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Synthesis and Antimicrobial Study of 3,5,6-Trichloropyridine-2-yl(arylthio)acetate Derivatives

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Present invention related to synthesis of novel ester derivatives of 3,5,6-trichloropyridine-2-ol with aryl/naphthyl thioglycolic acid and substituted derivatives thereof as pharmaceutically active ingredients. This invention consists of synthesis of new pharmaceutical entities by reacting 3,5,6-trichloropyridine-2-ol with aryl/naphthyl thioglycolic acid halide and substituted derivatives thereof to get ester derivatives and to their use as antibacterial/antifungal agent. All these compounds were characterized by means of their melting point, HPLC, IR and ^{1}H NMR spectroscopic data. The synthesized compounds (1a to 1d) have been screened for *in vitro* antibacterial activity against a variety of bacterial strains. Gram-negative strain of bacteria used were *Klebsiella* and *E. coli* while gram-positive bacterial strain used was Step. *Aureus* and *E. fecalis* The activity was determined using MIC. Ciprofloxacin was used as standard (2 µg/mL). The compounds have shown varying degree of antibacterial and antifungal activity.

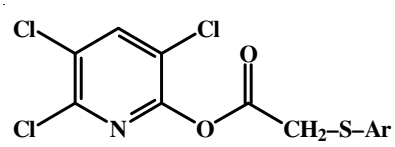
Key Words: Aryl thioacetate, 3,5,6-Trichloropyridinol, Naphthylthio, Antifungal and Antibacterial activity.

INTRODUCTION

Pyridinol substructures are of high interest because of their occurrence in numerous pharmaceuticals, drugs, insecticides and herbicides. Novel combinations of the antiprotozoal[1-4] naphthoquinone compound and a 4-pyridinol or an alkanoic ester thereof wherein the antiprotozoal activity of the combination is potentiated with respect to the corresponding activity of the components of the combination. The combinations are especially useful for the treatment or prophylaxis of malaria. Antimalarial activity of clopidol[5], 3,5-dichloro-2, 6-dimethyl-4-pyridinol and its esters, carbonates and sulphonate is well described in literature. Pyridinol substructures are of high interest because of their occurrence in numerous pharmaceuticals, drugs, insecticides and herbicides. Synthesis of some new linear and chiral macrocyclic pyridine carbazides reported by Amr[6] as analgesic and anticonvulsant agents. A simple pyridine derivatives show activity as an immunoregulator. Alkylation of 4-chloromethylpyridine with 1-hydroxy-ethane-2-thiol affords Ristianol[7]. We synthesized a series of arylthioacetate derivatives 3,5,6-trichloro pyridin-2-ol and tested for microbial property and found to be showing potential activity on micro-organisms.

EXPERIMENTAL

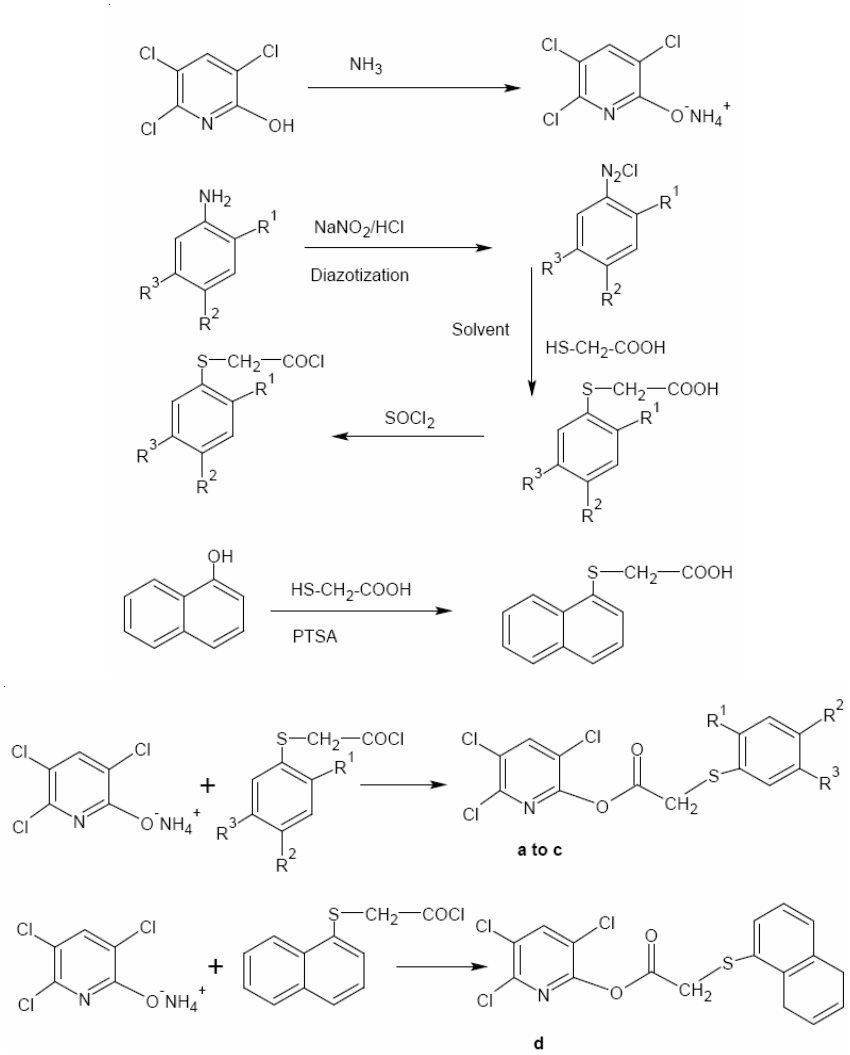
Melting points were determined on a LABINDIA MR. *viz.* visual melting range apparatus and are uncorrected. Purity of the compounds was checked by reverse phase system using Shimadzu SPD 10AV HPLC. Solvent system (mobile phase) acetonitrile:methanol:water (70:15:15) and 240 nm. HPLC column used was C_{18} and flow rate maintained was 1 mL/min. IR spectra in KBR (cm^{-1}) were recorded on Shimadzu FTRIR-410 series spectrophotometer and ^1H NMR spectra were recorded on Bruker 200 MHz (DMSO-d_6) using TMS as internal standard (chemical shifts are expressed in δ ppm).



