometer.^{1}HNMR spectra in DMSO on a BRUKER FT-NMR instrument using TMS as internal standard and chemical shift values were expressed in ppm.

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2-chloro-N-(2, 6-dimethylphenyl) acetamide**(2)** was prepared by reaction with Chloroacetyl Chloride .Compound **(2)** on amination with Hydrazine Hydrate yielded 2-hydrazinyl-N-(2, 6-dimethylphenyl) acetamide **(3)**.Compound **(3)** condensation with different aromatic aldehydes yielded Schiff Bases **(4a-h).**Compounds **4a-h** on reaction with Chloroacetyl Chloride in the presence of Triethyl amine to afford 4-aryl 3-chloro N-substituted 2-azetidinones**(5a-h).**These reactions are shown on Scheme1.The purity of the compounds was checked by TLC.The substituents of the compounds are shown by Table1.

Scheme 1.

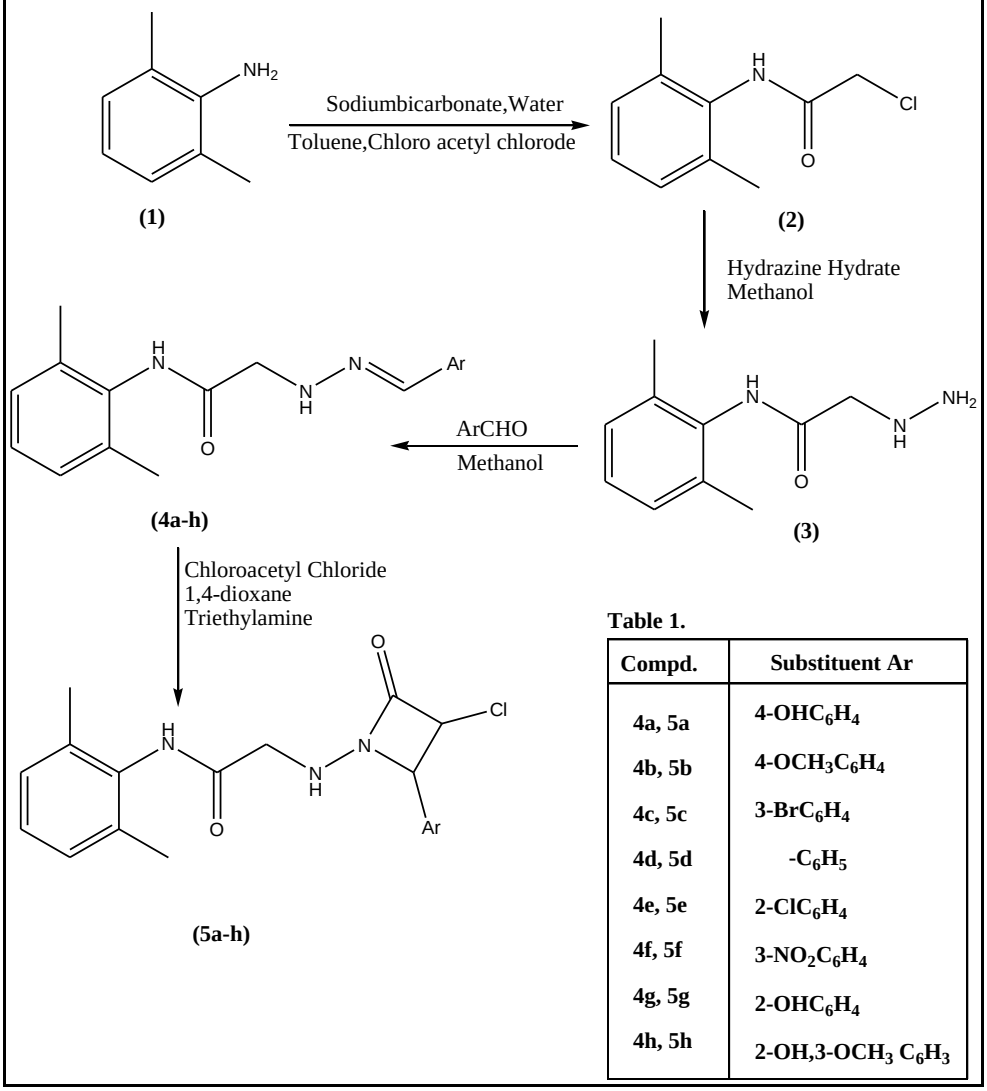

Table 1.

