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THE SYNTHETIC STRATEGY OF NEW PYRIDINE CLUBBED ACETAMIDES *VIA* N-ALKYLATION/C–N COUPLING REACTION, SULFONAMIDE DRUG AND THEIR BIOLOGICAL APPROACH

[1]Prabhunath Yogi, [2]Prakash Prajapat, [2]Nassir Hussain, [3]Heena Dhawan, and [1]Ajit Joshi

[1]Department of Chemistry, Mewar University, Chittorgarh-312901, India
[2]Department of Chemistry, Mohanlal Sukhadia University, Udaipur-313001, India
[3]Centre for energy studies, Indian Institute of Technology, New Delhi-110016, India
E-mail Id:- prabhunath1987@gmail.com, prajapatprakash11@yahoo.in

ABSTRACT:
A library of novel pyridine motifs assembled with isatin/thiazolidione/sulphonamide/pyrazolone designed and synthesized via N-alkylation **(**C–N coupling) approach is described. The target compounds were obtained by a two step synthetic strategy starting from substituted 2-amino pyridine using appropriate synthetic routes. The structures of all novel constructed derivatives were corroborated by elemental and spectral data (FT-IR, ^{1}H-NMR and Mass) and chemical tests. Subsequently, compounds were aimed to their *in-vitro* antimicrobial and *in-vivo* anti-inflammatory activity. Some of the compounds were found to be more active than the reference drugs.

1. INTRODUCTION

The increasing demand for new chemical entities urges synthetic organic chemists to pursue simple, efficient, selective and good yielding organic reactions. N-alkylation is an important methodology in organic synthesis which provides a route for transformation of primary and secondary amides into tertiary amides [1, 2]. Sulfonamides are extremely used in pharmaceutical chemistry because of their wide range of potential biological and medicinal properties, such as antibacterial [3-5], anticancer, anti-inflammatory, antiviral, antihypertensive, HIV protease inhibitor, and the phophodiesterase-5 inhibitor [6-9]. Nitrogen-containing heterocycles are the subject of continuous interest in organic synthesis owing to the fact that they occur ubiquitously in biologically active natural products, multipurpose oriented functional materials, as well as highly potent agrochemicals [10, 11].
Pyridine nucleus acts as a synthetic precursor in agrochemical and active pharma ingredients (API) industries. Many important alkaloids like atropine from Atropa belladonna plant contains saturated pyridine nucleus, in ancient time's woman have used the fluid of leaves of atropa to dilate pupils of eyes [12]. Pyridine and their derivatives have gained considerable attention as synthetic targets for researchers because of their valuable and significant pharmacological properties such as anti-inflammatory [13-16], antiviral [17-19],

antihypertensive [20-21], antidiabetic [22-24], anticancer [25-28], osteogenic activities [29-30], antimicrobial [31-32] and treatment of CNS disorders [33]. Some medically relevant bacteria, like *Granulicatella* and *Abiotrophia*, require pyridoxal for growth. Several pyridine based drugs like Nicotine, Isonicotinylhydrazide, Sulfapyridine, Pyribenzamine, Rosiglitazone and Etoricoxib [34] (fig.1) have been approved for therapeutic purposes in clinic and these selective drugs showed structural similarity with target sulfonamide derivative (fig. 2)**.**

If pyridine and isatin/thiazolidione/sulphonamide/pyrazolone scaffolds linked into one molecule by the N-alkylation/C–N coupling approach, the resultant molecule may enhance the pharmacological activity. Hence, this literature survey prompted us to explore the research work of such molecules. Thus, the present article describes the synthesis of some new pyridine assembled heterocycles that may be use as potent and effective bio-active agents.

2. EXPERIMENTAL

Material and methods. All chemicals were commercially procured and were used without further purification. All melting points were determined in open capillary tube and are uncorrected. The IR spectra were recorded on Perkin-Elmer-1800 spectrometer. The ^{1}H NMR spectra ($CDCl_3$) were scanned on a DRX-300 (300 MHz) spectrometer using TMS as internal standard and chemical shifts are expressed in δ, ppm. The mass spectra were recorded on Jeol SX-102 (FAB) spectrometer. Elemental analyses were done on "Heraeus Rapid Analyser". The purity of the synthesized compounds was checked by TLC using silica gel-G plates, n-hexane - ethyl acetate as developing solvent and the spots were exposed to UV light. Chemical shifts (δ) are referred in terms of ppm. The physical properties of the synthesized derivatives presented in Table 1.

Synthesis of 4-methyl-N-pyridin-2-ylbenzenesulfonamide **(1a).** 2-amino pyridine (0.01 m mol) and acetonitrile (25 mL) were taken in dry beaker then p-toluene sulfonyl chloride (0.01 m mole) added portion wise in above solution. ZnO added as a catalyst in small amount, progress of reaction checked by TLC. After complete the reaction solid appear, which was isolated, dried and recrystallized from DMF. IR (KBr) cm^{-1} : 3350 (N-H str), 3204 (Ar-H str), 2821 (CH_3, str.), 1631 (C=N str.), 1391(N-S str) ^{1}H-NMR (300 MHz , $CDCl_3$) δ: 7.30-7.80 (m, 8H, Ar-H), 6.50 (s, 1H, N-H), 2.31(s, 3H, CH_3); Anal. Calcd. For $C_{12}H_{12}N_2O_2S$ in wt % C, 58.05; H, 4.87; N, 11.28 and found to be C, 58.19; H, 4.96; N, 11.34; MS: *m/z* 248 $[M]^+$ 233, 157, 93, 78, 64, 38.

Similarly, compound **1b** was prepared with minor changes in stirrer time and work up process.

