SYNTHESIS AND BIOLOGICAL EVALUATION OF AMINOTHIAZOLES, THIAZOLYLACETONITRILE, IMIDAZO[1,2-A]PYRIDINE, IMIDAZO[2,1-B]THIAZOLE, CHROMENE AND BENZO[F]CHROMENE DERIVATIVES CONTAINING NAPROXENOYL MOIETY AS POTENTIAL ANTI-INFLAMMATORY AGENTS

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Abstract

In the present investigation, a series of newly synthesized N-(4-(2-aminothiazol-2-yl) **(4a,b)**, (2-hydrazinylthiazol-4-yl) **(6)** and (2-(cyanomethyl)thiazol-4-yl)phenyl-2-(6-methoxy-naphthalene-2-yl)propanamide **(8)** were synthesized from the cyclocondensation of 2-bromo-acetyl derivative **(2)** with reagents containing thioamide function. A one-pot synthesis of thiophene derivatives **(10**&**11)** was achieved from three-component reaction of **2** with malononitrile and/or ethyl acetoacetate and phenyl isothiocyanate catalyzed by DMF/KOH. Cyclocondensation of **2** with 2-aminopyridine and 2-aminothiazole gave imidazo[1,2-a]-pyridine and imidazo[2,1-b]thiazole derivatives **(12**&**13)**, respectively. The reactivity of **8** toward some electrophilic reagents was investigated, where 2-iminochromenes **(14, 15)** were obtained, respectively. The structures of the newly compounds were confirmed on the basis of IR, ^{1}HNMR, and mass spectral data. The synthesized compounds were screened for animal toxicity, analgesic, and anti-inflammatory studies.

Keywords: Aminothiazoles, thiazolylacetonitrile, chromene, benzochromene derivatives, analgesic and anti-inflammatory activities.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most useful clinical therapies for the treatment of pain, fever, and inflammation[1-3]. Also, many thiazoles[4-9], chromenes[10-12] and benzochromene[13,14] are known for their biological activities. In continuation of our research program directed for the development of a new, simple and efficient procedure for the synthesis of biologically active heterocyclic compounds[15-18], we herein report the synthesis of aminothiazoles, thiazolylacetonitrile, thiophene, chromene, benzochromene, imidazo[1,2-a]-pyridine, and imidazo[2,1-b]thiazole derivatives containing naproxenoyl moiety.

Results and discussion

Chemistry

The starting compound *N*-(4-(2-bromoacetyl) phenyl)-2-(6-methoxynaphthalen-2-yl)propanamide **(2)** was obtained via the reaction of acetyl derivative[19] **1** with bromine in acetic acid (Scheme 1). The molecular structure of **2** was established based on analytical and spectral data. IR spectrum of **2** revealed bands at 3312 (NH), 2930 (aliphatic CH) and 1672 cm^{-1} (C=O). ^{1}HNMR spectrum of **2** revealed a doublet and quartet at δ 1.51, 4.06 ppm for CH_3 & CH of asymmetric carbon atom, and three singlet signals at δ 3.85, 3.97 and 10.44 ppm for methylene, methoxy and imino groups, respectively in addition to aromatic protons. Also, mass spectrum of compound **2** showed a molecular ion peak at m/z 425 (20%) and the base peak was found in the spectrum at m/z 185 corresponding to 2-ethyl-6-methoxy-naphthalene cation (Scheme 1).

(Scheme 1)