Compd.	Substituent Ar
4a, 5a	**4-OHC_6H_4**
4b, 5b	**4-$OCH_3C_6H_4$**
4c, 5c	**3-BrC_6H_4**
4d, 5d	**-C_6H_5**
4e, 5e	**2-ClC_6H_4**
4f, 5f	**3-$NO_2C_6H_4$**
4g, 5g	**2-OHC_6H_4**
4h, 5h	**2-OH,3-OCH_3 C_6H_3**

Results and Discussion:

Synthesis of 2-chloro-N-(2, 6-dimethylphenyl) acetamide (2)

2-chloro-N-(2, 6-dimethylphenyl) acetamide (2)[13] was prepared by amixture of 2, 6-dimethylbenzenamine (**1**, 0.1mol),Toluene, Water, $NaHCO_3$ (0.1mol) and Chloroacetyl Chloride(0.1mol) was added slowly at room temperature then maintained at refluex for 8-10hr.After completion of reaction ,cool the reaction mass to room temperature and filtered then wash with Toluene and Water, dried. A white color solid was obtained.Yield:98%.

Synthesis of 2-hydrazinyl-N-(2, 6-dimethylphenyl) acetamide(3)

2-hydrazinyl-N-(2, 6-dimethylphenyl) acetamide(3)[14] was prepared by a mixture of 2-chloro-N-(2, 6-dimethylphenyl) acetamide (**2**, 0.1mol) and excess of Hydrazine hydrate in Methanol was refluxed for 4-

6hr.After completion of reaction cool to room temperature then charge Water and Ethyl acetate stir for 5Min and settle for 10Min. Separate the layers, distill off organic layer. A light yellow color liquid was obtained. Yield: 70%.

General procedure for the Synthesis of 2((E)-2-(arylidene) hydrazinyl) -N-(2, 6-dimethylphenyl) acetamide(4a-h)

A mixture of 2-hydrazinyl-N-(2, 6-dimethylphenyl) acetamide (**3**, 0.1mol), aromatic aldehyde(0.1mol), few drops of Carboxylic acid in Methanol was refluxed for 4hr.After completion of the reaction solvent was removed under vacuum below 40C^{o} .The obtained crude product was purified by using Methanol and Water mixture. Yield85%.

2-((E)-2-(4-hydroxybenzylidene) hydrazinyl)-N-(2, 6-dimethylphenyl) acetamide (4a).

IR(KBr, cm^{-1})3567(ArOH),3438(NH), 3004.23(-CH), 1695(C=O), 1610(N=C); ^{1}HNMR (400MHz, DMSO-d_6)δ ppm: 2.10(s,1H,NH),2.29(s,6H,CH_3), 3.85 (s,2H,CH_2),5.1 (s,1H,ArOH),6.82-7.46(m,7H,ArH), 7.99 (s,1H,CONH), 8.12(s,1H,N=CH).

2-((E)-2-(4-methoxybenzylidene) hydrazinyl)-N-(2, 6-dimethylphenyl) acetamide (4b).

IR (KBr, cm^{-1})3420(NH), 3032(-CH), 1641(C=O), 1607.40 (N=C),1210(-OCH_3); ^{1}H NMR(400MHz, DMSO-d_6)δ ppm: 2.14(s,1H,NH),2.27(s,6H,CH_3), 3.82 (s,2H,CH_2),3.74 (s,3H,ArOCH_3),6.80-7.48(m,7H,ArH), 7.97(s,1H,CONH),8.10(s,1H,N=CH).

2-((E)-2-(3-bromo benzylidene) hydrazinyl)-N-(2, 6-dimethylphenyl) acetamide (4c).

IR (KBr, cm^{-1}) 3408(NH), 3055(-CH), 1662(C=O), 1633(N=C),656(-Br); ^{1}H NMR(400MHz, DMSO-d_6)δ ppm: 2.12(s,1H,NH),2.31(s,6H,CH_3), 3.85 (s,2H,CH_2),6.70-7.50(m,7H,ArH),7.90(s,1H,CONH),8.08(s,1H,N=CH).

