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DESIGN AND SYNTHESIS OF 1, 3, 4-THIADIAZOLES AS ANTI-INFLAMMATORY CANDIDATE

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ABSTRACT

The N-substituted chloroacetamides (**A**), 2-chloropropionamides (**B**) and 3-chloropropionamides (**C**) were synthesized by acetylating respective amine using chloroacetylchloride, 2-chloropropanoyl chloride and 3-chloropropanoyl chloride respectively. These compounds were characterized by TLC, melting point and IR spectra.

The N –substituted 2-{ [5 - (pyridine-4-yl) - 1, 3, 4 – thiadiazol – 2 -yl]sulfanyl } acetamide (**4a-c**), N-substituted-2-{[5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl]sulfanyl} propanamide (**5a-c**) and N-substituted-3-{[5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl]sulfanyl} propanamide (**6a-c**) derivatives were prepared by condensing sodium salt of 5-(4-pyridyl)-2-mercapto-1,3,4-thiadiazole (**3**) and N-substituted chloroacetamides (**A**), N-substituted α-chloropropionamides (**B**) and N-substituted β-chloropropionamides (**C**) respectively. Structure of all synthesized compound was confirmed by IR, and ^{1}H NMR. All synthesized compounds were screened for their anti-inflammatory activity by carrageenan induced rat paw edema model compared to the standard drug diclofenac. The synthesized compounds showed anti-inflammatory activity ranging from 26.97% to 59.99%; whereas standard drug Diclofenac sodium showed 63.70% inhibition after 4 hr.

Keywords: NSAID's, Anti-inflammatory, Acetamide, Propanamide, 1, 3, 4-Thiadiazoles

INTRODUCTION

Non-steroidal anti-Inflammatory drugs (NSAIDs) are broadly used therapeutic class of drugs primarily for chronic as well as acute treatment of inflammation, pain, pyresis, arthritis and similar condition but these are associated with severe side effects **[1]**. Therefore, studies for developing safer NSAIDs lacking the gastrointestinal and renal side effects of currently used ones have recently been of interest for many researchers.

Although NSAIDs were in use from century ago, its mechanism of action was not known until 1970. In 1971s the break through occurred with elucidation of molecular mechanism of aspirin and other NSAIDs by John Vane **[2]**. He elucidated arachidonate pathway for prostaglandins (PGs) biosynthesis and identify prostaglandin synthase enzyme as a target for effective NSAIDs which is also called as cyclooxygenase (COX).

The 1990s was the new dawn in the inflammatory research; two isoforms of COX have been identified, namely COX-1 (constitutive) and COX-2 (inducible). The result of this study revealed the physiological function of COX-1 and major contribution of inducible COX-2 in the pathophysiology of inflammation. This allowed to differentiate between the beneficial and non-beneficial effects of COX is forms inhibition in the treatment of inflammation by NSAIDs and showed that it is sufficient to inhibit COX-2 only in order to get anti-inflammatory action.

In the last few years, more attention oriented towards 1, 3, 4-thiadiazole, mainly because of their diversity of pharmacological properties. 1, 3, 4-thiadiazole is a five member heterocyclic compound having two nitrogen and one sulfur atom in a structure. The first representative of this group was discovered by Emil Fischer in 1882 **[3]**. 1, 3, 4-thiadiazole derivatives possess interesting biological activity probably conferred to them by the strong aromaticity of this ring system **[4]** which leads to great *in vivo* stability and generally a lack of toxicity for higher vertebrates. During recent years there has been a large investigation on different classes of thiadiazoles compounds, many of which were found to possess an extensive spectrum of pharmacological activities such antimicrobial **[5, 6]**, antitubercular **[7-9]** anticancer **[10-12]** ,Anti-Helicobacter pylori **[13, 14]**, antioxidant **[15, 16]**, anticonvulsant **[17, 18]**, anti-inflammatory **[19-22]**.

Thus, the extensive literature survey of 1,3,4-thiadiazole derivatives has confirmed that there is a great scope in exploring this heterocyclic nucleus in

search of lead for various diseases to benefit the mankind.