N-(5-bromopyridin-2-yl)-4-methylbenzenesulfonamide **(1b).** IR (KBr) cm^{-1} : 3354 (N-H str), 3210 (Ar-H str), 2826(CH_3, str.), 1634 (C=N str.), 1394 (N-S str) ^{1}H-NMR ($CDCl_3$) δ: 7.34-7.85 (m, 7H, Ar-H), 6.64 (s, 1H, N-H), 2.33 (s, 3H, CH_3); Anal. Calcd. For $C_{12}H_{11}BrN_2O_2S$ in wt % C, 44.05; H, 3.39; N, 8.56 and found to be C, 44.15; H, 3.23; N, 8.78; MS: *m/z* 328 $[M]^+$ 330 $[M+2]^+$, 312, 236, 172, 158, 77, 63, 38.

Synthesis of 2-chloro-N-pyridin-2-ylacetamide **(2a).** 2-aminopyridine (0.1 m mole) and 1,4-dioxane (50 mL) were taken in dry beaker than added CH_3COONa (0.1m mole), mixed well above all component and make a clean solution. Chloroacetyl chloride (0.1 m mole) was added drop by drop in above solution, after complete the addition, reaction mass stay for 30 min. at RT and success of reaction checked by TLC. End of the reaction solid appear, it poured into ice cold water than filtered and recrystallized from Benzene. IR (KBr)cm^{-1} : 3410 (N-H str) 3069 (Ar-H, str.), 2925 (CH_2, str.), 1767 (C=N str.), 1649 (C=O,amide, str.), ^{1}H NMR (300 MHz , $CDCl_3$) δ: 7.10-7.50 (m, 4H, Ar-H), 6.80 (s, 1H, N-H), 4.28 (s, 1H, CH_2);

Anal. Calcd. For $C_7H_7ClN_2O$ in wt % C, 49.28; H, 4.14; N, 16.42 and found to be C, 49.31; H, 4.42; N, 16.53; MS: *m/z* 170 $[M]^+$, 121, 93, 78, 64, 38.

Similarly, compound **2b** was synthesised with some change in reaction conditions.

***N-(5-bromopyridin-2-yl)-2-chloroacetamide* (2b).** IR (KBr)cm^{-1} : 3415 (N-H str) 3071 (Ar-H, str.), 2927 (CH_2, str.), 1769 (C=N str.), 1652 (C=O, amide, str.), ^{1}H NMR (300 MHz , $CDCl_3$) δ: 7.15-7.60 (m, 3H, Ar-H), 6.84 (s, 1H, N-H), 4.32 (s, 1H, CH_2); Anal. Calcd. For $C_7H_6BrClN_2O$ in wt % C, 33.70; H, 2.42; N, 11.23 and found to be C, 33.65; H, 2.53; N, 11.38; MS: *m/z* 250 $[M]^+$, 252$[M+2]^+$, 200, 172, 156, 77, 63, 38.

***Synthesis of 2-(2,3-dioxo-2,3-dihydro-1H-indol-1-yl)-N-pyridin-2-ylacetamide* (3a).**

Compound **2a** (0.01 m mole), 1*H*-indole-2,3-dione (0.01 m mole), triethyl amine (0.025 m mole) and tetrahydrofurane (THF, 20 mL) were taken in dry round bottom flask and refluxed it to 5 hrs. Reaction progress checked by TLC, end of the reaction, resultant product poured into crushed ice , solid appear, which was isolated, dried and recrystallized from ethanol.

IR (KBr) cm^{-1}: 3420 (N-H, str.), 2915 (Ar-H, str.), 2834 (CH_2, str.), 1738 (C=N, str.), 1630 (C=O, str.); ^{1}H NMR (300 MHz , $CDCl_3$) δ: 6.94-8.25 (m, 8H, Ar-H), 6.46 (s, 1H, N-H,) , 4.28 (s, 2H, CH_2,),; Anal. Calcd. For $C_{15}H_{11}N_3O_3$ in wt % C, 64.05; H, 3.94; N, 14.94 and found to be C, 63.92; H, 3.99; N, 15.02; MS: *m/z* 281 $[M]^{+\cdot}$, 265, 249, 135, 93, 78, 64, 38.

Similarly, compound **3b** was prepared with some change in stirrer time and work up process.

***N-(5-bromopyridin-2-yl)-2-(2,3-dioxo-2,3-dihydro-1H-indol-1-yl)acetamide* (3b).** IR (KBr) cm^{-1}: 3424 (N-H, str.), 2920 (Ar-H, str.), 2836 (CH_2, str.), 1740 (C=N, str.), 1633 (C=O, str.), ^{1}H NMR (300 MHz , $CDCl_3$) δ: 6.98-8.32 (m, 7H, Ar-H), 6.49 (s, 1H, N-H,) , 4.31 (s, 2H, CH_2,),; Anal. Calcd. For $C_{15}H_{10}BrN_3O_3$ in wt % C, 50.02; H, 2.80; N, 11.67 and found to be C, 49.97; H, 2.64; N, 11.76; MS: *m/z* 361 $[M]^{+\cdot}$, 363 $[M+2]^+$, 344, 328, 214, 172, 156, 77, 63, 38.