2-((E)-2- benzylidene) hydrazinyl)-N-(2, 6-dimethylphenyl) acetamide (4d).

IR (KBr, cm^{-1}) 3424(NH), 3030(-CH),1658(C=O), 1610(N=C);^{1}H NMR (400MHz, DMSO-d_6)δ ppm: 2.14(s,1H,NH),2.32(s,6H,CH_3),3.82 (s,2H,CH_2),6.70-7.70(m,8H,ArH), 7.97(s,1H, CONH),8.12(s,1H,N=CH).

2-((E)-2-(2- chlorobenzylidene) hydrazinyl)-N-(2, 6-dimethylphenyl) acetamide(4e).

IR (KBr, cm^{-1}) 3446(NH), 3012(-CH),1664(C=O),1634(N=C),752.42(-Cl);^{1}H NMR (400MHz, DMSO-d_6)δ ppm: 2.11(s,1H,NH),2.30(s,6H,CH_3), 3.86 (s,2H,CH_2),6.70-7.76(m,7H,ArH),7.92(s,1H,CONH), 8.09 (s,1H,N=CH).

2-((E)-2-(3-nitrobenzylidene) hydrazinyl)-N-(2, 6-dimethylphenyl) acetamide(4f).

IR (KBr, cm^{-1}) 3460(NH), 3059(-CH), 1657(C=O), 1612(N=C),1528,1346(-NO_2); ^{1}H NMR (400MHz, DMSO-d_6)δ ppm: 2.12(s,1H,NH),2.31(s,6H,CH_3), 3.80 (s,2H,CH_2),6.70-7.76(m,7H,ArH), 7.97(s,1H,CONH), 8.16 (s,1H,N=CH).

2-((E)-2-(2-hydroxy-3-methoxybenzylidene) hydrazinyl)-N-(2, 6-dimethylphenyl) acetamide(4h).

IR (KBr, cm^{-1}) 3527(Ar OH), 3418(NH), 2997(-CH), 1661(C=O), 1609(N=C); ^{1}H NMR (400MHz, DMSO-d_6)δ ppm: 2.11(s,1H,NH),2.32s,6H,CH_3),3.72 (s,2H,CH_2),3.75(-OCH_3) ,5.12(s,1H,ArOH),6.61-7.10(m,6H,ArH), 8.12(s,1H,CONH),8.18(s,1H,N=CH).

General procedure for the Synthesis of 2-(3-chloro-2-(aryl)-4-oxoazetidin-1-ylamino) –N - (2, 6-dimethylphenyl) acetamide(5a-h)

A mixture of Schiff base (**4a-h,** 0.1mol), Triethyl amine (0.2mol) in Dioxane, Chloroacetyl Chloride (0.2mol) was added drop wise below room temperature. The reaction mixture was stirred for 6-8hr at 75-80C^{o} .After completion of the reaction cool to room temperature then filters the Triethyl amine hydrochloride salt. The filtrate was evaporated under vacuum. The solid was obtained wash with water, filtered and dried. The product obtained was purified by DMSO and Water mixture.Yield60%.

2-(3-chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-ylamino) -N - (2, 6-dimethylphenyl) acetamide(5a).

IR (KBr, cm^{-1}) 3586(Ar OH), 3461(NH), 2909.13(-CH), 1644(C=ONH), 1744 (C=O, β-lactam); ^{1}H NMR (400MHz, DMSO-d_6) δ ppm: 2.30(s, 6H, CH3),3.01(s, 1H, NH),3.52 (s, 2H, CH2),5.10(s, 1H, ArOH),5.21(d, 1H, Azetidin ring (CH)5.44(d, 1H, Azetidin ring (CH-Cl)6.61-6.90(m, 6H, ArH),8.02(s, 1H, CONH); MS:m/z:374.10$[M+1]^+$;m.p.125-129C^o.

2-(3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-ylamino) -N - (2, 6-dimethylphenyl) acetamide(5b).