MATERIAL AND METHODS:

All of these chemical and reagents used in these experiments were of synthetic grade. All melting points reported were uncorrected and determined in open glass capillary tubes in a paraffin bath. Purity of compounds was routinely measured by thin layer chromatography on glass plates using silica gel G as absorbent and Chloroform: Methanol (8:2) as solvent system. Characterization of synthesized compounds was done by IR spectra, and ^{1}HNMR spectra. The anti-inflammatory activity of the synthesized compounds was determined following the Carrageen-induced paw edema method in rats.

Experimental Work:

Step I: General procedure for preparation of potassium 2- (pyridine – 4 – yl carbonyl) hydrazinecarbodithioate (2) **[23]**

To the cool solution of 8.4 g (0.15 mol) of potassium hydroxide, 200 ml of absolute ethanol, 13.71 g (0.10 mol) of isonicotinic acid hydrazide (INH) **(1)** was added to get clear solution followed by drop wise addition of 11.4g (0.15 mol) of carbon disulfide at 10 to 15 ^{0}C. The above mixture was diluted with 150 ml of absolute ethanol and agitated for 12 to 16 hr. It was then diluted with 200 ml of dry ether, and the precipitated solid was filtered, washed with 100 ml of ether, and dried at 50^{0}C. The salt (**2**), prepared as described above, was obtained in nearly quantitative yield and employed without further purification. The yield was 93% **(Scheme)**.

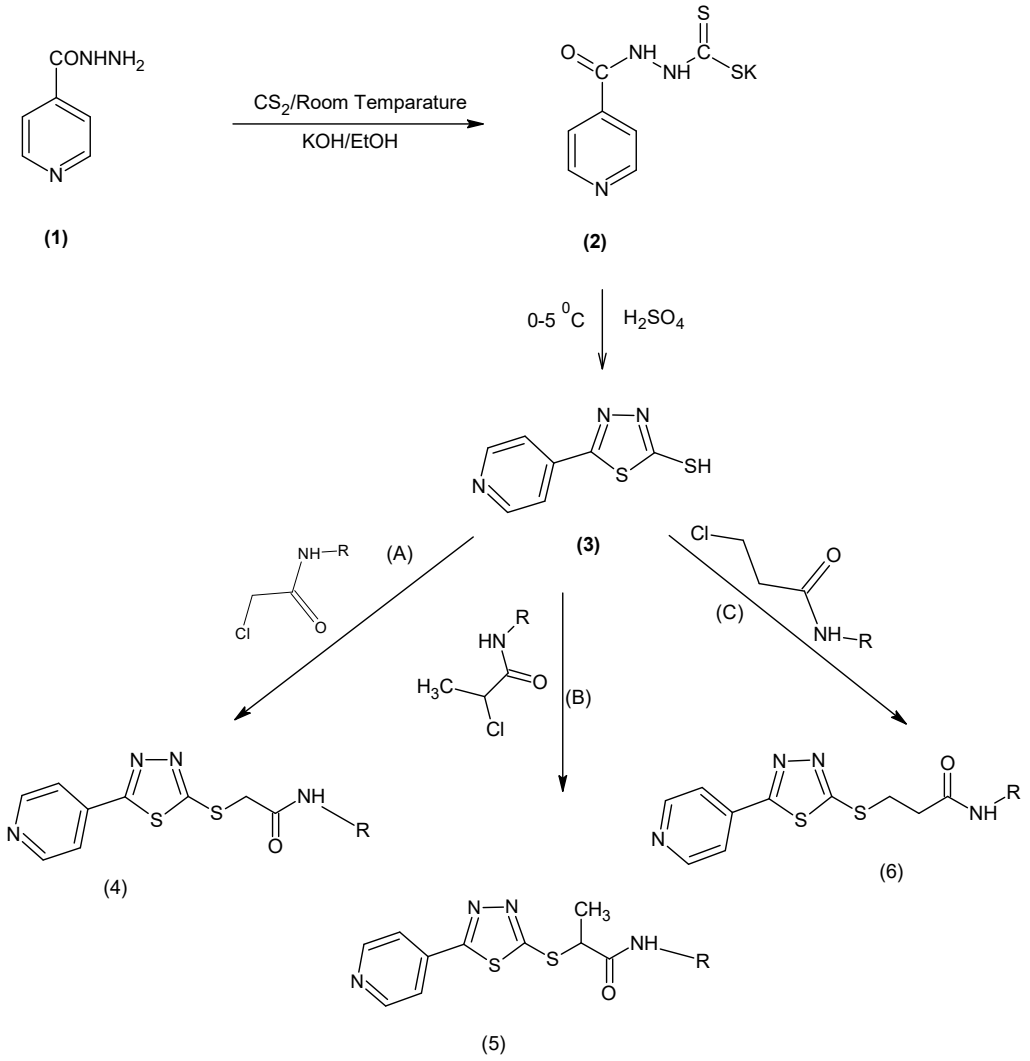
Step II: Procedure for synthesis of 5-(4-pyridyl)-2-mercapto-1, 3, 4-thiadiazole (3) [24, 25]