The behavior of ω-bromoacetyl derivative **2** towards some nucleophilic reagents was investigated. Thus, compound **2** was reacted with p-toluidine in ethanol under reflux temperature and gave the secondary amine derivative **3**. The mass spectrum of compound **3** showed a molecular ion peak at m/z 452 (15%). Cyclocondensation of compound **2** with thiocarbamide derivatives namely (thiourea, phenylthiourea) in boiling ethanol containing a catalytic amount of fused sodium acetate afforded thiazole derivatives **4a,b** according to the spectral data of the isolated products (Scheme 2). The infrared spectrum of the isolated product **4a** revealed bands at 3389, 3310, 3268 and 1660 cm^{-1} corresponding to amino and carbonyl groups, respectively. ^{1}HNMR spectrum of **4a** revealed a singlet at δ = 6.85 for thiazole-H_5 and two singlet signals at δ 6.92, 10.16 ppm for NH_2 and NH exchangeable with a D_2O. Moreover, when 2-bromoacetyl derivative **2** was subjected to react with thiosemicarbazide afforded 2-hydrazinylthiazole derivative **5**. ^{1}HNMR spectrum of **5** revealed singlet signal at 7.16 for thiazole-H_5 with three singlet signals at 8.60, 10.25 and 10.29 ppm for NH_2 and 2NH. Condensation of **5** with 4-methoxy-benzaldehyde gave the corresponding hydrazone derivative **7**. Structure of **7** was firmly established by the reaction of 2-bromoacetyl derivative **2** with 4-methoxy-benzylidenethiosemicarbazone **(6)** which gave thiazolidine derivative identical in all respects (m.p., mixed m.p. and spectral data) with the hydrazone derivative **7**. IR spectrum of **7** showed absorption bands at 3276 and 1658 cm^{-1} for NH and C=O groups. ^{1}HNMR spectrum of **7** revealed two singlet at 3.79, 3.98 for two methoxy groups, singlet at 7.15 for thiazole-H_5, multiplet aromatic protons with benzylidene-H at δ 6.98 – 8.06 ppm, two singlet signals at 10.18 and 11.90 for two imino groups. Furthermore, 2-(thiazol-2-yl)acetonitrile derivative **8** was obtained via the reaction of 2-bromoacetyl derivative **2** with cyanothioacetamide in refluxing dioxane (Scheme 2). Compound **8** was characterized by its elemental analysis and spectral data. IR spectrum showed three characteristic absorption bands at 3290, 2250 and 1662 cm^{-1} assignable to imino, nitrile and carbonyl groups. Mass spectrum of compound **8** showed a molecular ion peak at m/z 427 (24%) together with a base peak at m/z 141.

(Scheme 2)

In the present contribution, we investigated also the reaction of 2-bromoacetyl derivative **2** with a mixture of active methylene compound and isothiocyanate. Thus, the reaction of 2-bromoacetyl derivative **2** with a mixture of malononitrile and phenyl isothiocyanate in dry dimethylformamide at room temperature in the presence of potassium hydroxide afforded the corresponding thiophene derivative **10**

in high yield (85%). Similarly, reaction of **2** with a mixture of ethyl acetoacetate and phenyl isothiocyanate in DMF-KOH afforded thiophene derivative **11**. Infrared spectrum of **10** showed the characteristic absorption bands at 3260, 3200, 3178, 2204 and 1650 cm^{-1} for NH_2, NH, C≡N and C=O functional groups. ^{1}HNMR spectrum of **10** revealed signals at δ 2.99 (s, 2H, NH_2; cancelled with D_2O). ^{1}HNMR spectrum of compound **11** revealed signals at δ = 1.31 (t, 3H, CH_3-ester), 2.36 (s, 3H, 4-CH_3-thiophene), 4.32 (q, 2H, CH_2-ester). The formation of **10** and **11** was assumed to proceed via initial alkylation to afford the non-isolated intermediate **9** followed by intramolecular cyclization through Thorpe-Ziegler reaction[20] (Scheme 3). Treatment of compound **2** with heterocyclic amines namely (2-aminopyridine, 2-aminothiazole) in acetic acid under reflux yielded a single product in each case. On the basis of elemental analysis and spectral data, the products were assigned the structures: imidazo[1,2-a]pyridine **12** and imidazo[2,1-b]thiazole **13** respectively. The structures of **12** and **13** were confirmed by their elemental analyses and spectral data. Thus, mass spectrum of compound **12** gave a molecular ion peak at m/z 421 (24%) and the base peak at m/z 263 (M - 2-methoxynaphthalene). Also, ^{1}HNMR spectrum of **13** revealed signals at δ 7.22, 7.48 (2d, 2H, thiazole-H_4, H_5), 8.29 (s, 1H, imidazole-H) and singlet at δ = 10.27 ppm for NH group, (Scheme 3).