***Synthesis of 2-(2,4-dioxo-1,3-thiazolidin-3-yl)-N-pyridin-2-ylacetamide* (4a).** Compound **2a** (0.01 m mole), ethanolic solution of thiazolidione (0.01 m mole), triethyl amine (0.025 m mole) and tetrahydrofurane (THF, 20 mL) were taken in dry round bottom flask and refluxed it to 4 hrs. Reaction progress checked by TLC, end of the reaction, resultant product poured into crushed ice, solid appear, which was isolated, dried and recrystallized from ethanol. IR (KBr) cm^{-1}: 3423 (N-H, str.), 3239 (Ar-H, str.), 2936 (CH_2,str), 1720 (C=N, str.), 1699 (C=O, str.), 1438 (C-S, str.); ^{1}H NMR (300 MHz , $CDCl_3$) δ: 7.06-8.34 (m, 4H, Ar-H), 6.57 (s, 1H, N-H), 6.29 (s, 2H, CH_2, ring) 4.59 (s, 2H, CH_2) ; Anal. Calcd. For $C_{10}H_9N_3O_3S$ in wt % C, 47.80; H, 3.61; N, 16.72 and found to be C, 47.74; H, 3.81; N, 16.78; MS: *m/z* 251 $[M]^{+\cdot}$, 235, 219, 135, 93, 78, 64, 38.

Similarly, compound **4b** was synthesized with some change in reaction conditions.

N-(5-bromopyridin-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-3-yl)acetamide (4b). IR (KBr) cm^{-1}: 3425 (N-H, str.), 3244 (Ar-H, str.), 2939(CH_2,str), 1722 (C=N, str.), 1698 (C=O, str.), 1440 (C-S, str.); ^{1}H NMR (300 MHz , $CDCl_3$) δ: 7.09-8.40 (m, 3H, Ar-H), 6.59 (s, 1H, N-H), 6.32 (s,2H, CH_2, ring) 4.61 (s, 2H, CH_2); Anal. Calcd. For $C_{10}H_8BrN_3O_3S$ in wt % C, 36.28; H, 2.38; N, 12.73 and found to be C, 36.57; H, 2.56; N, 12.78; MS: *m/z* 331 $[M]^{+\cdot}$, 333 $[M+2]^+$, 314, 298, 214, 172, 156, 77, 63, 38.

***Synthesis of 2-{[(4-methyl phenyl) sulfonyl] (pyridine -2-yl) amino} -N-pyridin -2-ylacetamide* (5a).** Compound **2a** (0.01 m mole), ethanoloc solution of compound **1a** (0.01 m mole), triethyl amine (0.025 m mole) and tetrahydrofurane (THF, 25 mL) were taken in dry round bottom flask and refluxed it to 6 hrs. Reaction progress checked by TLC, end of the reaction, resultant product poured into crushed ice, solid appear, which was isolated, dried and recrystallized from ethanol. IR (KBr) cm^{-1}: 3434 (N-H, str.), 3050 (Ar-H, str.), 2910 (CH_3, str), 1702 (C=N, str.), 1635 (C=O,amide, str.), 1501 (N-S, str.); ^{1}H NMR (300 MHz , $CDCl_3$) δ: 7.21-7.95 (m, 12H, Ar-H), 6.54 (s, 1H, N-H) , 4.87 (s, 2H, CH_2), 2.33 (s, 3H, CH_3)

; Anal. Calcd. For $C_{19}H_{18}N_4O_3S$ in wt % C, 59.57; H, 4.64; N, 14.68 and found to be C, 59.70; H, 4.73; N, 14.63; MS: *m/z* 382 $[M]^{+\cdot}$, 367, 351, 335, 227, 149, 93,78, 64, 38.

Similarly, compound **5b** was prepared with minor change in stirrer time and work up process.

***N*-(5-bromopyridin-2-yl)-2-{[(4-methylphenyl)sulfonyl](pyridin-2-yl)amino}acetamide (5b).** IR (KBr) cm^{-1}: 3438 (N-H, str.), 3053 (Ar-H, str.), 2915 (CH_3, str), 1707 (C=N, str.), 1642 (C=O, amide, str.,), 1504 (N-S, str.), ^{1}H NMR (300 MHz , $CDCl_3$) δ: 7.23-7.98 (m, 11H, Ar-H), 6.59 (s, 1H, N-H) , 4.91 (s, 2H, CH_2), 2.38 (s, 3H, CH_3) ; Anal. Calcd. For $C_{19}H_{17}BrN_4O_3S$ in wt % C, 49.47; H, 3.75; N, 12.20 and found to be C, 49.42; H, 3.79; N, 12.11; MS: *m/z* 462 $[M]^{+\cdot}$, 464 $[M+2]^+$, 446, 430, 414, 306, 228, 172, 156, 77, 63, 37.

***Synthesis of 2-(3-methyl -5-oxo -4,5-dihydro -1H-pyrazol-1-yl)-N-pyridin-2-ylacetamide* (6a).** Compound **2a** (0.01 m mole), methanolic solution of pyrazolone (0.01 m mole), triethyl amine (0.025 m mole) and tetrahydrofurane (THF, 25 mL) were taken in dry round bottom flask and refluxed it to 4 hrs. Reaction progress checked by TLC, end of the reaction, resultant product poured into crushed ice, solid appear, which was isolated, dried and recrystallized from ethanol. IR (KBr) cm^{-1} : 3404 (N-H, str.), 3121 (Ar-H, str.), 2896 (CH_3, str), 2800 (CH_2, str.), 1750 (C=N, str.), 1690 (C=N, str., pyrazole), 1662 (C=O, str), 1557 (N-N, str.); ^{1}H NMR (300 MHz , $CDCl_3$) δ: 7.09-8.39 (m, 4H, Ar-H), 6.59 (s, 1H, N-H), 6.25 (s, 2H, CH_2, ring), 4.56 (s, 2H, CH_2), 2.35 (s, 3H, CH_3); Anal. Calcd. For $C_{11}H_{12}N_4O_2$ in wt % C, 56.89; H, 5.19; N, 24.12 and found to be C, 56.94; H, 5.44; N, 24.32; MS:*m/z* 232 $[M]^{+\cdot}$, 217, 201, 135, 93, 78, 64, 38.