0.1 Mole of the potassium salt (**2**) was powdered and added in small portions to cold (0-2 ^{0}C) concentrated sulfuric acid (*d* 1.82) (5 ml, per g of salt) with vigorous stirring. The temperature was not allowed to exceed 5-6 ^{0}C. The solid dissolves quite rapidly. Stirring was continued for 5-8 min after the addition has been completed. The solution was poured on ice (50 g ice per 1 g of potassium salt). The yellowish solid so obtained was separated and collected over Whatman filter paper, washed with water, and pressed to get dry product. Subsequently product was subjected to drying in hot air oven at 40-50 ^{o}C. The dried product was added slowly in NaOH and filtered. To the filtrate equimolar quantity of concentrate HCl was added to get the precipitate. The addition was continued till the solution slightly acidic to litmus and filtered. The precipitate was washed with water, dried and recrystallized from absolute ethanol.

The yield was 60% and M. P. -278 -280 °C

TLC: R_f=0.87 (chloroform: methanol, 8:2).

IR : 3434.80 (N - H Stretching) 2251.05 (S - H stretching) 1659.93 (c = o , stretchching) , 1255.44-1290.54 (pyridine ring) 1052.08 (N – C – S)



Where R is

a = o - Cl - C_6H_4

b = o - CH_3 - C_6H_4

c = $C_{10}H_7$

Step III: General method for the synthesis of N-substituted chloroacetamides (A) / 2-chloropropionamides (B) / 3-chloropropionamides (C) [26]

Chloroacetylchloride/ α – chloropropionylchloride/ β-chloropropionylchloride, (0.01 mol) respectively and amine were dissolved in 25 ml of benzene separately. Chloroacetylchloride/ α –

chloropropionylchloride/ β-chloropropionylchloride solution was added drop wise with stirring and cooling to a solution of amine (0.02 mol) in 25 ml of benzene. After completion of reaction, the mixture was diluted with water and benzene was removed by distillation under reduced pressure. The water insoluble amide was recrystalized from benzene.

Step IV: General procedure for the synthesis of N-substituted 2-{[5-(pyridine-4-yl)-1,3,4-thiadiazol-2-yl]sulfanyl} acetamide/ N-substituted-2-{[5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl]sulfanyl}propanamide/ N-substituted-3-{[5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl]sulfanyl}propanamide [27]

To a cool solution of metallic sodium (0.025 mol) in an absolute ethanol, 5-[4-pyridyl)-2-mercapto-1, 3, 4-thiadiazole (0.025 mol) (3) was added with stirring, at about 15 ^{0}C. The solution was filtered. The solvent was removed by heating on water bath and cold water was added to get a clear solution. The solution was again filtered to remove suspended particles. Then N-substituted chloroacetamides (A) / 2-chloropropionamides (B) / 3-chloropropionamides (C) (0.025 mol) was added in small portion at room temperature with stirring and then stirring was continue between 60 to 65 ^{0}C for 8 hr., the solid get precipitated out in between the stirring. The mixture kept at room temperature for two to three hours. The resultant mixture is then filter and product collected on Whatman filter paper and dried it. Then the product is recrystallized from super dried ethanol.