(Scheme 3)

The reactivity of 2-(thiazol-2-yl)acetonitrile derivative **8** toward some electrophilic reagents was investigated. Thus, cyclocondensation of compound **8** with salicylaldehyde and 2-hydroxy-naphthaldehyde in refluxing ethanol in the presence of a catalytic amount of ammonium acetate resulted in the formation of 2-iminochromene and 2-iminobenzo[f]chromene derivatives **14** and **15** (Scheme 4). The structure of isolated compounds **14** and **15** were confirmed on the basis of analytical and spectral data. Infrared spectra of the isolated products revealed in each case, the absence of C≡N characteristic absorption band and the presence of bands due to NH group. ^{1}HNMR of compound **14** showed three singlet signals at δ 8.64, 8.98, 10.25 ppm corresponding to chromene-H_4, and two imino groups, respectively. Michael addition of acetonitrile derivative **8** on the activated double bond of cinnamonitrile derivatives **16a,b** resulted in the formation of arylidene derivatives **18a,b.** The formation of compound **18** is believed to proceed via initial Michael addition of the methine carbanion formed from **8** to the activated double bond of arylidene derivative **16** to form acyclic Michael adduct **17** followed by elimination of malononitrile molecule. Further confirmation of **18** was achieved by reaction of acetonitrile derivative **8** with the corresponding aromatic aldehydes (Scheme 4).

(Scheme 4)

Biological activity

Animal toxicity studies

The acute toxicity is usually measured by LD_{50} (the median lethal dose) which is the dose that kills 50% of the experimental animals underspecified conditions. The LD_{50} will vary according to many factors, e.g. animal strain, room temperature, route of administration, season of the year, etc. all of which have to be taken into consideration. Acute toxicity studies have to be carried out on several animal species generally on mice and rats. The basic principle of the determination of the LD_{50} depends on the determination of the highest dose that fails to kill any animal and this refers as the threshold dose or the maximal tolerated dose and determination of the minimal dose that kills all the animals, the former dose is referred to as LD_0; while the latter dose is referred to as LD_{100}. In between these two doses, several doses are

chosen which produce different percentage of mortality. The methods of determination of the LD_{50} differ in the design of the experiment and the method of calculation of LD_{50}. The acute LD_{50} of the screened compounds were determined by Spearmane-Karber method[21]. The compounds **2, 4a, 4b, 5, 7, 8, 10, 14, 15** and **18a,b** were well tolerated up to the doses of 1200mg/kg without any toxic manifestations. The fact that compounds showed no toxic effects in doses up to1200mg/kg in mice (equivalent to oral LD_{50} of diclofenac sodium in mice) suggest a very low toxicity of compounds.

Analgesic screening

Experimental model used in this study were selected to investigate narcotic analgesic activity of some tested compounds. For this purpose, the hot-plate test[22] was utilized to reveal narcotic analgesic activity. In this method, female albino mice (Swiss strain) were put on a hot plate with constant temperature 55ºC, the time taken by the mice to lick its feet or to jump within a cylinder placed on a hot plate surface was determined. Five test compounds were injected i. p. at a dose level of 50mg/kg into mice. Control group of animals was similarly treated with1% CMC (carboxymethylcellulose). The reaction time was evaluated directly after 0.5 and 1h of injection. Comparison between the narcotic analgesic activity of the tested compounds and the standard diclofenac sodium (2mg/kg) from weak, moderate and potent analgesic activity was carried out (Table 1). From the tabulated data the following points could be picked out: Moderate to weak analgesic activity was shown for all tested compounds.

Table 1: Narcotic analgesic activity at the tested compounds

Compound No.	Analgesic activity in seconds (Mean)	
	0.5 h	1.0 h
Control	5.5	5.5 ± 0.3
2	13 ± 0.3	30 ± 0.3
4a	13 ± 0.3	30 ± 0.3
4b	13 ± 0.3	30 ± 0.3
5	11 ± 0.3	26 ± 0.3
7	11 ± 0.3	30 ± 0.3
8	11 ± 0.3	30 ± 0.3
10	11 ± 0.3	26 ± 0.3
11	11 ± 0.3	26 ± 0.3
Diclofenac sodium	13.20 ± 0.3	8.5 ± 0.39

In vivo anti-inflammatory studies;

All the newly synthesized compounds and diclofenac sodium, as a reference drug, were subjected to in vivo anti-inflammatory studies using carrageenin-induced rat paw oedema model[23]. From the tabulated value (Table 2) compound **(12)** possess the most potent anti-inflammatory activity (58.05%) comparable to the reference drug diclofenac sodium (72.13%). A mild to weak effect were exerted by the other compounds.