Similarly, compound **6b** was synthesized with minor change in reaction conditions

***N*-(5-bromopyridin-2-yl)-2-(3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl)acetamide(6b).** IR (KBr) cm^{-1} : 3410 (N-H, str.), 3125 (Ar-H, str.), 2898 (CH_3, str), 2806 (CH_2, str.), 1758 (C=N, str.), 1697 (C=N, str., pyrazole), 1671 (C=O, str), 1565 (N-N, str.); ^{1}H NMR (300 MHz , $CDCl_3$) δ: 7.15-8.42 (m, 3H, Ar-H), 6.65 (s, 1H, N-H), 6.29 (s, 2H, CH_2, ring), 4.61 (s, 2H, CH_2), 2.42 (s, 3H, CH_3); Anal. Calcd. For $C_{11}H_{11}BrN_4O_2$ in wt % C, 42.36; H, 3.56; N, 18.01 and found to be C, 42.40; H, 3.64; N, 17.95; MS:*m/z* 312 $[M]^{+\cdot}$, 314 $[M+2]^+$, 296, 280, 214, 172, 156, 77, 63, 38.

3. RESULT AND DISCUSSION

Chemistry. In the present research work an effort has been made to synthesize substituted pyridine based acetamide derivatives using two a step process. All the compounds were purified by recrystallization method using appropriate solvent. Structures of all compounds have been confirmed by the analytical and spectral studies. 4-methyl-*N*-pyridin-2-ylbenzenesulfonamide **(1a)** was achieved by reaction with 2-aminopyridine and p-toluene sulfonyl chloride. The structure of this compound is confirmed by ^{1}H-NMR, presence of a singlet at δ 2.31 due to (CH_3) group and IR absorptions at 1391 cm^{-1} due to the (N-S) group. Similarly, 2-chloro-*N*-pyridin-2-ylacetamide **(2a)** was synthesized by reaction of 2-aminopyridine and chloroacetyl chloride and it confirm by ^{1}H-NMR, presence of a singlet at δ 6.80 due to (N-H) group and IR absorptions at 1649cm^{-1} due to the (C=O) group (Scheme 1). Compound **3a** to **6a** were synthesized by N-Alkylation / C–N coupling reactions. In this reaction, compound **2a** reacts with variable secondary cyclic and acyclic amides to give targeted compounds. In next route, 2-(2,3-dioxo-2,3-dihydro-1*H*-indol-1-yl)-*N*-pyridin-2-ylacetamide **(3a)** was achieved by reaction of **2a** with isatin and it confirm by appearance of C=O group peak at 1630 cm^{-1}. Further 2-(2,4-dioxo-1,3-thiazolidin-3-yl)-*N*-pyridin-2-ylacetamide **(4a)** was synthesized by reaction of compound **2a** with ethanolic solution of thiazolidione and it exhibit singlet at δ 6.29 due to the CH_2 group of thiazolidione. In another path, compound **2a**, triethyl amine and ethanolic solution of compound **1a** were refluxed to give 2-{[(4-methyl phenyl) sulfonyl] (pyridine -2-yl) amino} -*N*-pyridin -2-ylacetamide **(5a)**,

which is confirmed by IR absorptions at 1504 cm^{-1} due to the (N-S) group and ^{1}H-NMR singlet at δ 2.33 due to the CH_3 group of p-toluene sulfonyl ring. In last route, compound **2a**, methanolic solution of pyrazolone and triethyl amine react together and give final 2-(3-methyl -5-oxo -4,5-dihydro -1*H*-pyrazol-1-yl)-*N*-pyridin-2-ylacetamide **(6a)**, it show sharp singlet at δ 6.25 corresponding to the CH_2 group of pyrazole and IR absorptions at 2896 cm^{-1} due to the CH_3 group. General reaction mechanism has been given for scheme 2. The synthesized compounds have also been characterized by their mass spectral and elemental analysis studies. These compounds were tested for their biological activities.

4. BIOLOGICAL EVALUATION

***In-vitro* antimicrobial Screening.** Compounds **3a,b** to **6a,b** have been studied for their *in-vitro* antibacterial activity against two gram-positive bacteria viz. *Staphylococcs aureus* (MTCC 96) and *S. pyogenes* (MTCC 443) and two gram-negative bacteria viz. *Escherichia coli* (MTCC 442) and *Pseudomonas aeruginosa* (MTCC 441) by using Ampicillin as the reference antibacterial drug. *In-vitro* antifungal activity was also studied against three fungal species - *Candida albicans* (MTCC 227), *Aspergillus niger* (MTCC 282) and *Aspergillus clavatus* (MTCC 1323) where Griseofulvin was used as the reference antifungal drug. The minimal inhibitory concentration (MICs, μg/mL) of the synthesized compounds was determined by the broth micro-dilution method [35] according to National Committee for Clinical Laboratory Standards. Some of the compounds have shown equal MIC values against almost microorganisms as compared to standard drugs. The outcome of this investigation is presented in Table 2.

