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SYNTHESIS AND CHARACTERIZATION OF SOME NOVEL NAPHTHALENE-PYRIMIDINE DERIVATIVES AS ANTI-INFLAMMATORY AGENTS

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Abstract

Some new 2-amino-4-[1-Napthlene amino]-5-phenyl Pyrimidine derivatives have been synthesized from N-(napthlene-1-yl)-3-aryl acryl amide derivatives and guanidine nitrate by introducing different heterocyclic nuclei. Compounds 2a-j has been screened for anti-inflammatory activity by HRBC Membrane Stabilization Method. The structures of these compounds have been elucidated by IR, H NMR and Mass spectroscopy.

Key words: *HRBC membrane, anti-inflammatory, Pyrimidine, quinoline.*

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INTRODUCTION

The discovery, development and identification of biologically active compounds has gain lot of importance in the recent years, even though there is considerable number of adverse effects, the medicinal chemists have always tried to design drug substance possessing maximum therapeutic application and minimum toxicity [1-3].

In the present study synthetic derivatives, simultaneously containing naphthalene and azetidine-2-one have been prepared and it is speculated to get a combined effect of both the moieties [4-6].

CHEMISTRY

Naphthalene containing drugs are available, such as Nafacillin, Naftifine, Tolnaftate and Terbinafine etc. which play vital role in the control of microbial infection. Naphthalene and its derivative have shown a large spectrum of antimicrobial activity. Several research has been done and has proved β-naphthol as an excellent lead moiety for designing a synthetic derivative, which would posses good biologically activity [7].

A large number of napthalen-2-amine fused ring system having substitution at position 1 and 4 posses' powerful antimicrobial and anti-tubercular activity.

Pyrimidines represent an important class of heterocycles and their structural framework is not only a key constituent of nucleic bases, alkaloids, and numerous pharmacophores with variety of potent biological activities. Pyrimidines occupy a distinct and unique place in medicine, large array of Pyrimidine non-nucleoside derivatives possess a variety of pharmacological properties. These properties include anticancer, antiviral, antibacterial, anti-inflammatory and central nervous activities.

EXPERIMENTAL

All the reagents and solvents used were of laboratory grade. All melting points were determined in open capillary tube and were uncorrected. IR spectra were recorded in potassium bromide pellets on FTIR8300 (Shimadzu) spectrometer; H-NMR spectra were recorded on AVANCE 300 MHz TMS as internal standard. Mass spectra were recorded on SHIMADZUQP2010 PLUS at IIT-Chennai. All the reactions were monitored by thin layer chromatography carried out on 0.25 mm thick silica gel-G plate using iodine vapour for detection (solvent system- Ethanol, Dichloromethane (1:2))