Table 2. Result of anti-inflammatory activity of the tested compounds against carrageenin-induced rat paw oedema in rats.

Compounds	Mean % increase in paw weight ± SE	Inhibition of paw % oedema from control group
Control	1.03 ± 29.13	-
Diclofenac	$^{\delta}$0.49 ± 8.12	72.13
2	$^{\delta}$0.46 ± 14.93	48.74
5	18.54 ± 0.45 $^{\delta}$	36.35
7	25.73 ± 0.42 $^{\delta}$	14.17
8	19.93 ± 0.44 $^{\delta}$	31.88
10	23.50 ± 0.33 $^{\delta}$	19.32
11	20.10 ± 0.25 $^{\delta}$	31.68
12	12.22 ± 0.36$^{\delta}$	58.05

$^{\delta}$ Significant difference from diclofenac-treated group using unpaired student's «*t*» test $p < 0.05$.

Experimental

All melting points are uncorrected. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer (v, cm-^{1}). The ^{1}HNMR spectra were recorded in DMSO-d_6 at 300 MHz on a Varian Gemini NMR spectrometer (δ, ppm) using TMS as an internal standard. Mass spectra were obtained on GC Ms-QP 1000 EX mass spectrometer at 70 ev. Elemental analyses were carried out by the Microanalytical Research Centre, Faculty of Science, Cairo University.

N-(4-(2-Bromoacetyl)phenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (2):

A solution of acetyl derivative **1** (0.01 mole) and bromine (0.01 mole) in acetic acid (30 ml) was stirred at room temperature for 3h, then it was poured into

ice/water. The resulting precipitate was filtered off, dried and recrystallized to give **2** as yellow crystals.

Yield: 70%, yellow crystals (methanol), m.p.: 185-187ºC. IR spectrum ν_{max}/cm^{-1}; 3312 (NH), 2930 (CH-aliph.) and 1672 (C=O). ^{1}HNMR (DMSO-d_6): δ = 1.51 (d, 3H, CH_3), 3.85 (s, 2H, CH_2), 3.97 (s, 3H, OCH_3), 4.06 (q, 1H, CH), 7.49-8.06 (m, 10H, Ar-H), 10.44ppm (s, 1H, NH); MS: m/z (%) 425 (M^+, 20), 374 (25), 185 (100), 126 (43) and 51 (35). Anal. Calc. for $C_{22}H_{20}NO_3Br$ (426.30): C, 61.98; H, 4.73; N, 3.29. Found: C, 61.50; H, 4.45; N, 3.10.

2-(6-Methoxynaphthalen-2-yl)-N-(4-(2-(p-tolylamino)acetyl)-phenyl)propanamide (3): Equimolar amount of **2** (0.01 mole) and p-toluidine (0.01 mole) in presence ethanol (30 mL) were refluxed for 3 hr. the resulting precipitate was filtered off, dried and recrystallized to give **3** as yellow crystals.

Yield: 65%, yellow crystals (ethanol), m.p 250-252˚C, IR spectrum ν_{max} /cm^{-1}; 3250 (NH), 2940 (CH-aliph.) and 1674 (C=O). MS: m/z (%) 452 (M^+, 25%), 358 (20), 263 (50), 184 (40), 141 (63) and 65 (100). Anal. Calc. for $C_{29}H_{28}N_2O_3$ (452.54): C, 76.97; H, 6.24; N, 6.19. Found: C, 76.50; H, 6.00; N, 6.10.

Formation of compounds 4a, 4b: General procedure:

Equimolar amounts of 2-bromoacetyl derivative **2** (0.01 mole) thiourea and/or phenylthiourea (0.01 mole) in ethanol (30 mL) containing a catalytic amount of fused sodium acetate (1g) were refluxed for 3h. The resulting precipitate was filtered off, dried and recrystallized from the proper solvent to give **4a** and **4b**.