***In-vivo* anti-inflammatory activity.** The synthesized compounds **3a-b** to **6a-b** were tested for their *in-vivo* anti-inflammatory activity using carrageenan induced paw edema test in rats [36]. Diclofenac sodium (20 mg/kg) was administered as standard drug for comparison. Rats were divided in to 10 groups, each group containing 2 rats. Group 1 was treated with tween-80 (1%) suspension which served by vehicle control. Group 2 to 9 were treated with the suspension of the test compounds at a dose of 20 mg/kg. Group 10 was administered with standard drug Diclofenac sodium. After 40 minutes, the animals were injected with 0.1 mL of carrageenan (1%w/v), in the sub planter region of left hind paw of rats. The paw volume was measured using the mercury displacement technique with the help of a plethysmograph after 2 h and 4 h of carrageenan injection. The percent reduction value calculated according to the following formula given below**:-**

$$\% \text{ reduction of edema} = [1 - Vt / Vc] \times 100$$

Where, Vt and Vc are the mean relative changes in the volume of paw edema in the test and control respectively. The results of *in vivo* study indicated that the test compounds were able to effectively inhibit the paw edema. All over result is that compound (**3a,** 41.30%: **3b** & **6b** 43.47%) exhibit good activity. Similarly, compound (**5a**, 47.82%; **6a**, 45.65%) show stronger activity against carrageenan induced paw edema. The results of this investigation are showed in Table 3.

5. CONCLUSION

In this work, pyridine and their derivatives were synthesized using C-N coupling/N-alkylation process with a wide range of medicinal applications. The synthesized derivatives **3a, b** to **6a, b** were examined for antibacterial, antifungal and anti-inflammatory activities. These derivatives showed good to moderate activity. Results indicated that the compounds **3a, 3b, 5a, 6a** and **6b** showed significant activities towards bacterial, fungal pathogenic strains and animal as well when compared to standard drugs. Hence, the conclusion can be drawn that compound **5a** is better antibacterial, antifungal and stronger anti-inflammatory

agent than the other derivatives. It can be developed as potent chemotherapeutic agent. Our ongoing research focuses on the same combinations with incorporation of more effective substituents in search of novel bioactive agents.

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REFERENCES

I. Moore, J. L.; Taylor, S. M.; Soloshonok, V. A. ARKIVOC **2005**, (vi), 287.
II. Clay, C.M.; Abdallah, H.M.; Jordan, C.; Knisley, K.; Ketcha, D. M. ARKIVOC, **2012**, (vi), 317.
III. Richards, I. C.; Thomas, P. S. Pestic Sci **1990**, 30, 275.
IV. Dinsmore, C. J.; Williams, T. M.; Neill, T.J.; Liu, D.; Rands, E.; Culberson, J. C.; Bioorg Med Chem Lett **1999**, 9, 3301.
V. Abraham, D.J. Burger's medicinal chemistry & drug discovery. **2003**.
VI. Supuran, C.T.; Casini, A.; Scozzafava Med Res Rev **2003**, 5, 535.
VII. Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C.T. Curr Med Chem **2003**, 10, 925.
VIII. McMohan, J.B.; Gulakowsky, R.J.; Weislow, O.S.; Schultz, R.J.; Narayanan, V.L.; Clanton, D.J Chemother **1993**, 37,754.
IX. Ohta, K.; Itoh, S.; Yamada, J.; Masumoto, K.; Yoshikawa, H.; Ishida, Y. J Pest Sci **1993**, 18, 183.
X. Balaban, A. T.; Oniciu, D. C.; Katritzky, A. R. Chem Rev 2004, 104, 2777; b) Candeias, N. R.; Branco, L. C.; Gois, P. M. P.; Afonso, C. A. M.; Trindade, A. F.; Chem Rev **2009**, 109, 2703.
XI. Zhang, L.; Peng, X. M.; Damu, G. L. V.; Geng, R. X.; Zhou, C.H. Med Res Rev **2014**, 34, 340.
XII. Henry, G.D.; Novo, D. Tetrahedron, **2004**, 60, 6043.
XIII. Boschelli, D.H.; Wu, B.; Barrios, A.C.; Chen, J.; Asselin, M.; Cole, D.C. Bioorg Med Chem Lett **2008**, 18, 2850.
XIV. Madhusudana, K.; Shireesha, B.; Naidu, V.G.; Ramakrishna, S.; Narsaiah, B.; Rao, A.R.; Diwan, P.V. Eur J Pharmacol **2012**, 678, 48.
XV. Nathan, T. L.; Boschelli, D.H.; Lee, J.; Chaudhary, D. Bioorg Med Chem Lett **2008**, 18, 4420.
XVI. Liu, H.; Li, Y.; Wang, X. Y.; Wang, B.; He, H. Y.; Liu, J. Y, Bioorg. Med Chem Lett **2013**, 23, 2349.
XVII. Schnute, M. E.; Anderson, D. J.; Brideau, R. J.; Ciske, F. L.; Collier, S. A. Bioorg Med Chem Lett **2007**, 17, 3349.
XVIII. Shuck-Lee, D.; Chen, F.; Willard, R.; Raman, S.; Ptak, R. Antimicrob Agents. Chemother **2008**, 52, 3169.
XIX. Pinheiro, L. C. S.; Borges, J. C.; Oliveira, C. D.; Ferreira, V. F. Romeiro, G. A. ARKIVOC **2008**, 17, 77.
XX. Adachi, I.; Hiramatsu, Y.; Ueda, M.; Kawakami, M. US Patent, **1987**, 4, 703.
XXI. Ueda, M.; Matsumura, S.; Masui, M.; Matsuura, E.; Kawakami, M.; Fujitomo, H. Arzneimittelforschung **1993**, 43, 1282.
XXII. Bahekar, R. H.; Jain, M. R.; Goel, A.; Patel, D. N.; Prajapati, V. M.; Gupta, A. A.; Jadav, P. A.; Patel, P. R. Bioorg Med Chem **2007,** 15, 3248.