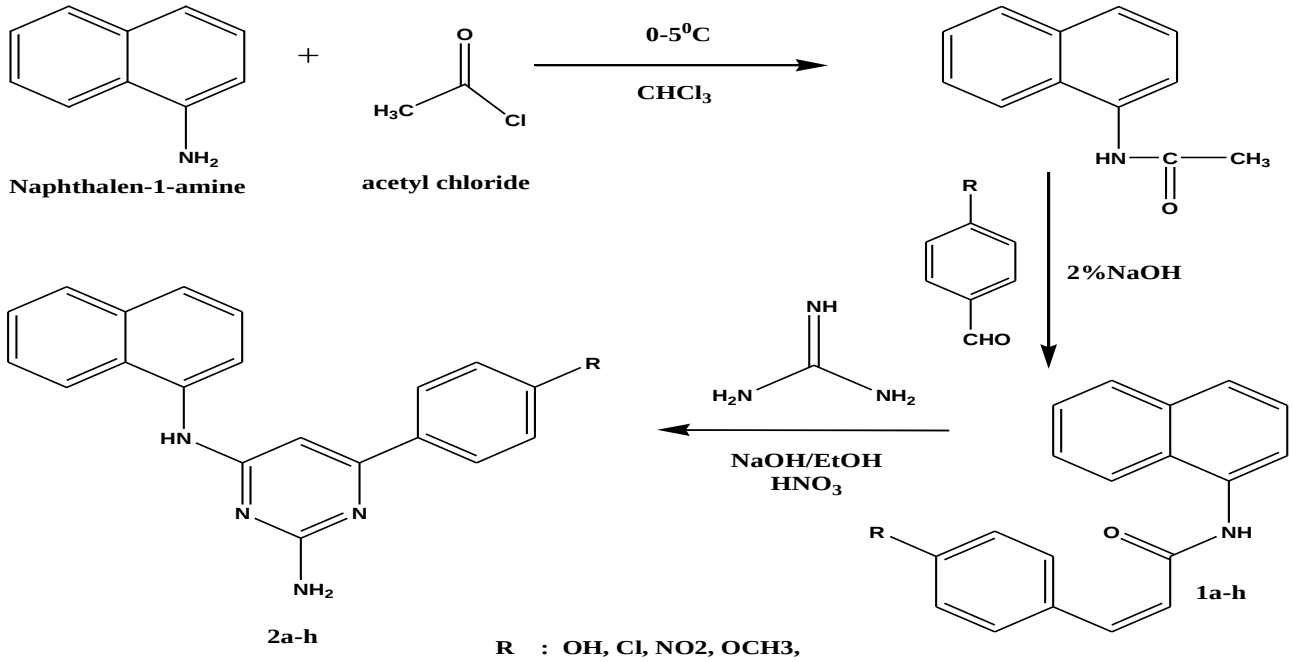

Fig: 1 Scheme of Synthesized Title Compounds

Synthesis of N-(napthelne-1-yl) acetamide

To a solution of napthelene-1-amine (0.01mole) in chloroform (dry, 100ml), acetyl chloride (0.02 mole) is added drop wise at 0-5^{0}C with constant stirring. The reaction mixture was stirred for 2 hrs by magnetic stirrer. The excess solvent was distilled of and the separated mass was poured into ice water and recrystallised from methanol. The recrystallised product purity was checked by TLC by using solvent system Ethanol, Dichloromethane (1:2) ratio. The synthesized compound functional group was confirmed by IR spectral analysis.

Synthesis of N-(napthelne-1-yl)-3-aryl acryl amide derivatives

To a mixture of N-(napthlene-1-yl)acetamide (0.01 mole) in methanol (50ml) appropriate aromatic aldehydes (0.01mole) are added in the presence of 2% NaOH solution (5ml). The reaction mixture is stirred for 10 hrs at room temperature and then refluxed for 6 hrs. The excess solvent was distilled off and poured into ice water. The resulting solid thus separated, is filtered, washed with water and recrystallised from ethanol. The recrystallised product purity was checked by TLC by using solvent system Ethanol, Dichloromethane (1:2) ratio. The synthesized compound functional group was confirmed by IR spectral analysis.

Synthesis of 2-amino-4-[1-Napthlene amino]-5-phenyl pyrimidine derivatives

To a mixture of N-(napthlene-1-yl)-3-aryl acryl amide derivatives (0.01 mole) in absolute ethanol (50ml, dry), guanidine nitrate (0.01 mole) and solid NaOH (0.4 g) are added. The reaction mixture was refluxed for 5 hrs and poured into ice water. The solid thus separated was filtered, washed with water and re-crystallized from acetone. The recrystallised product purity was checked by TLC by using solvent system Ethanol, Dichloromethane (1:2) ratio. The synthesized compound functional group was confirmed by IR spectral analysis.

Table 1: Physio-Chemical Properties of Synthesized Compounds

Compound	Appearance	Melting point (^{o}C)	Molecular weight	Molecular formula	R_f value
2a	Brick red	135	328.41	$C_{20}H_{16}N_4O$	0.56
2b	Pale brick red	129	346.83	$C_{20}H_{15}N_4Cl$	0.71
2c	White	130	312.39	$C_{20}H_{15}N_4$	0.82
2d	Light brown	125	372.42	$C_{22}H_{20}N_4O_2$	0.65
2e	Cream	137	328.41	$C_{20}H_{16}N_4O$	0.74
2f	Brick red	120	357.76	$C_{20}H_{15}N_5O_2$	0.65
2g	White	110	358.79	$C_{21}H_{28}N_4O_2$	0.77
2h	White	115	346.83	$C_{20}H_{15}N_4Cl$	0.79
2i	Pale brick red	129	386.31	$C_{20}H_{15}N_5O_2$	0.64
2j	White	133	372.42	$C_{22}H_{20}N_4O_2$	0.59

4-(2-Amino-6-(naphthalen-1-yl-amino) pyrimidin-4-yl) phenol (2a):
Yield: 74%, m.p.133ºC, IR (KBr): 3420 (N-H str), 3084(Ar-CH str), 1209(C-N str), 2865 (C-H str), 3368 (O-H phenol str).^{1}H-NMR (DMSO)(δppm): 6.2-7.66 (m, 11H, Ar-CH), 4.5 (d, 1H,CH), 1.6-1.9(2H, Methylene). EI-MS m/z: 333.

6-(4-Chlorophenyl)-N-4-(naphthalene-1-yl) pyrimidine-2,4-diamine (2b):
Yield: 70%, m.p.129ºC, IR (KBr): 605 (C-Cl str), 3360 (N-H str), 2916(Ar-CH str), 1087(C-N str), 2859 (C-H str), 1654 (C=N str).^{1}H-NMR (DMSO)(δppm): 6.5-7.7 (m, 10H, Ar-CH), 4.6 (d, 1H,CH), 1.5-1.9(2H, Methylene). EI-MS m/z: 347.