N-(4-(2-Aminothiazol-4-yl)phenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (4a): Yield: 66%, yellow crystals (dioxane), m.p. 220-222ºC, IR spectrum ν_{max} /cm^{-1}; 3389, 3310, 3268 (NH_2/NH), 2976 (CH-aliph.) and 1660 (C=O). ^{1}HNMR (DMSO-d_6): δ = 1.52 (d, 3H, CH_3), 3.97 (s, 3H, OCH_3), 4.03 (q, 1H, CH), 6.85 (s, 1H, thiazole-H), 6.92 (s, 2H, NH_2; cancelled with a D_2O), 7.49-8.06 (m, 10H, Ar-H), 10.16 (s, 1H, NH). Anal. Calc. for $C_{23}H_{21}N_3O_2S$ (403.50): C, 68.46; H, 5.25; N, 10.41. Found: C, 68.22; H, 5.05; N, 10.13.

2-(6-Methoxynaphthalen-2-yl)-N-(4-(2-(phenylamino)thiazol-4-yl)phenyl)propanamide(4b): Yield: 71%, yellow crystals (acetic acid), m.p. 230-232ºC, IR spectrum ν_{max} /cm^{-1}; 3228 (NH), 3080 (CH-arom.) and 1680 (C=O). ^{1}HNMR (DMSO-d_6): δ = 1.52 (d, 3H, CH_3), 3.83 (s, 3H, OCH_3), 4.07 (q, 1H, CH), 7.19 (s,

1H, thiazole-H), 6.95-8.07 (m, 15H, Ar-H), 10.25, 10.29 ppm (2s, 2H, 2NH). Anal. Calc. for $C_{29}H_{25}N_3O_2S$ (479.59): C, 72.63; H, 5.25; N, 8.76. Found: C, 72.49; H, 5.10; N, 8.54.

N-(4-(2-Hydrazinylthiazol-4-yl)phenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (5): Equimolar amounts of 2-bromoacetyl derivative **2** (0.01 mole) and thiosemicarbazide (0.01 mole) in ethanol (30 mL) containing a catalytic amount of fused sodium acetate (2 g) were refluxed for 3h. The resulting precipitate was filtered off, dried and recrystallized to give **5**.

Yield: 65%, yellow crystals (dioxane), m.p. 228-230ºC, IR spectrum ν_{max} /cm^{-1}; 3377, 33202, 3292 (NH_2/NH), 2972 (CH-aliph.) and 1660 (C=O). ^{1}HNMR (DMSO-d_6): δ = 1.52 (d, 3H, CH3), 3.97 (s, 3H, OCH_3), 4.04 (q, 1H, CH), 7.16 (s, 1H, thiazole-H), 7.49-8.06 (m, 10H, Ar-H), 8.60 (s, 2H, NH_2; cancelled with a D_2O), 10.25, 10.29 ppm (2s, 2H, 2NH; cancelled with a D_2O). Anal. Calc. for $C_{23}H_{22}N_4O_2S$ (418.51): C, 66.01; H, 5.30; N, 13.39. Found: C, 65.82; H, 5.10; N, 13.15.

N-(4-(2-(2-(4-Methoxybenzylidene)hydrazinyl)thiazol-4-yl)-phenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (7): Method A: Equimolar amounts of 2-hydrazinylthiazole derivative **6** (0.01 mole) and 4-methoxybenzaldehyde (0.01 mole) in dioxane (30 ml) were refluxed for 3h. The resulting precipitate was filtered off, dried and recrystallized from acetic acid to give **7** in 74% yield.

Method B: Equimolar amounts of 2-bromoacetyl derivative **2** (0.01 mole) and 4-methoxybenzylidenethiosemicarbazone **(6)** (0.01 mole) in boiling ethanol (30 mL) containing a catalytic amount of fused sodium acetate (2g) were refluxed for 3h. The resulting precipitate was filtered off, dried and recrystallized from acetic acid as to give **7** in 63% yield.

Yellow crystals (dioxane),m.p. 226-228ºC, IR spectrum ν_{max}/cm^{-1}; 3276 (NH), 3010 (CH-arom.) and 1658 (C=O). ^{1}HNMR (DMSO-d_6): δ = 1.51 (d, 3H, CH_3), 3.79, 3.98 (2s, 6H, $2OCH_3$), 4.07 (q, 1H, CH), 7.15 (s, 1H, thiazole-H), 6.98-8.06 (m, 15H, Ar-H + benzylidene-H), 10.18, 11.90 ppm (2s, 2H, 2NH). Anal. Calc. for $C_{31}H_{28}N_4O_3S$ (536.64): C, 69.38; H, 5.26; N, 10.44. Found: C, 69.21; H, 5.05; N, 10.18.