where Ar = phenyl, substituted phenyl, naphthyl or substituted naphthyl *etc*. These compounds exhibit good antibacterial and antifungal activity and can be used as antimicrobial drug.

General procedure for the preparation of ammonium salt of 3,5,6-trichloro-pyridin-2-ol: To a 500 mL capacity 3 neck round bottom flask with overhead stirrer added 250 mL water and 0.25 mol of 3,5,6-trichloropyridinol. Then slowly passed ammonia gas into the mass under stirring till ammonical pH and maintaining temperature of 30-35 ºC. Then filtered the mass and washed with water. This isolated 3,5,6-trichloro-pyridinol salt dried at 60-80 ºC. This salt further purified with methanol.

General procedure for the preparation of aryl thioglycolic acyl halide: A mixture of 0.1 mol of aromatic amine (**a**, **b** or **c**) and 100 mL of 5N HCl was taken together in a 4 neck round bottom flask and heated to 50-55 °C and maintained for 1 h. This was then cooled to below 0 °C and slow addition of 0.1-0.11 mol of $NaNO_2$ was done below surface maintaining above temperature. The obtained diazotised mass filtered to remove some insoluble particles and to clear solution, added 100 mL of tetrachloro ethylene solvent. This mixture was kept under stirring and slowly added 0.1-0.11 mol of thioglycolic acid solution at 0.0-5.0 °C. Then temperature was slowly brought up to 30 °C over 3 h and maintained for 2-2.5 h till complete evolution of nitrogen. The product precipitated out as pale yellow fluffy slurry. This was then cooled to 0-5 °C and filtered the slurry. The solid cake washed with 100 mL of tetra chloro ethylene followed by water. The crude product obtained was crystallized 40 mL of toluene. Yield: 70-75 %, purity: 96-98 %. The isolated product (s) analyzed by GLC. To a reaction flask added isolated aryl thioglycolic acid (0.07 mol) and 25 mL of dichloromethane solvent. Then added 0.1 mol of thionyl chloride and heated to 40 ºC reflux condition. Scrubbed out off gases over a maintaining period of 2 h. Further distilled out dichloromethane solvent as well as unreacted $SOCl_2$ up to reaction mass temperature 40-70 ºC.



Scheme-I

Preparation of the (1-naphthylthio) acetic acid and acyl halide: In a 1.0 L. 4 neck round bottom flask, added 1.0 gm. mole of α-naphthol, 0.3 mol of *p*-toluene sulphonic acid and 1.1 mol of 80 % thioglycolic acid. This mixture was heated to 108-110 °C under nitrogen atmosphere for 15 h. This was cooled to 80 °C and further added 500 mL water. Filtered the mass and washed with water to displace any unreacted thioglycolic acid. Yield: 85.0 %: m.p. 106 °C.

Acyl chloride prepared by reacting with thionyl chloride as per process described above.

General procedure for the preparation of 3,5,6-trichloropyridin-2-yl (aryl/naphthyl)thioacetate (a-d): In a separate 250 mL capacity 3 necks round bottom flask with magnetic stirring and reflux system, charged 50 mL dichloromethane

solvent. To this flask added 0.05 mol of ammonium salt of 3,5,6-trichloropyridin-2-ol and it was slurry. Then added 0.07 mol of above prepared acid chloride and addition was exothermic. The reaction maintained for 2 h at 40-42 ºC reflux condition. Cooled the mass to 30 ºC and added 50 mL water and separated layers. Organic layer washed with 50 mL of 0.1N NaOH solution to remove non reacted phenol and acid part. Further washed organic layer with water till neutral pH. Crude product crystallized using 50 mL of methanol, as product was sparingly soluble.