4a) *N*-(2-chlorophenyl)-2-{[5-(pyridin-4-yl)-1, 3, 4-thiadiazol-2-yl] sulfanyl} acetamide (4a)

Molecular weight: 362.85; yield: 59.14%; melting point-284- 286**°C**; R_f-0.57.FTIR-(KBr) - 3434.80 (N-H Str amide), 1650 (C=O Str of amide), 1595(2^0N-H), 1440, 1310, (C... C, C...N ring str), 1080(N-C-S), 1395 (S-CH_2), 690(C-S), 754 (ArC-H bend). ^{1}H NMR (DMSO) δppm-9.79(s, 1H NH Secondary amide), 8.78-8.79 (dd, 4H-4-pyridine), 7.73-7.09 (m, 5H- benzene), 4.429 (s, 2H CH_2 methylene)

4b) *N*-(2-methylphenyl)-2-{[5-(pyridin-4-yl)-1, 3, 4-thiadiazol-2-yl] sulfanyl} acetamide (4b)

Molecular weight: 342.43; yield: 66.34%; melting point-278-280**°C**; R_f-0.52.FTIR-(KBr) -3295 (N-H Str amide),1660 (C=O Str of amide, (1600-1430), 1585 (2^0N-H), 1446,1312,1172 (C...C, C...N ring str), 680 (C-S), 1075 (C-N str), 1415 (S-CH_2)). ^{1}H NMR (DMSO) δppm-10.33 (s, 1H NH Secondary amide), 8.75-7.99 (dd, 4H-4-pyridine), 7.47-7.75 (m, 5H- benzene), 4.05 (s, 2H CH_2-methylene)

4c) *N*-(naphthalen-1-yl)-2-{[5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl]sulfanyl}acetamide

Molecular weight: 378.47; yield: 68.25%; melting point-150-152°C; R_f-0.62.FTIR-(KBr) -3310 (N-H Str amide), 3080 (C-H Str),1650 (C=O Str of amide),1580 (2^0N-H),1410,1310,1200 (C...C, C...N ring str), 1390 (S-CH_2), 1075 (N-C-S str), 660 (C-S). ^{1}H NMR (DMSO) δppm-8.77 (s, NH Secondary amide), 7.72-7.71 (dd, 4H-4-pyridine, 7.29-7.19 (m, 5H-benzene), 4.47 (s, 2H methylene), 4.06 (s, 2H, methylene)

5a) *N*-(2-chlorophenyl)-2-{[5-(pyridin-4-yl)-1, 3, 4-thiadiazol-2-yl] sulfanyl} propanamide (5a)

Molecular weight: 376.88; yield: 58.08%; melting point-268-270°C; R_f-0.49.FTIR-(KBr) -3295 (N-H Str amide), 3011 (C-H Str), 1640 (C=O Str of amide),1446,1309,(C...C, C...N ring str), 1415 (S-CH2), 1090 (N-C-S str), 690 (C-S). ^{1}H NMR (DMSO) δppm-10.01 (s, 1H NH Secondary amide), 8.76-8.82 (dd, 4H-4-pyridine), 7.77 (m, 5H-benzene), 3.29-3.71 (q, 1H-methine), 2.4-2.50 (d, 3H-methyl)

5b)*N*-(3-methylphenyl)-2-{[5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl]sulfanyl}acetamide (5b)

Molecular weight: 376.88; yield: 58.08%; melting point-268-270°C; R_f-0.49.FTIR-(KBr) -3310 (N-H Str amide), 2995 (C-H Str), 1670 (C=O Str of amide), 1501, 1295, 1210(C...C, C...N ring str), 1405 (S-CH_2), 1080 (N-C-S), 690 (C-S). ^{1}H NMR (DMSO) δppm-9.60 (s,1H, NH Secondary amide), 7.53-7.50 (dd, 4H,4-pyridine), 7.26-7.23 (m, 5H benzene),4.75 (q, 1H, methine), 1.78 (d, 3H methyl)