N-(4-(2-(cyanomethyl)thiazol-4-yl)phenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (8): Equimolar amounts of 2-bromoacetyl derivative **2** (0.01 mole) and

cyanothioacetamide (0.01 mole) in boiling ethanol (30 mL) containing a catalytic amount of fused sodium acetate (2g) were refluxed for 3h, then the reaction mixture was poured into ice/water. The resulting precipitate was filtered off, dried and recrystallized to give **8.**

Yield: 68%, yellow crystals (acetic acid), m.p. 138-140ºC, IR spectrum ν_{max} /cm^{-1}; 3290, 3250 (NH), 2950 (CH-aliph.), 2250 (C≡N) and 1662 (C=O). MS: m/z (%) 427 (M^+, 24), 263 (60), 184 (75), 141 (100) and 115 (80). Anal. Calc. for $C_{25}H_{21}N_3O_2S$ (427.52): C, 70.24; H, 4.95; N, 9.83. Found: C, 70.00; H, 4.72; N, 9.64.

Formation of thiophene derivatives 10, 11: General procedure: Malononitrile and/or ethyl acetoacetate (0.01 mole), phenyl isothiocyanate (0.01 mole) and finely powdered potassium hydroxide (0.01 mole) in dimethylformamide (30 ml) was stirred at room temperature for 3h, then 2-bromoacetyl derivative **2** (0.01 mole) was added and the mixture was stirred for additional 2 h. The reaction mixture was poured into acidified ice/water. The resulting precipitate was filtered off, dried and recrystallized from the methanol to give **10** and **11.**

N-(4-(3-amino-4-cyano-5-(phenylamino)thiophene-2-carbonyl)phenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (10).

Yield: 61%, yellow crystals (methanol), m.p. 225-227ºC, IR spectrum ν_{max} /cm^{-1}; 3260, 3200, 3178 (NH_2/NH), 2934 (CH-aliph.) and 1650 (C=O). ^{1}HNMR (DMSO-d_6): δ = 1.50 (d, 3H, CH_3), 2.99 (s, 2H, NH_2; cancelled with a D_2O), 3.97 (s, 3H, OCH_3), 4.03 (q, 1H, CH), 7.15-8.05 (m, 15H, Ar-H), 10.37, 10.50 ppm (2s, 2H, 2NH; cancelled with a D_2O). Anal. Calc. for $C_{32}H_{26}N_4O_3S$ (546.64): C, 70.31; H, 4.79; N, 10.25. Found: C, 70.20; H, 4.52; N, 10.03.

Ethyl 5-(4-(2-(6-methoxynaphthalen-2-yl)propanamido)benzoyl)-4-methyl-2-(phenylamino)thiophene-3-carboxylate (11)

Yield: 69%, yellow crystals (methanol), m.p. 260-262ºC, IR spectrum ν_{max} /cm^{-1}; 3248 (NH), 2972 (CH-aliph.) and 1654 (C=O). ^{1}HNMR (DMSO-d_6): δ 1.31 (t, 3H, CH_3), 1.50 (d, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.98 (s, 3H, OCH_3), 4.06 (q, 1H, CH), 4.30 (q, 2H, CH_2-ester), 7.40-8.07 (m, 15H, Ar-H), 10.25, 10.43 ppm (2s, 2H, 2NH; cancelled with a D_2O). Anal. Calc. for $C_{35}H_{32}N_2O_5S$ (592.70): C, 70.92; H, 5.44; N, 4.73. Found: C, 70.79; H, 5.26; N, 4.43.

Formation of imidazo[1,2-a]pyridine and imidazo[2,1-b]thiazole derivatives 12, 13: General procedure: Equimolar amounts of ω-bromoacetyl derivative **2** (0.01

mole) and heterocyclic amines namely (2-aminopyridine, 2-aminothiazole) (0.01 mole) in acetic acid (30 mL) were refluxed for 3h. then allowed to cool. The solid product was collected and recrystallized to give **12** and **13**.