IR (KBr, cm^{-1}) 3449(NH), 3046(-CH), 1641(C=ONH), 1735 (C=O, β-lactam), 1251(O-CH_3); ^{1}H NMR (400MHz,DMSO-d_6) δ ppm: 2.35(s, 6H, CH3), 3.10(s, 1H, NH), 3.50 (s, 2H, CH_2), 3.74(s, 1H, $ArOCH_3$),5.14(d, 1H, Azetidin ring (CH)5.42(d, 1H, Azetidin ring (CH-Cl),6.61-6.90(m, 6H, ArH),8.01(s, 1H, CONH);MS:m/z:388.14$[M+1]^+$; m.p.133-138C^o.

2-(2-(3-bromophenyl)-3-chloro-4-oxoazetidin-1-ylamino) -N - (2, 6-dimethylphenyl) acetamide(5c).

IR (KBr, cm^{-1}) 3450(NH), 3062(-CH), 1637(C=ONH), 1764 (C=O, β-lactam),689(-Br); ^{1}H NMR (400MHz, DMSO-d_6) δ ppm: 2.29(s, 6H, CH3), 3.14(s, 1H, NH), 3.54 (s, 2H, CH_2), 5.18(d, 1H, Azetidin ring (CH), 5.49(d, 1H, Azetidin ring (CH-Cl), 6.65-7.51(m, 6H, ArH),8.04(s, 1H, CONH);MS: m/z:437.05$[M+1]^+$; m.p.120-124C^o.

2-(3-chloro-2-oxo-4-phenylazetidin-1-ylamino) -N - (2, 6-dimethylphenyl) acetamide(5d).

IR (KBr, cm^{-1}) 3459(NH), 3033(-CH), 1659(C=ONH), 1744 (C=O, β-lactam); ^{1}H NMR (400MHz, DMSO-d_6) δ ppm: 2.31(s, 6H, CH3),3.06(s, 1H, NH), 3.58 (s, 2H, CH_2),5.11(d, 1H, Azetidin ring (CH),5.45(d, 1H, Azetidin ring (CH-Cl),6.62-7.42(m, 8H, ArH),8.11(s, 1H, CONH);MS: m/z:458.11$[M+1]^+$;m.p.165-169C^o.

2-(3-chloro -2-(2-chlorophenyl)-4-oxoazetidin-1-ylamino) -N - (2, 6-dimethylphenyl) aceta- mide(5e).

IR (KBr, cm^{-1}) 3444(NH), 3021(-CH), 1651(C=ONH), 1743 (C=O, β-lactam),724(-Cl);^{1}H NMR (400MHz, DMSO-d_6) δ ppm: 2.35(s, 6H, CH3),3.11(s, 1H, NH), 3.52 (s, 2H, CH_2),5.07(d, 1H, Azetidin ring (CH),5.41(d, 1H, Azetidin ring (CH-Cl),6.64-7.36(m,7H, ArH),8.03(s, 1H, CONH); MS: m/z:393.07$[M+1]^+$;m.p.112-117C^o.

2-(3-chloro -2-(3-nitrophenyl)-4-oxoazetidin-1-ylamino) -N - (2, 6-dimethylphenyl) acetamide(5f).

IR (KBr, cm^{-1}) 3456(NH), 3007(-CH), 1632(C=ONH), 1752 (C=O, β-lactam) 1520, 1331(NO_2); ^{1}H NMR (400MHz, DMSO-d_6) δ ppm: 2.32(s, 6H, CH3),3.03(s, 1H, NH),3.55 (s, 2H, CH_2),5.11(d, 1H, Azetidin ring (CH),5.45(d, 1H, Azetidin ring (CH-Cl),6.68-8.32(m, 7H, ArH),8.11(s, 1H, CONH);MS: m/z:403.10$[M+1]^+$; m.p.154-159C^o.

2-(3-chloro -2-(2-hydroxy-3-methoxyphenyl)-4-oxoazetidin-1-ylamino) -N - (2, 6-dimethylphenyl) acetamide (5h).