5c *N*-(naphthalen-1-yl)-2-{[5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl]sulfanyl}propanamide

Molecular weight: 394.51; yield: 62.44%; melting point-140-142°C; R_f-0.53.FTIR-(KBr) -3314 (N-H Str amide), 1637 (C=O Str of amide), 1533, 1312, 1207(C...C, C...N ring streching), 1066 (N-C-S str), 1404 (S-CH_2), 687 (C-S). ^{1}H NMR (DMSO) δppm-8.87 (s, 1H, NH Secondary amide), 8.75-7.99 (dd, 4H-4-pyridine), 7.33-7.23 (m, 5H benzene), 4.40 (s, 2H methylene), 3.65 (q, 1H, methine), 1.42 (d, 3H-methyl),

6a*N*-(2-chlorophenyl)-3-{[5-(pyridin-4-yl)-1, 3, 4-thiadiazol-2-yl] sulfanyl} propanamide (6a)

Molecular weight: 394.51; yield: 62.44%; melting point-140-142°C; R_f-0.53.FTIR-(KBr) -3290 (N-H Str amide), 1700(C=O Str of amide, 1600-1430(C...C, C...N ring str),995 (C-N stre), 1080(N-C-S), 1415 (S-CH_2), 690 (C-S bend) ^{1}H NMR (DMSO) δppm-10.09 (s, 1H, NH Secondary amide), 8.105-7.94 (dd, 4H-4-pyridine), 7.47-7.166(m, 5H benzene), 3.47 (t, 2H methylene), 2.51(t, 2H methylene)

6b*N*-(2-methylphenyl)-3-{[5-(pyridin-4-yl)-1, 3, 4-thiadiazol-2-yl] sulfanyl} propanamide (6b)

Molecular weight: 356.46; yield: 54.33%; melting point-276-278**°C**; R_f-0.52.FTIR-(KBr) –3285 (N-H Str amide), 3150 (C-H Str), 1660 (C=O Str of amide),1601(2^0N-H),1446,1312,1172 (C...C, C...N ring str), 1404 (S-CH_2), 1070 (N-C-S str), 690 (C-S). ^{1}H NMR (DMSO) δppm-8.77(s, 1H, NH Secondary amide), 8.75-7.99 (dd, 4H-4-pyridine), 7.99-7.47 (m, 5H benzene), 3.45 (t, 2H methylene), 2.63 (t, 2H methylene)

6c *N*-(naphthalen-1-yl)-3-{[5-(pyridin-4-yl)-1, 3, 4-thiadiazol-2-yl] sulfanyl} propanamide

Molecular weight: 392.49; yield: 52.83%; melting point-78-80**°C**; R_f-0.65.FTIR-(KBr) –3267 (N-H Str amide), 3087 (C-H Str), 1638 (C=O Str of amide), 1560 (2^0N-H), 1439,1361,1225(C...C, C...N ring streching), 1071 (N-C-S stre), C-N Str, 1415 (S-CH_2), 694 (C-S).). ^{1}H NMR (DMSO) δppm-8.73 (s, 1H NH Secondary amide), 8.77-7.33(4H, CH_2 4-pyridine), 7.32-7.6.02 (CH benzene), 4.48 (s, 2H methylene), 3.71 (t, 2H methylene), 2.90 (t, 2Hmethylene)

Evaluation of Anti-inflammatory Activity: [28]

All the compounds were subjected for preliminary toxicity studies, according to organization for economic and co-operation and development (OECD) guidelines in mice28. Compounds were found safe up to 2000 mg/kg body weight. Therefore 1/10^{th} of the maximum tolerated dose i.e. 200 mg/kg was used as therapeutic dose.

Female albino rats with a body weight between 150 and 180 g were used. The animals were starved overnight and were divided into ten groups of 6 each. One group was control in which only the vehicle given, the second group was given the standard drug and remaining group was given synthesized compound. The compounds were given as an oral suspension in a suitable vehicle (water for injection). After thirty minutes 0.1 ml of carrageenan (1%) in a normal saline was injected into the sub plantar region of left hind paw. The paw edema volume was measured with the help of digital plethysmometer. The same procedure was repeated after 180 min. the difference between zero min. and 180 min. readings was taken as actual paw edema volume. The percentage inhibition of edema in the various treated groups were calculated by following formula,

% Inhibition = $(1 – V_t / V_c) \times 100$,

Where, V_t is edema volume in the drug treated group.