N-(4-(Imidazo[1,2-a]pyridin-2-yl)phenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (12).

m.p. 255-257ºC, IR spectrum ν_{max} /cm^{-1}; 3150 (NH), 2972 (CH-aliph.) and 1666 (C=O). MS: m/z (%) 421 (M^+, 24), 347 (25), 308 (22), 263 (100), 184 (80) and 141 (75). Anal. Calc. for $C_{27}H_{23}N_3O_2$ (421.49): C, 76.94; H, 5.50; N, 9.97. Found: C, 76.78; H, 5.22; N, 9.84.

N-(4-(Imidazo[2,1-b]thiazol-6-yl)phenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (13).

m.p. 280-282ºC, IR spectrum ν_{max} /cm^{-1}; 3286 (NH) and 1656 (C=O). ^{1}HNMR (DMSO-d_6): δ = 1.50 (d, 3H, CH_3), 3.96 (s, 3H, OCH_3), 4.00 (q, 1H, CH), 7.22, 7.48 (2d, 2H, thiazole-H_4, H_5), 7.61-8.10 (m, 10H, Ar-H), 8.29 (s, 1H, imidazole-H), 10.27 ppm (s, 1H, 1NH; cancelled with a D_2O). Anal. Calc. for $C_{25}H_{21}N_3O_2S$ (427.52): C, 70.24; H, 4.95; N, 9.83. Found: C, 70.05; H, 4.68; N, 9.71.

Formation of chromene and benzo[f]chromene derivatives 14, 15: General procedure: Equimolar amounts of **8** (0.01 mole) and o-hydroxyaldehydes namely (salicylaldehyde and or 2-hydroxy-naphthaldehyde) (0.01 mole) in boiling ethanol (30 mL) containing a catalytic amount of ammonium acetate (2g) were refluxed for 1h. The resulting precipitate was filtered off, dried and recrystallized from the proper solvent**.**

N-(4-(2-(2-imino-2H-chromen-3-yl)thiazol-4-yl)phenyl)-2-(6-methoxynaphthalen-2-yl)propanamide (14)

Yield: 73%, beige crystals (dioxane), m.p. 240-242ºC, IR spectrum ν_{max} /cm^{-1}; 3286 (NH), 2920 (CH-aliph.) and 1654 (C=O). ^{1}HNMR (DMSO-d_6): δ = 1.54 (d, 3H, CH_3), 3.85 (s, 3H, OCH_3), 3.98 (q, 1H, CH), 7.19 (s, 1H, thiazole-H), 7.22-8.11 (m, 14H, Ar-H), 8.64 (s, 1H, chromene-H), 8.98, 10.25 ppm (2s, 2H, 2NH; cancelled with a D_2O). Anal. Calc. for $C_{32}H_{25}N_3O_3S$ (531.62): C, 72.30; H, 4.74; N, 7.90. Found: C, 72.08; H, 4.53; N, 7.74.

N-(4-(2-(3-imino-3H-benzo[f]chromen-2-yl)thiazol-4-yl)phen-yl)-2-(6-methoxy-naphthalen-2-yl)propanamide (15)

Yield: 77%, beige crystals (EtOH/Benzene), m.p. >300ºC, IR spectrum ν_{max} /cm^{-1}; 3418 (NH) and 1660 (C=O). ^{1}HNMR (DMSO-d_6): δ = 1.54 (d, 3H, CH_3), 3.86 (s, 3H, OCH_3), 3.98 (q, 1H, CH), 7.20 (s, 1H, thiazole-H), 7.50-8.80 (m, 16H, Ar-H), 9.74 (s, 1H, chromene-H), 10.28, 11.80 ppm (2s, 2H, 2NH; cancelled with a D_2O). Anal. Calc. for $C_{36}H_{27}N_3O_3S$ (581.68): C, 74.33; H, 4.68; N, 7.22. Found: C, 74.11; H, 4.48; N, 7.04.

Formation of benzylidene derivatives 18a,b: General procedure: Method A: Equimolar amounts of **8** (0.01 mole) and 2-(4-chloro-benzylidene)malononitrile **16a** and/or 2-(4-methoxy-benzylidene)malononitrile **16b** (0.01 mole) in boiling ethanol (30 mL) containing a catalytic amount of piperidine (0.5 ml) were refluxed for 3h. The resulting precipitate was filtered off, dried and recrystallized to give **18a,b**.