XXIII. Bahekar, R. H.; Jain, M. R.; Jadav, P. A.; Prajapati, V. M.; Patel, D. N.; Gupta, A. A. Bioorg Med Chem **2007**, 15, 6782.

XXIV. Kamata, M.; Yamashita, T.; Kina, A.; Funata, M.; Mizukami, A., Sasaki, M. Design, Bioorg Med Chem Lett **2012**, 22, 3643.

XXV. Willemann, C.; Grunert, R.; Bednarski, P. J.; Troschutz, R. Bioorg Med Chem **2009**, 17, 4406.

XXVI. Wu, J. P.; Fleck, R.; Brickwood, J.; Capolino, A.; Catron, K. Bioorg Med Chem Lett **2009**, 19, 5547.

XXVII. Feng, L.; Reynisdóttir, I.; Reynisson, J. Eur J Med Chem **2012**, 54, 463.

XXVIII. Mohareb, R. M.; Wardakhan, W.; Elmegeed, G. A.; Ashour, R. M. Steroids **2012**, 77, 1560.

XXIX. Saito, K.; Nakao, A.; Shinozuka, T.; Shimada, K.; Matsui, S.; Oizumi, K. Bioorg Med Chem **2013**, 21, 1628.

XXX. Ohba, S.; Nakajima, K.; Komiyama, Y.; Kugimiya, F.; Igawa, K.; Itaka, K. Biochem Biophys Res Commun **2007**, 357, 854.

XXXI. Bernardino, A. M.; Silva, L. C.; Rodrigues, C. R.; Loureiro, N. I.; Castro, H. C.; Rangel, A. L. Bioorg Med Chem **2006**, 14, 5765.

XXXII. Al-Trawneh, S. A.; El-Abadelah, M. M.; Zahra, J. A.; Al-Taweel, S. A.; Zani, F.; Incerti, M. Bioorg Med Chem **2011**, 19, 2541.

XXXIII. Mohler, E. G.; Shacham, S.; Noiman, S.; Lezoualch, F.; Robert, S.; Gastineau, M. Ragozzino, Neuropharmacology **2007**, 53, 563.

XXXIV. Baumann, M.; Baxendale, I. R. Beilstein J Org Chem **2013,** 9, 2265.

XXXV. Collee, G. J.; Fraser, G. A., Marmion, P. B.; Simmons, A.; Practical Medical Microbiology **1996**, 14, 163.

XXXVI. Winter, C. A.; Risley, E. A.; Nuss, G. W. ProcSoc Exp Biol Ther **1962**, 111, 544.

Table 1: Physical and analytical data of new synthesized compounds**.**

Comp.	Mol. formula	MW	mp (°C)	Yield (%)
1a	$C_{12}H_{12}N_2O_2S$	248	218	80
1b	$C_{12}H_{11}BrN_2O_2S$	327	224	78
2a	$C_7H_7ClN_2O$	170	203	82
2b	$C_7H_6BrClN_2O$	249	210	81
3a	$C_{15}H_{11}N_3O_3$	281	233	70
3b	$C_{15}H_{10}BrN_3O_3$	360	242	68
4a	$C_{10}H_9N_3O_3S$	251	176	75
4b	$C_{10}H_8BrN_3O_3S$	330	188	72
5a	$C_{19}H_{18}N_4O_3S$	382	238	64
5b	$C_{19}H_{17}BrN_4O_3S$	461	252	61
6a	$C_{11}H_{12}N_4O_2$	232	196	74
6b	$C_{11}H_{11}BrN_4O_2$	311	214	70

Table 2: *In-vitro* antimicrobial activity (MICs µg/mL) of the synthesized compounds
S_1 = Ampicillin, **S_2** = Griseofulvin

Comp.	Antibacterial activity				Antifungal activity		
	Gram +ve		Gram –ve				
	S.aureus MTCC *96*	*S.pyogenes* MTCC 443	*E.coli* MTCC 442	*P.aeruginosa* MTCC 441	*C.albicans* MTCC 227	*A.niger* MTCC 282	*A.clavatus* MTCC 1323
3a	**250**	500	250	**250**	1000	1000	200
3b	500	200	>1000	**200**	>1000	200	>1000
4a	500	**125**	500	**100**	**500**	250	**125**
4b	>1000	200	250	**>1000**	1000	500	500
5a	**200**	**100**	***62.5**	**125**	**500**	**125**	200
5b	**250**	200	250	**500**	**250**	200	**125**
6a	1000	500	200	**250**	>1000	**100**	250
6b	500	**100**	100	**125**	500	500	1000
S_1	250	100	100	---	-	-	-
S_2	-	-	-	-	500	100	100

MICs (µg/mL) values in bold letters indicate that the synthesized compounds are comparatively active as standard drugs.

Table 3: *In-vivo* anti-inflammatory activity of synthesized compounds**.**

Group.	edema volume 2 h	4 h	% reduction in edema after 2h	4h
1% Tween-80	0.46±0.01	0.51±0.03	-	-
3a	0.27±0.00	0.31±0.01	***41.30**±2.81	39.21±1.20
3b	0.26±0.00	0.30±0.02	***43.47**±1.42	41.17±2.65
4a	0.30±0.01	0.34±0.03	34.78±2.75	33.33±2.94
4b	0.31±0.00	0.36±0.01	32.60±1.59	29.41±2.10
5a	0.24±0.00	0.29±0.02	***47.82**±1.54	43.13±1.40
5b	0.28±0.01	0.32±0.01	39.13±1.53	37.25±3.76
6a	0.25±0.00	0.30±0.03	***45.65**±1.75	41.17±1.18
6b	0.26±0.00	0.31±0.01	***43.47**±1.98	39.21±2.80
S_3	0.22±0.01	0.28±0.03	52.17±1.92	45.09±0.54

S_3 = Diclofenac
All values are mean ± SEM values.
* % reduction values in bold letters showing good anti-inflammatory activity as compare to standard drugs.