IR (KBr, cm^{-1}) 3521(OH), 3445(NH), 3004(-CH), 1652(C=ONH), 1764 (C=O, β-lactam), 1132(OCH_3); ^{1}H NMR (400MHz, DMSO-d_6) δ ppm: 2.36(s, 6H, CH3),3.11(s, 1H, NH),3.58 (s, 2H, CH_2),3.69(s, 3H, CH3),5.01(d, 1H, Azetidin ring (CH),5.10(s, 1H, ArOH),5.44(d, 1H, Azetidin ring (CH-Cl),6.38-7.02(m, 6H, ArH),8.08(s, 1H, CONH);MS:m/z:404.14$[M+1]^+$; m.p.139-144C^o.

Biological activity:

The antimicrobial activity was done by using the cup plate agar diffusion method [15];the synthesized compounds were examined against gram positive and gram negative bacteria and fungi. The activities of these compounds were tested at a con.of 100 µg/ml.ciprofloxacin and flucanazole as the reference antibiotics. DMSO was used as solvent control. The biological activity data is shown in table 2.

Table 2. Antibacterial and anti fungal data of Compounds (5a-h).

Comp	Diameter of zone of inhibition.(mm)					
	S.aureus	***B.subtilis***	***P.aeruginosa***	***E.coli***	***C.albicans***	***A.niger***
5a	10	12	10	11	11	10
5b	12	11	11	09	10	11
5c	10	11	09	11	10	12
5d	11	10	11	10	11	11
5e	11	12	11	11	12	12
5f	12	11	12	12	11	11
5g	11	10	12	10	10	10
5h	11	12	11	11	10	11
DMSO	-	-	-	-	-	-
Ciproflacin	25	26	24	26	-	-
Flucanazole	-	-	-	-	20	21

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References:

1. Patel, K. D., Mistry, B.D., and Desai, K.R., Ori.J.of Chem,.2003; Vol19(1); pp: 245-246.
2. Ning, field &Sternback, J. of Heterocyclic Chem.., 7,475(1970).
3. Keneriya, C.R., ori. J. of Chem., 2003; Vol19 (3): pp: 677-680.
4. Srivastava, S.K, SoumyaSrivastava, and Srivastava, SD, Ind. J. of Chem., 2002; Vol-41B: 2357-2363.
5. Pandey, V.K., Ind. J. of Chem., 2005; Vol-44B: pp: 158-162.
6. Srivastava, S.K, Srivastava, S.L., and Srivastava, SD, Ind. J. of Chem.., 2000; Vol-39B: pp: 464-467.
7. Tapar, G.S., Krishnamurthy, A., Ind. J. of Chem., 1990; Vol 29B; pp: 1134-1137.
8. Ryman T, Peterssson J, Hogestatt E D Pharmacol. Toxixol, 1999, Aug; 85(2)80-4.
9. Patel K.H and Mehta A.G., Synthesis and antifungal activity of azetidinones and thiazolidi- nones derivative of 2-amino-6-(2-naphthalenyl) thiazolo [3, 2-d] thiadiazole, E.J.Chem., 2006, 3(13), 267-273.
10. Freddy H.Havaladar and Sushil Kumar J. Mishra., Synthesis of some azetidi-2-ones and Thiozolidin-4-ones as potential antimicrobial Agents. Indian J. Heterocyclic., Chem.2004, 13, 197-200.
11. AmeyaA.Chavan and NandiniR.Pai., Synthesis and biological Acitivity of N- Substituted-3- Chloro-2-azetidinones, Molecules. 2007, 12, 2467-2477.
12. F. Valexzuela and F. HuidobroJournal of Pharmacology and Experimental Therapeutics, Vol.92, Issue 1, 1-14, 1948.
13. Michel Joseph Mautice Andre Guillaume,JozefLudo Jan Cuypers,lavan Joseph MariaVervest, Stefan Marcel Herman Leurs, Dirk de Smaele. Processs for the preparation of N-(2, 6-dimethyl-phenyl)-2-poperzin-1-yl-acetamide.US8541578B2, 2013.
14. Ramakanth Pagadala, JyostsnaS, Meshram, HimaniN, Chopde, Venkateshwarlu Jetti, Praveen Chidurala, Uppalaiah Kasumpally. Journal of Hetero cyclic Chemistry.2012,Vol.49#5, P.1151-1155.
15. Cruichshank R, Duguid JP, Marmoin BP, Swan HA, The practice of Medical Micro Biology, Vol 2,12thedn, Churchill Livingstone, London, 1975,190.

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