N-4-(Naphthalen-1-yl)-6-phemylpyrimidine-2,4-diamine(2c):
Yield: 65%, m.p.130 ºC, IR (KBr): 3368 (N-H str), 3064(Ar-CH str), 1087(C-N str), 2965 (C-H str), 1654 (C=N str).^{1}H-NMR (DMSO)(δppm): 6.6-7.6 (m, 10H, Ar-CH), 4.5 (d, 1H,CH), 1.5-1.9(2H, Methylene). EI-MS m/z: 327.

6-(2,5-Dimethoxyphenyl)-N-4-(naphthalene-1-yl)pyrimidine-2,4- diamine (2d):
Yield: 70%, m.p.125 ºC, IR (KBr): 1255 (C-O-C str), 3270 (N-H str), 2931(Ar-CH str), 1087(C-N str), 2965 (C-H str), 1653 (C=N str).^{1}H-NMR (DMSO)(δppm): 6.5-7.6 (m, 10H, Ar-CH), 4.5 (d, 1H,CH), 1.6-1.9(2H, Methylene). EI-MS m/z: 337.

4-(2-Amino-6-(naphthalen-1-yl-amino) pyrimidin-4-yl) phenol (2e):
Yield: 61%, m.p.137 ºC, IR (KBr): 3420 (N-H str), 3084(Ar-CH str), 1209(C-N str), 2865 (C-H str), 3368 (O-H phenol str).^{1}H-NMR (DMSO)(δppm): 6.2-7.66 (m, 11H, Ar-CH), 4.5 (d, 1H,CH), 1.6-1.9(2H, Methylene). EI-MS m/z: 333.

N-4-(Naphthalen-1-yl)-6-(2-nitrophenyl) pyrimidine-2,4-diamine (2f):
Yield: 53%, m.p.120 ºC, IR (KBr):1418 (C-NO_2str), 3049(Ar-CH str), 1210 (C-N str), 1654 (C=N str).^{1}H-NMR (DMSO)(δppm):7.1-8.5 (m, 10H, Ar-CH), 3.5-3.8 (s, 1H,CH), 1.5-1.9 (s, 2H,methylene). EI-MS m/z: 333.

4-(2-Amino-6-(naphthalen-1-yl-amino) pyrimidin-4-yl)-2- methoxyphenol (2g):
Yield: 70%, m.p.110 ºC, IR (KBr): 1122 (C-O-C str), 3269 (O-H str), 3270 (N-H str), 2931(Ar-CH str), 1219(C-N str), 2925 (C-H str), 1653 (C=N str).^{1}H-NMR (DMSO)(δppm): 6.5-7.6 (m, 10H, Ar-CH), 4.5 (d, 1H,CH), 1.6-1.9(2H, Methylene). EI-MS m/z: 327.

6-(2-Chlorophenyl)-N-4-(naphthalen-1-yl) pyrimidine-2,4-diamine (2h):
Yield: 70%, m.p.115 ºC, IR (KBr): 628 (C-Cl str), 326960 (N-H str), 2916(Ar-CH str), 1080(C-N str), 2859 (C-H str), 1654 (C=N str).^{1}H-NMR (DMSO)(δppm): 6.5-7.7 (m, 10H, Ar-CH), 4.6 (d, 1H,CH), 1.5-1.9(2H, Methylene). EI-MS m/z: 327.

N-4-(Naphthalene-1-yl)-6-(4-nitrophenyl) pyrimidine-2,4-diamine (2i):
Yield: 53%, m.p.129 ºC, IR (KBr):1449 (C-NO_2str), 3049(Ar-CH str), 1210 (C-N str), 1654 (C=N str).^{1}H-NMR (DMSO)(δppm):7.1-8.5 (m, 10H, Ar-CH), 3.5-3.8 (s, 1H,CH), 1.5-1.9 (s, 2H,methylene). EI-MS m/z: 333.

6-(3,4-Dimethoxyphenyl)-N-4-(naphthalene-1-yl) pyrimidine-2,4-diamine (2j):
Yield: 70%, m.p.133 ºC, IR (KBr): 1255 (C-O-C str), 3270 (N-H str), 2931(Ar-CH str), 1087(C-N str), 2965 (C-H str), 1653 (C=N str).^{1}H-NMR (DMSO)(δppm): 6.5-7.6 (m, 10H, Ar-CH), 4.5 (d, 1H,CH), 1.6-1.9(2H, Methylene). EI-MS m/z: 327.

Biological Screening
Inflammation is normal protective response to tissue injury caused by physical trauma, noxious chemicals or microbiological agents and local response of living mammalian tissue to injurious agents.
In the present study *in-vitro* anti-inflammatory activity is checked for the synthesized compounds.