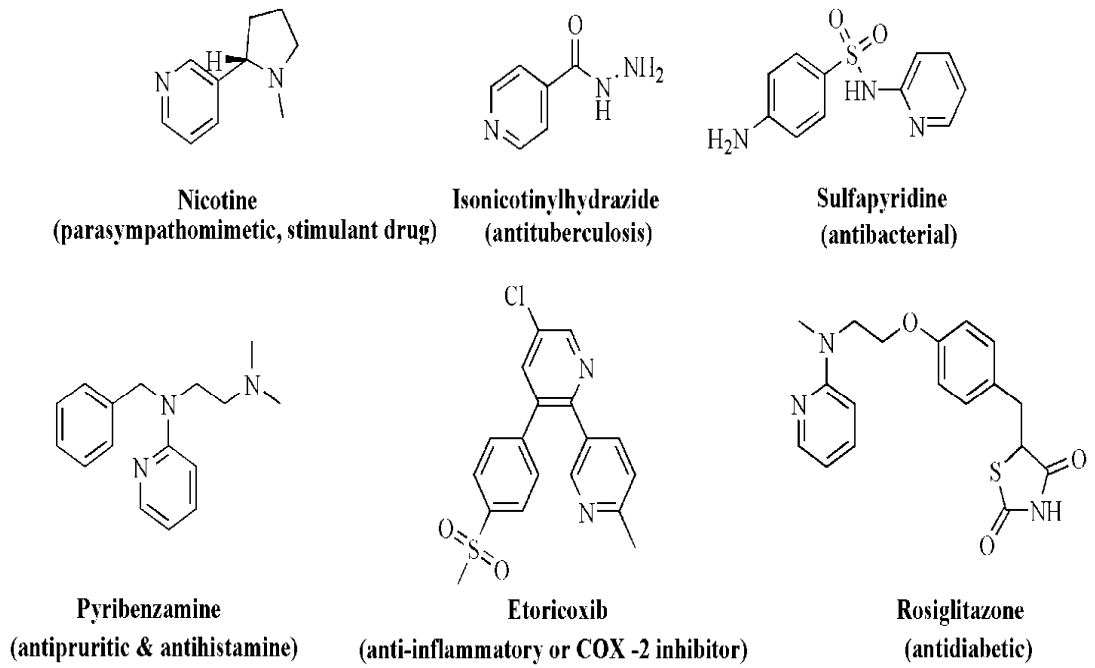


Figure 1. Pyridine Containing Active Therapeutic Agents

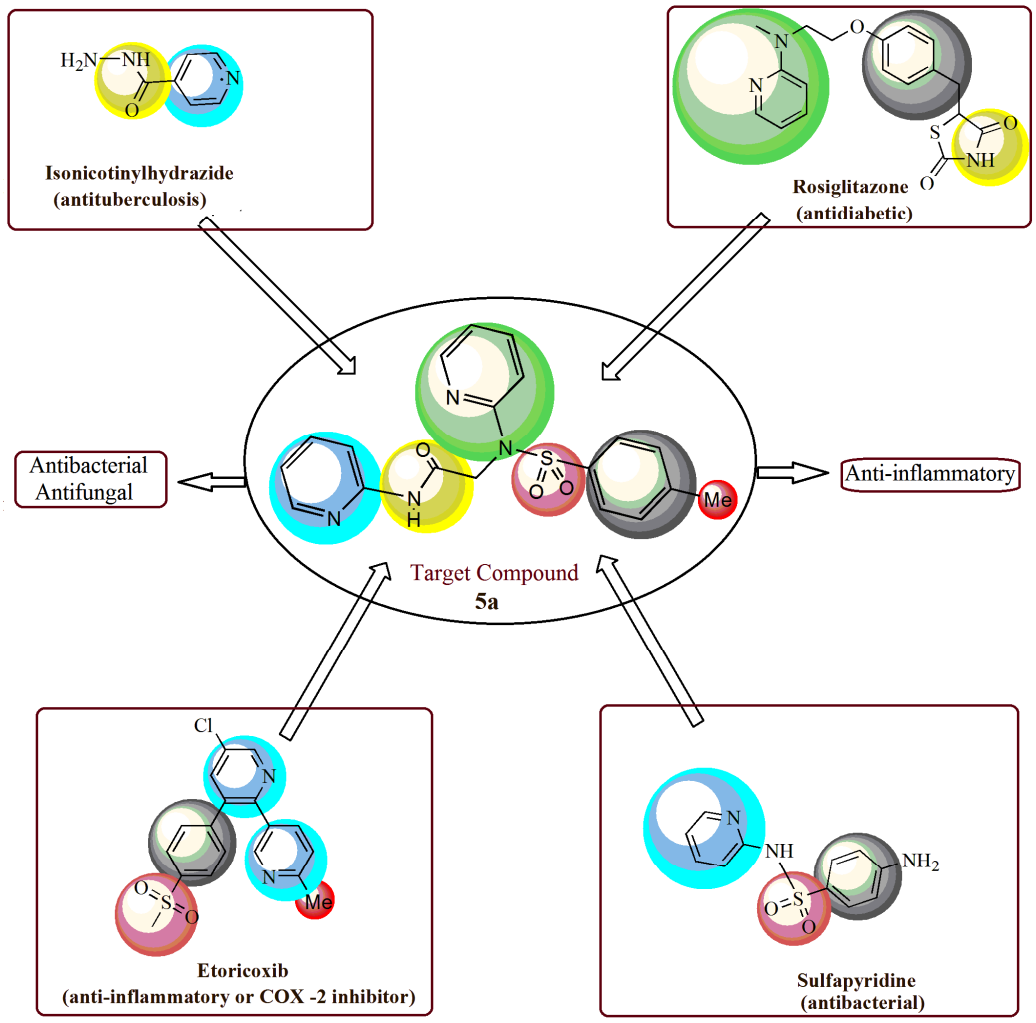
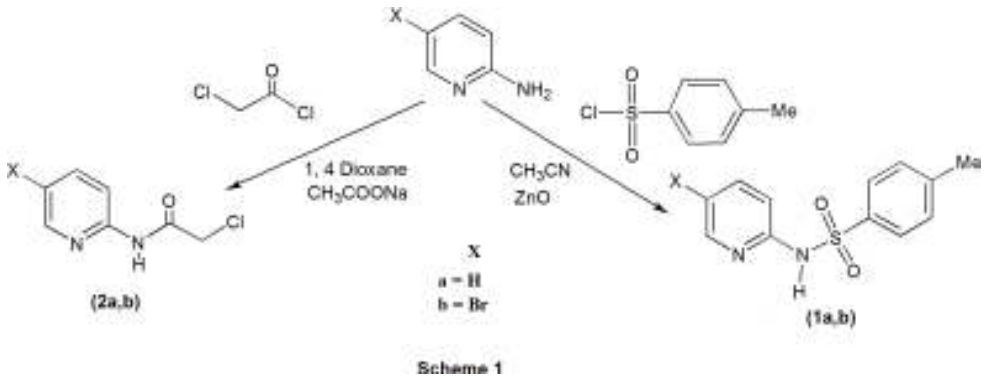
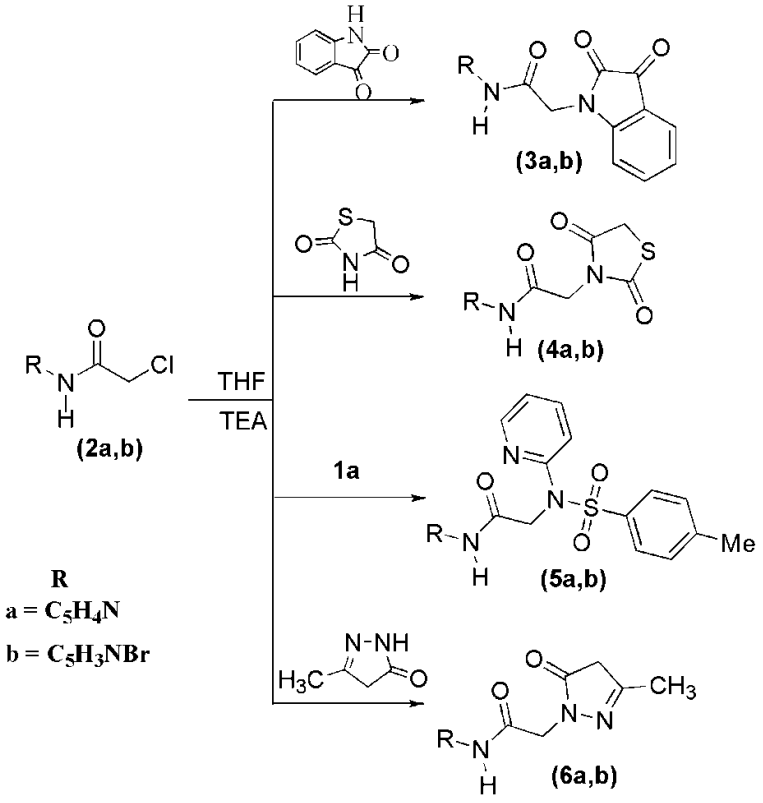