RESULTS AND DISCUSSION

The analytical and spectral data are given in Tables 1 and 2, respectively. In general, most of the compounds showed significant antibacterial and antifungal activity but some compounds are more specific to particular strains of bacteria and fungi. The synthesized compounds (**a-d**) have been screened for *in vitro* antibacterial activity (Table-3) against a variety of bacterial strains. Gram-negative strain of bacteria used were *Klebsiella* and *E. coli* while gram-positive bacterial strain used was *S. aureus* and *E. fecalis.* The activity was determined using MIC. Ciprofloxacin was used as standard (2 µg/mL). The compounds have shown varying degree of antibacterial activity. The synthesized compounds (**a-d**) have also shown varying degree of antifungal activity (Table-4). The compound 3,5,6-trichloropyridin-2-yl[(2,5-dichloro-4-nitrophenyl)sulfanyl acetate (**c**) having strong electron withdrawing group ($-NO_2$) on benzene ring has showed high degree of antibacterial and antifungal activity.

TABLE-1
ANALYTICAL DATA OF THE SYNTHESIZED COMPOUNDS (**a-d**)

Comp.	R_1	R_2	R_3	m.f.	m.p. (°C)	Yield (%)
a	-Cl	-Cl	-Cl	$C_{13}H_5NO_2SCl_6$	133-134	61.7
b	-Cl	-H	-Cl	$C_{13}H_6NO_2SCl_5$	114-115	46.0
c	-Cl	$-NO_2$	-Cl	$C_{13}H_5N_2O_4SCl_5$	95-96	49.0
d	–	–	–	$C_{17}H_{10}NO_2SCl_3$	111-112	55.0

TABLE-2
SPECTRAL DATA OF THE SYNTHESIZED COMPOUNDS (**a-d**)

Compd.	IR (KBr, ν_{max}, cm^{-1})	^1H NMR (DMSO-d_6 ppm)*
a	3070 (C-H *str.*), 1780 (C=O *str.*), 1326 (C-O-C *str.*),	4.6 (2H, s, $-CH_2-$), 7.5-7.9 (3H, aroma.)
b	3080 (C-H *str.*), 1741 (C=O *str.*), 1323 (C-O-C *str.*)	4.0 (2H, s, $-CH_2-$), 7.24-7.52 (4H, arom.)
c	3100 (C-H *str.*), 1730 (C=O *str.*), 1340 (C-O-C *str.*)	3.6 (2H, s, $-CH_2-$), 7.94-8.4 (3H, arom.)
d	3060 (C-H *str.*), 1759 (C=O *str.*), 1320 (C-O-C *str.*)	4.41 (2H, s, $-CH_2-$), 7.5-8.6 (8H, arom.)

*s = Singlet.

TABLE-3
in vitro ANTIBACTERIAL ACTIVITIES CHIRAL AMIDE DERIVATIVES OF TRICHLORO PYRIDINOL ESTER (MIC, µg/mL); Ciprofloxacin: 2 µg/mL as standard

Compound	*S. aureus*	*E. fecalis*	*Klebsiella*	*E. coli*
a	> 25.0	6.25	50	100.0
b	25.0	1.60	25	50.0
c	0.8	0.40	< 100	12.5
d	50.0	25.00	100	100.0

TABLE-4
in vitro ANTIFUNGAL ACTIVITIES TRICHLORO PYRIDINOL ESTER DERIVATIVES (MIC, μg/mL); Standard: Fluconazole: 2 μg/mL

Compound	*Aspargillus*	*Candida*
a	25.0	50.000
b	12.5	12.500
c	0.8	3.125
d	25.0	25.000

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REFERENCES

1. P. Blumbergs, M.P. LaMontagne, A. Markovac, J.G. Moehring and A.B. Ash and C.L. Stevens, *J. Med. Chem.*, **15**, 808 (1972).
2. P.S. Humphries, Q.Q. Do and D.M. Wilhite, *Beilstein J. Org. Chem.*, **2** , 21 (2006).
3. V.S. Latter, A.T. Hudson, W.H.G. Richards and A.W. Randall, US Patent 5053418 (1991).
4. V.S. Latter, W.H.G. Richards, A.T. Hudson and A.W. Randall, Eur. Patent EP0401875 (1984).
5. L.D. Markley, J.C. Van Heertum and H.E. Doorenbos, *J. Med. Chem.*, **15**, 1188 (1972).
6. A.-G. E. Amr, *Z. Naturforsch*. **60b**, 990 (2005).
7. D. Lednicer and L.A. Mitscher, The Organic Chemistry of Drug Synthesis, Vol. 4, p. 102 (1977).

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