V_c is edema volume in the control treated group.

The same procedure was repeated on rats of 8 groups of 6 each at the dose of 50 mg/kg of test sample. Percentage inhibition shown by the tested compounds is recorded in **Table 1**.

Table 1: Anti-inflammatory activity data

Compound	Anti-inflammatory % Reduction after 3 hr	Anti-inflammatory % after 4 hr
4a	**36.10**	**47.15**
4b	**33.06**	**47.20**
4c	**46.95**	**59.66**
5a	**26.97**	**43.12**
5b	**37.62**	**58.63**
5c	**31.03**	**44.57**
6a	**44.11**	**49.74**
6b	**34.07**	**42.29**
6c	**39.55**	**55.53**
Standard-Diclofenac	**58.92**	**63.70**

RESULTS AND DISCUSSION:

The N-substituted chloroacetamides (**A**), 2-chloropropionamides (**B**) and 3-chloropropionamides (**C**) were synthesized by acetylating respective amine using chloroacetylchloride, 2-chloropropanoyl chloride and 3-chloropropanoyl chloride respectively. These compounds were characterized by TLC, melting point and IR spectra that showed characteristic absorption bands at 3230-3340 and 1610-1665 cm^{-1} of N-H and C=O respectively.

The N –substituted 2-{ [5 - (pyridine-4-yl) - 1, 3, 4 – thiadiazol – 2 -yl]sulfanyl } acetamide (**4a-c**), N-substituted-2-{[5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl]sulfanyl} propanamide (**5a-c**) and N-substituted-3-{[5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl]sulfanyl} propanamide (**6a-c**) derivatives were prepared by condensing sodium salt of 5-(4-pyridyl)-2-mercapto-1,3,4-thiadiazole (**3**) and N-substituted chloroacetamides (**A**) , N-substituted α-chloropropionamides (**B**) and N-substituted β-chloropropionamides (**C**) respectively.

Spectral analyses were in accord with the suggested structure. The IR spectra of 5-(4-pyridyl)-2-mercapto-1,3,4-thiadiazole (**3**) showed characteristic absorption band at 2251.o5 cm^{-1} was attributed to SH, which was disappeared by the formation (**4**, **5** & **6**). The disappearance of SH proton signal confirmed that the thiadiazoles were converted to **4**, **5** & **6**. 1H NMR spectra of compounds **4a-c** displayed the singlet at 4.05-4.42 ppm for ($S-CH_2$). In the series **5a-c** all the compounds displayed the quartet at 4.42 & doublet at 2.40-2.50 for (-CH_-) and ($C-CH_3$) respectively. The NMR spectra of **6a-c** displayed doublet at 3.45-3.71 and 2.51-2.90 for S-methylene and C=O-methylene proton. All the compounds

displayed NMR singlet for N-H of amide bond at 8.73-10.33 ppm. The NMR spectra of all the compounds displayed appropriate multiplates in the aromatic region indicating the presence of pyridine and aromatic rings and the type of its substitution. The IR spectra of compounds are also in agreement with the structures. All the synthesized compounds showed characteristic absorption IR band at 3267-3434 (N-H), 1637-1700 (C=O) and at 1066-1090 (C-N).

The tested compounds showed anti-inflammatory activity ranging from 26.97% to 59.99%, whereas standard drug Diclofenac sodium showed 63.70% inhibition after 4 hr **Table 1**. It was observed that the thiadiazole derivative (**4**) condensed with naphthalene substituted acetamide possess highest activity (46.95%), whereas when naphthalene was replaced with chlorine or methyl substituted phenyl moiety activity decreases sharply. Interestingly in the series **5a-c**, compound prepared by condensation of thiadiazole and toulyl substituted 2-propanamide exhibited excellent activity (58.63%).

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