Evaluation of Anti-Inflammatory Activity:
The anti-inflammatory activity can be carried out by following method:-
***In-vitro* anti-inflammatory activity**

HRBC Membrane Stabilization Method:
The method involves the stabilization of human red blood cell membrane by hypotonicity induced membrane lysis.
The lysosomal enzymes released during inflammatory condition produce a variety of disorders. The extra cellular activity of these enzymes is said to be related to acute or chronic inflammation. The anti-inflammatory agents act by either inhibiting the lysosomal enzymes or by stabilizing the lysosomal membrane since the human red blood cell membrane are similar to lysosomal membrane components. The prevention of hypotonicity induced HRBC membrane lysis is taken as a measure of anti-inflammatory activity of the drug.

RESULTS AND DISCUSSION
All the compounds were subjected to *in-vitro* anti-inflammatory activity using diclofenac sodium as a standard. Activity revealed that all the synthesized

compounds shown significant anti-inflammatory activity when compared to that of standard drug. The compounds **2a, 2c, 2d** and **2f** showed more activity as compared to that of other derivatives. **2e, 2i** were showed less activity as compared to the other derivatives**. 2a, 2d, 2h** showed maximum activity at 50% concentration**. 2f** showed very less activity when compared to diclofenac sodium drug.

Table 2: *In-vitro* Anti-Inflammatory Activity of Synthesized Compound

Compound code	Absorbance	% stabilization
Control	1.9813	-
2a	0.8612	56.76
2b	0.8928	48.41
2c	0.7948	54.07
2d	0.9463	55.32
2e	0.8741	33.49
2f	0.8248	52.31
2g	1.2121	29.96
2h	1.0938	54.85
2i	1.4238	37.73
2j	0.9110	38.56
Standard	0.7028	78.75

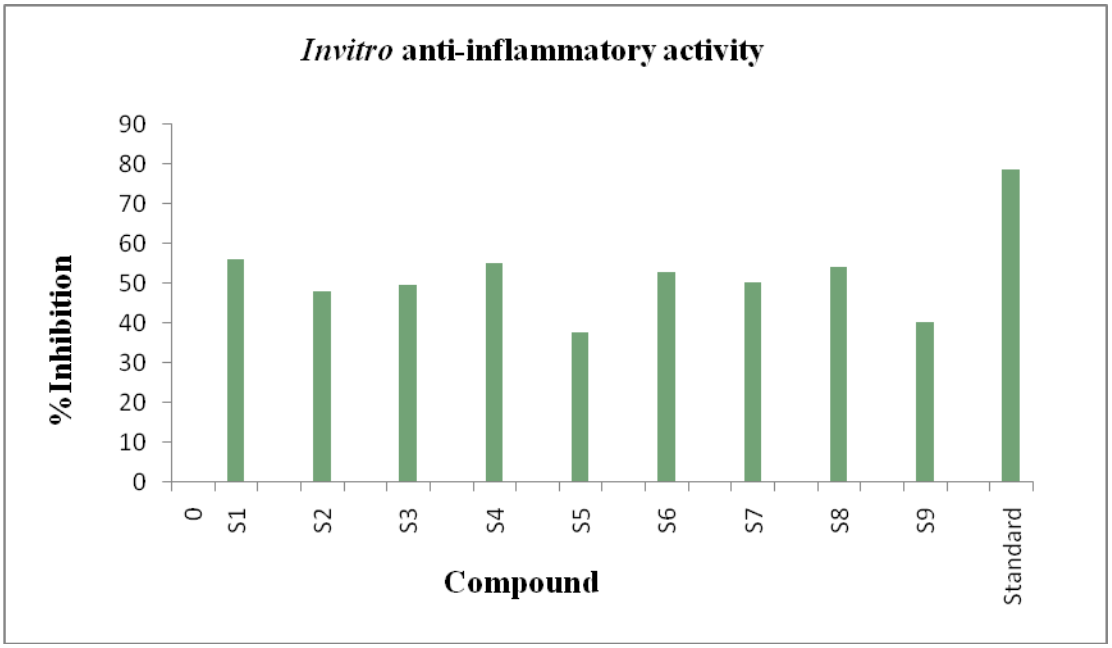

Fig 2: In-vitro anti-inflammatory activity

CONCLUSION

In the present study, some novel 4, 5-disubstitued 1, 3-pyrimidinyl derivative of naphthalene-1-amine were synthesized and screened for their biological activities. The synthesized compounds were characterized by IR, ^{1}HNMR, Mass spectroscopy.

In-vitro Anti-inflammatory activity suggests that all the synthesized compounds have shown significant anti-inflammatory activity when compared with that of the standard by HRBC Membrane stabilization method.

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