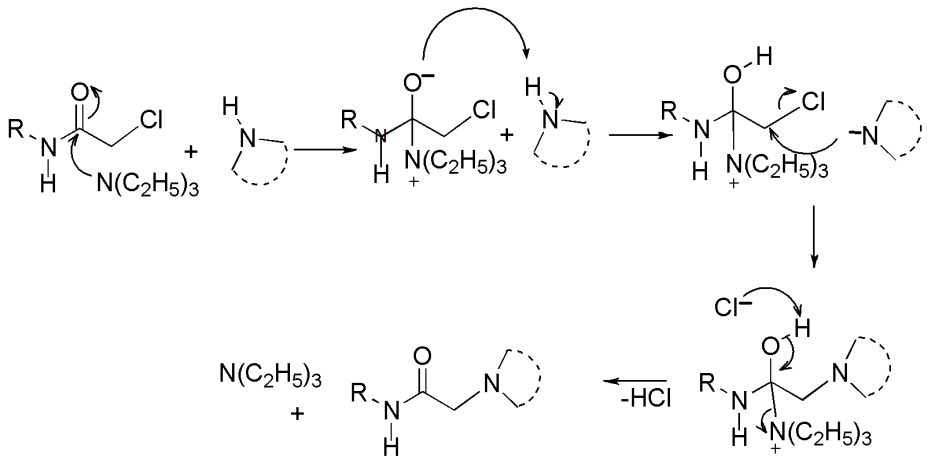
Figure 2. Structure Similiraty Between Target Compound 5a and Selective Drugs



Scheme 1



Scheme 2



General reaction mechanism for compounds 3a,b to 6a,b

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