Method B: Equimolar amounts of **8** (0.01 mole) and 4-chloro-benzaldehyde and/or 4-methoxybenzaldehyde (0.01 mole) in boiling ethanol (30 mL) containing a catalytic amount of piperidine (0.5 ml) were refluxed for 3h. The resulting precipitate was filtered off, dried and recrystallized to give **(18a,b)**.

N-(4-(2-(2-(4-Chlorophenyl)-1-cyanovinyl)thiazol-4-yl)phenyl)-2-(6-methoxy-naphthalen-2-yl)propanamide (18a)

Yield: 65%, white crystals (dioxane), m.p. 180-182ºC, IR spectrum ν_{max} /cm^{-1}; 3250 (NH), 2920 (CH-aliph.) and 1660 (C=O). MS: m/z (%) 549 (M^+, 23), 333 (10), 185 (100) and 141(25) Anal. Calc. for $C_{32}H_{24}N_3O_2SCl$ (550.07): C, 69.87; H, 4.40; N, 7.64. Found: C, 69.59; H, 4.17; N, 7.50.

N-(4-(2-(1-Cyano-2-(4-methoxyphenyl)vinyl)thiazol-4-yl)phenyl)-2-(6-methoxy-naphthalen-2-yl)propanamide (18b)

Yield: 69%, white crystals (dioxane), m.p. 195-197ºC, IR spectrum ν_{max} /cm^{-1}; 3290 (NH), 2956 (CH-aliph.) and 1650 (C=O). MS: m/z (%) 545 (M^+, 24), 333 (40), 265 (35), 185 (100) and 153 (43). Anal. Calc. for $C_{33}H_{27}N_3O_3S$ (545.65): C, 72.64; H, 4.99; N, 7.70. Found: C, 72.51; H, 4.82; N, 7.49.

Biological Activity

Experimental

Animal toxicity studies Method (Spearmane-Karber method)[21] and several doses 75, 150, 300, 600, and 1200mg/kg are chosen. At equal logarithmic dose interval and each dose was injected orally1ml oral suspension in 1% CMC (carboxymethyl cellulose) sodium salt by a stomach tube to each mice in a group of 6 animals and the number of dead animals by each dose was recorded.

Analgesic screening (hot-plate method)[23] In this method, female albino mice (Swiss strain) were put on a hot plate with constant temperature 55ºC, the time taken by the mice to lick its feet or to jump within a cylinder placed on a hot plate surface was determined. This reaction time was taken as the end point and the increase in hot plate latency was taken as a measure of the analgesic activity. Animals which showed positive pain response (elevation of paws licking of fore-paws or jumping out of the hot plate) within 15 s were selected. Mice were divided into twelve groups, each of six animals. Five test compounds and the reference drug were injected i. p. at a dose level of 50 mg/kg into mice. Control group of animals was similarly treated with 1% CMC. The reaction time was evaluated directly after 0.5 and 1 h of injection.

Anti-inflammatory screening.

Anti-inflammatory activity was evaluated using in vivo carrageenin- induced rat paw oedema model[24], which is considered the most conventional one for acute inflammation. Adult albino rats of both sexes weighing (120-200 g) were randomly distributed in twelve groups of six animals each. The rats were kept fasted for 24 h prior to the experiment but allowed free access to water. The rats were injected

intraperitoneally with equimolar doses (equivalent to 0.169 M/kg) of the tested compounds and reference drug (diclofenac sodium).

One hour later, 0.05 ml of freshly prepared suspension of carrageenan (1% w/v in saline suspension) was injected subcutaneously in to the subplantar region of the right hind paw. The left hind paw of each rat received a subplantar injection of equal volume of normal saline. Three hours after carrageenan injection, rats were killed by cervical dislocation then the right and the left hind paws of each rat were cut at the tibiotarsic articulation and weighed. The difference in weight between right and left paws was recorded for each rat. The percentage increase in weight of the carrageenan- injected paw over the other paw was calculated and percentage reduction of eodema from the control group was used as a measure of the activity.

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